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Authors

Cuomo, Raphael E

Mackey, Tim K

Purushothaman, Vidya

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Tobacco/nicotine dependence as a risk factor for substance use disorders and related mental health conditions among cancer patients

Raphael E. Cuomo^{1,2}  | Tim K. Mackey^{2,3,4,5} | Vidya Purushothaman^{2,3}

¹University of California, San Diego, School of Medicine, San Diego, California, USA

²Global Health Policy and Data Institute, San Diego, California, USA

³San Diego Supercomputer Center, San Diego, California, USA

⁴Department of Anthropology, University of California, San Diego, San Diego, California, USA

⁵S-3 Research, San Diego, California, USA

Correspondence

Raphael E. Cuomo, 9500 Gilman Dr, La Jolla, CA 92093, USA.

Email: racuomo@ucsd.edu

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Abstract

Background: Cancer patients often face multiple comorbidities and are at risk for various mental health conditions and substance use disorders. Tobacco/nicotine dependence (TND) is a known risk factor for poor health outcomes and has been associated with psychiatric disorders including substance use disorder. However, the specific relationship between TND and the risk of substance use disorder and mental health conditions among cancer patients remains underexplored. This study aimed to assess the association between TND and the risk of comorbid conditions among cancer patients.

Methods: Data were obtained from a database of electronic health records for patients from the University of California health system. The odds for every condition among cancer patients with TND were calculated and compared with those for cancer patients without TND. ORs were adjusted for gender, ethnicity, and race.

Results: Three thousand seven hundred and ninety-one cancer patients with TND had 252,619 total conditions, and 51,711 cancer patients without TND had 2,310,880 conditions. After adjusting for confounders, the condition for which TND most exacerbated risk was psychoactive substance-induced organic anxiety disorder (OR = 16.3, $p < 0.001$). This appeared consistent with the second, third, and fifth most-exacerbated conditions: stimulant use disorder (OR = 12.8, $p < 0.001$), cocaine induced mental disorder (OR = 11.0, $p < 0.001$), and cocaine use disorder (OR = 11.0, $p < 0.001$). Different conditions exacerbated by TND include acute alcoholic intoxication (OR = 11.4, $p < 0.001$), opioid use disorder (OR = 7.6, $p < 0.001$), schizoaffective disorder (OR = 7.4, $p < 0.001$), and cannabis use disorder (OR = 6.3, $p < 0.001$).

Conclusions: Our findings reveal a strong association between TND and an increased risk of substance use disorder and mental health conditions among cancer patients. Specifically, cancer patients with TND were at an elevated risk for psychoactive substance-induced organic anxiety disorder, stimulant use disorder, and cocaine-related disorders. Additionally, TND was associated with an increased risk of acute alcoholic intoxication, opioid use disorder, schizoaffective disorder, and cannabis use disorder. These findings underscore the need for comprehensive screening and interventions to address TND and comorbid conditions among cancer patients.

KEYWORDS

cancer, comorbidities, oncology, substance use disorder, tobacco

1 | INTRODUCTION

Cancer is a complex disease characterized by the uncontrolled growth of abnormal cells, and it remains a leading cause of morbidity and mortality worldwide.¹ In addition to the physical burden of cancer, patients often experience an array of psychosocial challenges, including mental health conditions and substance use disorder.² A key risk factor associated with both mental health and substance use disorders is tobacco/nicotine dependence (TND).³ Tobacco use is a well-established risk factor for the development of various types of cancer, and nicotine dependence has been implicated in the progression and adverse outcomes of cancer treatment.^{4,5} Additionally, it's crucial to note that cancer patients, including those with a history of substance use disorder and those without, may require opioids for cancer pain management, thus placing them at risk for non-medical opioid use or opioid use disorder.

