



Smoking Status Among Cancer Patients and its Impact on Health-related Quality of Life (HRQoL): A U.S Nationwide Representative Analysis.

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"Smoking Status Among Cancer Patients and its Impact on Health-related Quality of Life (HRQoL): A U.S Nationwide Representative Analysis"

by

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A Dissertation Submitted to the Faculty of Harvard Medical School

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I have reviewed this thesis. It represents work done by the author under my guidance/ supervision.

Primary mentor: **Steven Lee Chang, M.D., M.S.**

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BACKGROUND

By 2023, an alarming 1,958,310 new cancer cases will arise across the United States.(1) To put things into perspective, in January 2019, 16.9 million people--roughly 5% of the population--were living with cancer in the USA.(2) Smoking is the leading risk factor for both cancer development and cancer mortality - over one-third (35%) of tobacco-related cancer cases can be linked back to smoking, and an alarming one-fifth of all cancers are directly attributable to this dangerous addiction.(3)

Smoking contributes to the onset of cancer and detrimentally affects smokers' quality of life and life expectancy.(4)(5) Cancer patients often endure diminished quality of life alongside elevated mortality rates compared to the general population.(6)(7) Consequently, healthcare professionals must strive to prevent smoking within this susceptible population.

Primary, secondary, and tertiary prevention strategies hold paramount importance and prove more efficient than addressing the aftermath of their shortcomings. The healthcare system typically focuses on treating specific illnesses as they arise, similar to "extinguishing fires," rather than proactively preventing diseases from occurring. Consequently, while preventive medicine should be the responsibility of all healthcare professionals, it frequently ends up being primarily shouldered by primary care practitioners. This unintentionally creates a setting where specialists might not give due weight to prevention within their particular areas of expertise.

Despite the substantial efforts invested in creating groundbreaking cancer treatments, there remains a profoundly concerning disparity in the focus given to disease

prevention initiatives. The widespread and harmful belief that irreversible damage is already done when a patient receives a cancer diagnosis, and any additional action would be pointless, can pose significant risks. This belief system hinders effective preventive measures and undermines the potential for positive change and improved health outcomes. Emphasizing the critical importance of disease prevention strategies implemented by all medical specialists is crucial. Brief interventions, including physician tobacco cessation guidance or referrals to specialized tobacco cessation programs, can significantly enhance patients' chances of survival and overall well-being. These seemingly minor measures can create a lasting, positive influence on the lives of those affected by tobacco-related health issues.

Physicians hold a unique position to influence patient conduct through personalized interactions.(8) It is vital to intensify smoking cessation consciousness and provide physicians with the essential resources to assist their patients in triumphing over smoking.(9) This responsibility encompasses all medical practitioners, transcending primary care providers. Regrettably, the integration of smoking cessation counseling is not yet widespread among numerous physicians.(10)(11)(12)(13)(14)(15)

In order to explore the prevailing circumstances of smoking cessation in cancer survivors and the impact of smoking behaviors on patients' HRQoL, we embarked on two interconnected research endeavors, drawing upon data from the Behavioral Risk Factor Surveillance System (BRFSS).(16) The CDC oversees this extensive and nationally representative database (Centers for Disease Control and Prevention).

Our first paper examined the supposition that distinct medical specialties correlate with diverse tobacco cessation rates among tobacco-related cancer patients. We

hypothesize that smoking prevalence among cancer survivors would diverge depending on the medical specialties involved in cancer care.

In our second paper, we explored the relationship between the smoking habits of cancer survivors and their HRQoL. We hypothesized an existing link between a patient's smoking behavior and a decline in HRQoL, emphasizing the detrimental association of this particular risk factor with cancer survivors' well-being.

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PAPER 1

Smoking Status Among Cancer Patients by Medical Specialty: A Us Nationwide Representative Analysis

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Smoking Status Among Cancer Patients by Medical Specialty: A U.S. Nationwide Representative Analysis

Abstract

Background:

Persistence in tobacco use among cancer survivors has been associated with a multitude of clinicodemographic factors. However, there is a paucity of understanding regarding the role the healthcare professional's specialty plays in tobacco cessation in tobacco-related cancer survivors.