Research has demonstrated that TND is associated with several mental health conditions, such as depression and anxiety, as well as an increased risk of substance use disorders.⁶ Co-occurrences between TND, mental health conditions, and/or substance use disorder has been linked to poorer treatment adherence and reduced quality of life among cancer patients.^{7,8} In fact, previous studies have highlighted that individuals experiencing these co-occurring conditions tend to face notable barriers to receiving adequate healthcare, often due to a combination of stigma, lack of resources, and health system barriers. Furthermore, the complex interactions between these conditions can exacerbate each other, amplifying the negative impact on a patient's quality of life and prognosis. This has also contributed to increased mortality risk among this patient group, underscoring the crucial need for comprehensive interventions.^{9,10} However, the specific relationship between TND and the risk of substance use disorders and mental health conditions in cancer patients remains underexplored.

Given the substantial public health implications of TND and its potential impact on cancer outcomes, it is crucial to better understand the relationship between TND and other comorbidities among cancer patients. Therefore, this study aimed to investigate the association between TND and increases in co-morbid conditions among cancer patients using data from the COVID-19 Research Data Set (CORDS). Understanding the complex interplay between TND, cancer, and co-morbid conditions may provide valuable insights into the development of targeted interventions to improve the overall well-being of cancer patients.

2 | METHODS

This retrospective observational study was conducted in two phases: (1) data collection from the CORDS by the University of California Health Data Warehouse (UCHDW)¹¹ and (2) data cleaning and

stratified data analysis for comparing the odds for comorbid conditions among cancer patients with and without TND. This study utilized a database of medical records with protections for personally identifiable information that permitted designation as "non-human subjects research" by directors of Institutional Review Boards of the University of California (UC) system.

Electronic health record (EHR) data for any patient tested for COVID-19 across the five UC medical centers (UC Davis, UC Irvine, UCLA, UCSD, and UCSF) were obtained from the CORDS database created by the UCHDW. The CORDS database includes over 500 million data points for over 500,000 patients. The dataset included variables specific to drug exposures, including TND. Patient-level demographic information was also available for gender, race, and ethnicity. Patient data obtained from CORDS included entire clinical records prior to COVID-19 testing. Data files generated from querying the CORDS database were securely stored on a virtual, internet-disabled machine managed by UCSD Altman Clinical and Translational Research Institute. All query results and analytical datasets were securely saved and analyzed on remote machine, and no data were exported from the virtual instance.

An extensive list of cancer-related terms (see Table S1) was curated to filter the dataset for patients with cancer-related conditions. These terms were selected for their wide coverage of cancer-related diagnoses and conditions. The selection of these terms was based on an iterative process involving review of publicly-available glossaries of cancer-related terms^{12,13} and expert input from the research team, which includes cancer epidemiologists and researchers with expertise in assembling keyword lists for database queries. The list was validated by each member of the team and adjusted as per their individual feedback to reach consensus. These terms cover a broad range of cancer types and related conditions, from more general terms like "cancer" and "malignancy" to specific types of cancers or conditions, such as "melanoma" or "myelodysplastic."

Two datasets were then generated: (i) cancer patients with TND and (ii) cancer patients without TND. Clinical observations were coded using SNOMED Clinical Terms, which provide codes, terms, synonyms, and definitions used in clinical documentation and reporting. Therefore, clinician observations are classified into available SNOMED Clinical Terms, including "tobacco dependence" and "nicotine dependence," the main exposure variables for this analysis, and the terms used in this paper to describe other conditions are also taken directly from SNOMED Clinical Terms used in the EHR database.

Structured Query Language scripts were written to join patient identifier variables with a sub-query for all comorbidities. The first set of datafiles obtained included a patient ID and condition ID for each comorbidity, gender, race, and ethnicity for all cancer patients. Redundant patient-condition data rows were deduplicated to

preserve only unique patient ID-condition ID data. Further, data rows with unknown condition IDs were also considered as missing data and removed from further data analyses. Condition names for each of comorbidities were generated using a condition ID data dictionary.

A total of 3,458,897 rows of unique patient-condition data rows were generated for all cancer patients with and without TND. Using unadjusted logistic regression, odds ratios were generated for each of the comorbidities to observe the odds of the condition among cancer patients with TND and cancer patients without TND. Specifically, odds ratios were generated for 7856 comorbidities. The top 20 comorbidities with the highest unadjusted odds ratio were also generated. Further, logistic regression models were run to calculate the odds ratio for the top 20 comorbidity conditions after adjusting for gender, race, and ethnicity. A *p*-value of 0.05 was considered the significance threshold level for all statistical analyses. In order to account for multiple comparisons, post-hoc pairwise comparisons were conducted to apply Bonferroni corrections to the *p*-values for the different subgroups in the adjusted logistic regression model. All statistical analyses were conducted in SPSS version 27.

3 | RESULTS

Three thousand seven hundred and ninety-one cancer patients with TND had 252,619 total conditions (mean of 67 observations per patient), and 51,711 cancer patients without TND had 2,310,880 conditions (mean of 45 observations per patient). The top three most common conditions among all cancer patients were essential hypertension ($n = 27,147$ observations), hyperlipidemia ($n = 23,769$ observations), and gastro-esophageal reflux disease without esophagitis ($n = 18,696$ observations). Hypertension and hyperlipidemia were the two most common clinical observations for cancer patients with TND (54% and 43% of patients, respectively) and without TND (38% and 33% of patients, respectively). The third most common clinical observation for cancer patients with TND was chronic pain (39% of patients), whereas gastro-esophageal reflux was observed as the third most common clinical observation among cancer patients without TND (26% of patients). The relative order of these were flipped between the two populations, with the fourth most common clinical observation for cancer patients with TND being gastro-esophageal reflux (37% of patients), and the fourth most common clinical observation for cancer patients without TND being chronic pain (26% of patients).

For the purposes of generalizability, assessment of conditions more common in cancer patients with TND compared to those without TND were limited to those with sample sizes of at least 30 patients (see Table 1). Among these, the top condition was tobacco dependence (OR = 29.1, $p < 0.001$), but this is excluded from further reporting due to clear conflation with the risk factor itself. Therefore, in unadjusted comparisons, the conditions most common for cancer patients with TND, compared to those without TND, were psychoactive substance-induced organic anxiety disorder (OR = 19.2, $p < 0.001$), cocaine induced mental disorder (OR = 16.3, $p < 0.001$),

and stimulant use disorder (OR = 15.4, $p < 0.001$). After adjusting for differences in the distributions of gender, race, and ethnicity, the three conditions most common in the TND population were psychoactive-induced organic anxiety disorder (OR = 16.3, $p < 0.001$), stimulant use disorder (OR = 12.8, $p < 0.001$), and acute alcoholic intoxication in alcoholism (OR = 11.4, $p < 0.001$).

Though conditions associated with stimulant dependence had the highest relative odds in cancer patients with TND, conditions associated with other substances of abuse were also observed among the 20 conditions having highest relative odds. These were acute alcoholic intoxication in alcoholism (unadjusted OR = 14.1, rank = 6; adjusted OR = 11.4, rank = 4), nondependent opioid use disorder in remission (unadjusted OR = 10.5, rank = 11; adjusted OR = 9.2, rank = 10), acute alcohol intoxication (unadjusted OR = 9.9, rank = 13; adjusted OR = 8.8, rank = 12), opioid use disorder (unadjusted OR = 9.0, rank = 15; adjusted OR = 7.6, rank = 15), alcohol withdrawal syndrome (unadjusted OR = 7.4, rank = 18; adjusted OR = 6.3, rank = 18), and cannabis use disorder (unadjusted OR = 7.4, rank = 19; adjusted OR = 6.3, rank = 19). Among the top 20 conditions having highest relative odds for cancer patients with TND was schizoaffective disorder (unadjusted OR = 8.0, rank = 17; adjusted OR = 7.4, rank = 16), which has documented associations with substance use disorder but also has alternate etiologies. All odds ratios were statistically significant with a *p*-value of < 0.001 after applying Bonferroni corrections.