Methods:

We conducted a cross-sectional analysis of data from cancer survivors with a smoking history using the Behavioral Risk Factor Surveillance System (BRFSS) database to examine differences in the proportion of patients continuing tobacco use among patients with a diagnosis of cancer segregated by cancer site specialty over the 2016-2020 period. We accounted for complex survey design and used sampling weights to obtain a nationwide representative sample. We employed modified Poisson regression adjusting for age, gender, education, income, race, marital status, and medical specialty.

Results:

We analyzed 19,855 cancer survivors with a current or past history of tobacco use, of whom 5,222 (26,3%) self-reported to be current smokers. Patients with urological and gynecological tobacco-related malignancies had a higher relative risk of being current smokers with a relative risk (RR) of 1.30 (95% confidence interval, 1.12 to 1.51) and 1.25 (95% confidence interval, 1.12 to 1.39) respectively. Malignant Hematology had the

lowest relative risk of smoking status among all other specialties RR 0.85 (95% confidence interval, 0.59 to 1.21).

Conclusions:

Continuing smoking rates among tobacco-related cancer survivors were different between specialties. One in four cancer survivors were current smokers; this emphasizes health professionals' paramount role in tobacco cessation counseling.

Keywords: Tobacco, Smoking Cessation, Physicians, Cancer Survivors

INTRODUCTION

Smoking is the leading preventable cause of death worldwide.(1) In 2019, approximately one-fifth of U.S. adults (50.6 million) reported being current users of some form of tobacco.(2) Tobacco is associated with many types of cancer, including lung, laryngeal, oral, esophageal, pharyngeal, bladder, kidney, liver, gastric, pancreatic, colon rectum, cervical, and acute myeloid leukemia.(3) Continued smoking among cancer patients can increase the odds ratio of disease recurrence and progression(4) (5) (6)decrease the quality of life for cancer survivors(7) (8) and places this population at an increased risk of developing second primary malignancies. (9) (10)

Because of the deleterious aspects of tobacco use, the diagnosis of cancer may serve as a “turning point” leading some patients to adopt a healthier lifestyle after a cancer diagnosis and quit smoking. At the same time, other patients in a similar situation fail to institute any meaningful change and will continue to smoke. Although prior studies have

identified patient factors associated with tobacco cessation versus continued smoking among cancer patients, there remains an incomplete understanding of this multifactorial issue.

Although prior investigations have focused primarily on patient characteristics, it is recognized that medical counseling plays a fundamental role in tobacco cessation; therefore, the tobacco cessation rate might be substantially influenced by the healthcare professional factor.(11) While some physicians actively defer a discussion regarding tobacco cessation to other healthcare professionals, other physicians may actively incorporate this discussion to capitalize on the “teachable moment” of cancer diagnosis to pursue this challenging task of tobacco cessation. It is critically important to identify all the risk factors associated with continuing to smoke in cancer patients to increase the effectiveness of tobacco cessation efforts. Some studies have investigated the factors associated with continuing to smoke after cancer diagnosis.(12) (13) (14) (15) (16) However, no previous studies have evaluated the relationship between continuing smoking after cancer diagnosis and cancer site by the medical or surgical specialty which primarily manages the disease. It is unknown if certain specialties are associated with higher smoking rates in cancer patient survivors. We hypothesize that there is a difference in continuing smoking depending on cancer type by specialty. This study aimed to test the hypothesis that different medical specialties are associated with different tobacco cessation rates in tobacco-related cancer patients.

MATERIAL AND METHODS

Study Design/Data Source

We perform a cross-sectional study using the BRFSS (Behavioral Risk Factor Surveillance System) database. This database is the largest continuously conducted health survey in the world, which collects data using telephone surveys of > 400,000 adults each year from all 50 states as well as the District of Columbia and three U.S. territories. BRFSS is conducted by the CDC's (Center for Disease Control and Prevention) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) and collects data about health-related risk behaviors, chronic health conditions, and the use of preventive services.(17)

BRFSS collects comprehensive and detailed data about participants' health status. This data includes demographic (including age, education, income, and occupation), health status (including several chronic conditions such as hypertension, diabetes, and arthritis), health history (history of cancer, type of cancer, and course of treatment), healthcare access and behavioral data (exercise, tobacco use, marijuana use, alcohol consumption, diet, vaccination status) among others. We appended data from the years 2016 to 2020 BRFSS annual surveys assembling the analyzed dataset.

Study Cohort.

The study cohort was comprised of individuals aged 18 years or older who reported a history of cancer and a current or past smoking history. Cancer survivor patients were identified based on their responses to the survey question, "What type of cancer was it?"

(Variable name: CNCRTYP1). Current and former smokers were identified through the survey question SMQ100 “Have you ever smoked more than 100 cigarettes in your life?”. Among individuals with a smoking history, smokers were classified as those who continue to smoke or quit smoking based on their response to SMOKDAY2 “Do you now smoke cigarettes every day, some days, or not at all?” (Table S1). We divided the cancer cohort into tobacco-related cancers and non-tobacco-related cancers. We define tobacco-related cancers as those specified on the National Cancer Institute (NIH) website. (Table S2.) We create the variable “specialty” according to the cancer site origin. Thoracic surgery included (lung and esophageal cancers), colorectal surgery (colon and rectum cancers), malignant hematology (leukemia), head and neck surgery (head, neck, oral, pharyngeal, and laryngeal cancers), surgical oncology (liver, pancreas, and gastric cancers), urology (kidney and bladder cancers) and, gynecology (cervical cancer). (Table S3). We used respondents with non-tobacco-related cancers as the reference group for all specialties.

Outcomes and Procedures

The outcome of interest was the continuation of smoking. This was defined as the proportion of patients currently smokers despite a cancer diagnosis. The exploratory variables were age, gender, education level, income status, marital status, race, and type of specialty for tobacco-related cancers. Using these variables, we also conducted a multivariate analysis to identify independent predictors for continued smoking in cancer survivors. BRFSS database is a publicly available database offered by the CDC which contains de-identified data (<http://www.cdc.gov/brfss>) and is not categorized as human

subjects research, so it does not require an institutional review board approval.

Statistical Analysis

Categorical variables were summarized by frequency tables. Chi-square tests were used to compare two groups of categorical variables. We accounted for complex survey design by adjusting for stratification and clustering at the primary sampling unit. Further, we used sampling weights to calculate the nationwide representative frequencies and proportions. We used multiple imputations via predictive mean matching ($k = 5$ imputations) to address missing values which represented 15.4% for the income variable and less than 0.2% for education, insurance, and gender. We used modified Poisson regression adjusting for age, gender, education, income, race, marital status, and different medical specialties to estimate the relative risk of being a current tobacco user among cancer survivors who had ever used tobacco. Modified Poisson regression was chosen over the more common logistic regression because the incidence of the outcome of interest (continuing smoking) was higher than 10%. Thus, the risk ratio, which is derived from Poisson regression, is more appropriate than the odds ratio derived from logistic regression(18) (19) The outcomes of Poisson regression are Risk Ratios to measure the association between the exposures and the outcome accurately. In secondary analyses, we examined interactions with age and education. Sensitivity analyses were performed to evaluate the robustness and consistency of the findings. First, we assessed the impact of considering only tobacco-related cancers by excluding all non-tobacco-related cancers from the analysis. The comparison group used was malignant hematology, the only nonsurgical specialty among tobacco-related cancers. Second, we analyzed the different types of cancer by their "origin site" among tobacco-related cancers. Third, we run a

complete case analysis excluding all missing data. Statistical significance was defined as $\alpha < 0.05$. Data were analyzed using STATA/BE version 17.0.

RESULTS

Study Population:

A total of 2,193,981 participants were surveyed between the years 2016 and 2020. We analyzed 19,855 cancer survivors (Weighted: 7,384,612 cancer survivors) who were lifetime or current smokers. As shown in Table 1, active smokers tended to be younger, lower educated, lower income, belong to underrepresented racial minorities, and lack insurance as compared to those participants who quit smoking. Details of the characteristics of the participants are provided in Table 1. There were no statistically significant differences between cohorts. The self-reported smoking prevalence within the cohort was 26.3%. Among patients with non-tobacco-related cancer, the smoking prevalence was 19.6%. Patients with urological, gynecological, and surgical oncologic cancers related to tobacco use exhibited the highest smoking rate within the population diagnosed with tobacco-related cancer. (Table 2.)