4 | DISCUSSION

The present study aimed to compare associations between TND and risk for a broad set of comorbid conditions among cancer patients. Our findings reveal a significant association between TND and an increased risk of psychoactive substance-induced organic anxiety disorder, cocaine-induced mental disorder, and stimulant use disorder. After adjusting for gender, race, and ethnicity, the conditions most common in the TND population were psychoactive-induced organic anxiety disorder, stimulant use disorder, and acute alcoholic intoxication in alcoholism. Furthermore, we observed conditions associated with other substances, such as opioid use disorder and cannabis use disorder, which were also observed among the top 20 conditions having the highest relative odds for cancer patients with TND. In addition to these key findings, we observed that among all cancer patients, regardless of TND status, the top three most common conditions were hypertension, hyperlipidemia, and gastro-esophageal reflux disease. These findings are consistent with previous research in the oncology field, which identifies hypertension as one of the most prevalent comorbidities across various cancer patient cohorts, with its prevalence ranging from approximately 15%-20% among patients.¹⁴ Similarly, diabetes is another common comorbidity, found in roughly 5% of patients in these cohorts. Interestingly, our study contributes to the existing literature by shedding light on the prevalence of hyperlipidemia and gastro-esophageal reflux disease, conditions whose prevalence rates

TABLE 1 Top 20 conditions having highest unadjusted odds ratios between cancer patients with tobacco/nicotine dependence and cancer patients without tobacco/nicotine dependence ($n = 55,502$ patients), by adjusted ratios, with rank shown for both unadjusted and adjusted ratios.

Condition	OR (unadjusted)	Rank (unadjusted)	OR (adjusted ^a)	Rank (adjusted ^a)
Tobacco dependence, in remission	29.1	1	28.0	1
Psychoactive substance-induced organic anxiety disorder	19.2	2	16.3	2
Stimulant use disorder	15.4	4	12.8	3
Acute alcoholic intoxication in alcoholism	14.1	6	11.4	4
Cocaine induced mental disorder	16.3	3	11.0	5
Cocaine use disorder	15.3	5	11.0	6
Stimulant dependence	13.3	7	10.8	7
Psychostimulant dependence	12.9	8	10.4	8
Disorder due to psychoactive substance use disorder	12.1	9	10.1	9
Drug use disorder	11.0	10	9.2	10
Nondependent opioid use disorder in remission	10.5	11	9.2	11
Acute alcohol intoxication	9.9	13	8.8	12
Psychoactive substance use disorder	9.3	14	8.0	13
Drug withdrawal	8.2	17	7.9	14
Opioid use disorder	8.9	15	7.6	15
Schizoaffective disorder	8.0	18	7.4	16
Nondependent cocaine use disorder in remission	10.1	12	7.2	17
Drug dependence in remission	8.9	16	7.2	18
Alcohol withdrawal syndrome	7.4	19	6.3	19
Cannabis use disorder	7.4	20	6.3	20

Note: All odds ratios were statistically significant at the $\alpha = 0.05$ level after applying Bonferroni corrections.

^aAdjusted for gender, race, and ethnicity.

have not been as commonly reported as those for hypertension and diabetes. This suggests that the full landscape of common comorbidities in cancer patients may be more diverse than previously understood.

Our study supports previous research that has demonstrated an association between TND and various mental health conditions and substance use disorders.⁶ The observed association between TND and psychoactive substance-induced organic anxiety disorder is particularly noteworthy and aligns with the established link between nicotine dependence and anxiety disorders.⁷ Additionally, the increased risk of acute alcoholic intoxication in alcoholism among cancer patients with TND suggests that these patients may be more vulnerable to alcohol-related disorders, a finding consistent with prior studies showing a high co-occurrence of nicotine and alcohol dependence.⁸

The results of this study also highlight the relationship between TND and stimulant use disorder, including cocaine-induced mental disorder. Stimulant use disorder is associated with several adverse health outcomes, and its co-occurrence with TND in cancer patients raises concerns about the potential impact on treatment adherence, treatment response, and overall prognosis.¹⁵ Importantly, the

presence of stimulant use disorder and other substance use disorders in cancer patients with TND may further exacerbate psychological distress and negatively affect quality of life.