Predictors of Continuing Smoking

In our multivariate model, we identify independent predictors for continued smoking in cancer survivors. (Table 3.) The strongest predictor for continued smoking was age which was characterized by younger patients, less than 40 years, having a risk of smoking over nine times higher compared to those older than 80 years (relative risk

[RR] 9.92; 95% confidence interval [CI]: 7.46 to 13.9; $p < 0.001$). As compared to college graduates, participants with less than a high school diploma presented twice the risk of smoking (RR 2.06; 95% CI: 1.80 to 2.42; $p < 0.001$). The relative risk of continuing smoking was 36% higher among single or unmarried participants when compared with those with married or partner status (RR 1.36; 95 % CI: 1.26 to 1.48; $p < 0.001$). Compared with Whites, Hispanic and Black patients were more likely to continue smoking despite the diagnosis of cancer (for Hispanic: RR 1.33; 95% CI: 1.09 to 1.62; $p = 0.003$; for Black, RR 1.15; 95% CI: 1.01 to 1.32; $p = 0.040$). Other races and ethnicities did not have a statistically significant association with smoking status following a diagnosis of cancer. There was also no association between smoking status and gender, with similar rates for males and females.

Analysis of Continuing Smoking by Specialty

When compared to all non-tobacco-related cancers as a reference group, tobacco-related cancers have a different tobacco cessation rate by specialty. Malignant Hematology had the lowest relative risk of smoking continuation among the evaluated specialties (RR 0.85; 95% CI: 0.59 to 1.21; $p = 0.370$). In contrast, there was a clearly elevated relative risk for continuing smoking among patients with a diagnosis of a urologic or gynecologic tobacco-related cancer (RR: 1.30; 95% CI: 1.12 to 1.51; $p < 0.001$) (RR 1.25; 95% CI: 1.12 to 1.39; $p < 0.001$) respectively. (Figure 1). Thoracic surgery and surgical oncology tend to have a higher risk of continuing to smoke, although statistical significance was not met to support this association.

Analysis of Interactions with Age and Education

We conducted an interaction analysis by age to investigate whether relative risks (RRs) of continued smoking were consistent between elderly and non-elderly populations. (Table 4) We found that the overall effect was driven by the non-elderly population (<65 years) ($F_7 = 7.5$, $p_{int} < 0.001$), with significantly higher RRs observed in urology (RR:1.26, 95% CI 1.27 to 1.57) and gynecology (RR: 1.41; 1.05 to 1.52) ($F_2 = 23.3$, $p_{int} < 0.001$) and no other significantly elevated RRs among the other TRC specialties ($F_5 = 0.78$, $p_{int} = 0.567$). Furthermore, we found that the overall null finding for thoracic surgery (RR =1.12, 95% CI 0.96 to 1.32), when disaggregated by elderly and non-elderly population, was significantly elevated among those over 65 years old (RR=1.36; 95% CI: 1.07-1.73) and was not elevated in the non-elderly population. These results suggest that older patients are more likely to continue smoking than their younger counterparts across all cancer specialties studied here, regardless of type or location within the body.

Further, we conducted an interaction analysis by education to investigate whether relative risks (RRs) of continued smoking were consistent between different levels of educational attainment. (Table 5) We found that the overall association between educational attainment and continuing to smoke after diagnosis was driven by the subpopulation with higher levels of education. (High school diploma or more) ($F_7 = 7.5$, $p_{int} < 0.001$), with significantly higher RRs observed in urology (RR:1.35, 95% CI 1.15 to 1.60) and gynecology (RR: 1.36; 1.21 to 1.53) ($F_2 = 18.5$, $p_{int} < 0.001$) and also a significantly elevated RR in surgical oncology (RR:1.49, 95% CI 1.15 to 1.93) ($F_5 = 2.23$,

$p_{\text{int}} = 0.048$). These results suggest that individuals with less than a high school diploma were significantly less likely to continue smoking after diagnosis compared to those with higher levels of education.