Schizoaffective disorder was among the top 20 conditions having the highest relative odds for cancer patients with TND. Schizoaffective disorder has documented associations with substance use disorder, including nicotine dependence, but also has alternate etiologies. The presence of schizoaffective disorder in this population underscores the need for comprehensive mental health assessments and interventions for cancer patients with TND.¹⁶

Recognizing the complex interplay between cancer and mental health, our findings shed new light on exposure to tobacco or nicotine dependence as possible risk factors and potential areas for targeted interventions. Concordantly, future research may seek to emphasize on the development and evaluation of interventions tailored to cancer patients exhibiting tobacco or nicotine dependence. These interventions should encapsulate measures to mitigate the associated risk of anxiety and substance use disorders, particularly those linked to stimulants and opioids. Furthermore, to better understand the associations observed in this study, it is essential to delve deeper into underlying mechanisms. This can entail

investigating potential mediating factors such as the interplay between individual susceptibility, environmental factors, psychological resilience, and socio-economic variables. In this context, longitudinally designed studies could provide invaluable insights, helping us move beyond correlation to better understand causal dynamics. Hence, a multifaceted area of future study on the influence of nicotine exposure on cancer patients, informed by our current findings uncovering associations with mental health and substance use disorders, could potentially pave the way for a more comprehensive and effective management strategy for cancer patients grappling with tobacco or nicotine dependence.

4.1 | Clinical implications

Our findings have important clinical implications. Health care providers should be cognizant of the increased risk of substance use disorder and mental health conditions among cancer patients with TND. Early screening for TND, as well as other substance use disorders and mental health conditions, should be integrated into routine cancer care. Tailored interventions, such as smoking cessation programs, counseling, and pharmacotherapy, may be beneficial in addressing TND and comorbid conditions to improve health outcomes and quality of life for cancer patients.

4.2 | Limitations

Several limitations of this study should be acknowledged. Firstly, given the large breadth of patients included in the sample, it is possible for coding inaccuracies and deficits in documentation to occur, leading to misclassification. However, it is unlikely that there is differential misclassification between exposures or outcomes. This, nonetheless, represents a notable limitation which merits attention. The retrospective design of the study further precludes causal inferences. Additionally, clinical observations are made at the time of patient encounter, but dates of comorbidity were not available. This unclear temporality therefore raises the possibility of reverse causality, whereby the comorbid conditions identified in this study serve as risk factors for tobacco or nicotine dependence. Lastly, the sensitive nature of substance use disorder can present a challenge in the data collection process. While the gold standard for diagnosing substance use disorder is through a confidential psychiatric diagnostic interview based on DSM-5 criteria, it was not possible for us to determine the diagnostic methodology for conditions included in our study. We suspect that the proportion of diagnoses documented via this gold standard is unlikely to differ across comparison groups in this study (e.g. cancer patients with/without TND). Nevertheless, the potential for underreporting, as many patients may be unwilling to reveal dependence on illicit products, such as cocaine or opioids, could bias effect estimates toward the null due to lower overall counts across the patient population.

5 | CONCLUSIONS

In conclusion, this study provides evidence of an association between TND and an increased risk of substance use disorder and related mental health conditions among cancer patients. Our findings underscore the need for a comprehensive approach to cancer care that addresses both physical and psychosocial aspects of the disease. Future research should explore the underlying mechanisms of these associations and develop effective interventions to address TND and comorbid conditions in cancer patients.

AUTHOR CONTRIBUTIONS

Raphael E. Cuomo: Conceptualization; methodology; software; validation; formal analysis; investigation; resources; data curation; writing – original draft; writing – review & editing; visualization; supervision; project administration; funding acquisition. **Tim K. Mackey:** Writing – review & editing. **Vidya Purushothaman:** Software; formal analysis; data curation; visualization; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This study is exempt from human subject protection under IRB protocol 1604619-1 of the University of California Health System.

ORCID

Raphael E. Cuomo  <https://orcid.org/0000-0002-8179-0619>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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