Sensitivity Analysis

In order to ensure the robustness of our findings and to gain further insight into the smoking status among cancer patients, we conducted several sensitivity analyses. These analyses aimed to assess the impact of different factors and potential confounding variables on our results. By conducting these additional analyses, we could demonstrate the consistency and reliability of our results, even under various scenarios.

First, we sought to evaluate the impact of considering only tobacco-related cancers on our findings. This was done by excluding all non-tobacco-related cancers from the analysis. The comparison group used in this sensitivity analysis was malignant hematology, as it was the only nonsurgical specialty among the tobacco-related cancers group. The results of the sensitivity analysis reinforced our original findings as they showed that tobacco-related cancer survivors with gynecological malignancies had a significantly higher relative risk (RR: 1.71; 95% CI 1.18-2.46) of continuing to smoke compared to the malignant hematology group. This was also true for patients with urological malignancies, who had a higher relative risk (RR: 1.48; 95% CI 1.02-2.14) of smoking compared to the malignant hematology group.

Second, we did a sensitivity analysis utilizing the "site of origin" to study the relationship between smoking behavior and different types of cancer. The grouping of tobacco-related cancers based on their site of origin allowed for a more in-depth

examination of potential differences in smoking behavior across various cancer types and the identification of confounding factors. Isolating the impact of each cancer site type enhanced our understanding of the connection between smoking and cancer, thereby reinforcing the robustness of the original findings. The results of this sensitivity analysis showed that patients with cervical cancer (RR: 1.70; 95% CI 1.18-2.46) and urological cancers (Bladder and Kidney) (RR: 1.48; 95% CI 1.02-2.15) had a significantly higher relative risk of continuing to smoke compared to the malignant hematology group.

As a third sensitivity analysis, we evaluated only complete cases with no missing data (n: 15,891). The findings of this analysis were in line with our previous results after multiple imputations and revealed that patients with tobacco-related cancers in the urological and gynecological specialties had a significantly higher risk of continuing to smoke (RR: 1.36; 95% CI 1.18-1.56 and RR: 1.21; 95% CI 1.08-1.36, respectively) compared to non-tobacco-related cancers. These observations further support the robustness of our initial results, emphasizing the consistent association between smoking continuation and tobacco-related cancers in these specialties.

DISCUSSION

This study found that more than one-fourth (26.3%) of cancer survivors were current smokers. While our results are consistent with previously reported findings between younger age and lower education associated with smoking in tobacco-related cancer patients,(12) (13) (20) (21) (22) we interestingly found that the rate of individuals

continuing to smoke varied according to the specialty involved in cancer care thus highlighting the likely important role of the healthcare professional with respect to tobacco cessation. It is feasible that these findings are due to a difference in tobacco cessation counseling by the treating physician.(23) Specifically, we identified that having urological or gynecological cancer was significantly associated with continuation of smoking after a cancer diagnosis. These findings suggested that urologists and gynecologists might not offer adequate counseling about tobacco cessation to patients compared to other specialists.

The strengths of this study include the analysis of the world's largest continuously conducted health survey system, including five recent years. Thus, our findings largely reflect the current status regarding smoking attitudes among cancer patients in the United States. To the best of our knowledge, our study is the first nationwide study to identify differential rates of tobacco use among patients with tobacco-related cancers. However, our results are supported by a recent national sample study where 1,058 physicians from six different specialties were surveyed regarding adherence to the U.S Public Health Service (USPHS) Clinical Practice tobacco cessation guidelines, Schaer et al. found overall low adherence (18%) as well as differential implementation among the medical specialties.(24)

Our study identified urology and gynecology as the specialties with the highest rates of patients continuing to smoke despite their cancer diagnosis. According to a national survey centered on urologists in the United States, only 19.8% of respondents declared always discussing tobacco cessation with their bladder cancer patients.(25) This low rate of providing smoking cessation assistance may explain the higher rate of

continuing smoking we found in urologic cancer survivors. Additionally, Swoboda et al. analyzed the Health Information National Trends Survey and reported a continuing smoking prevalence of 31.2% in cervical cancer survivors, representing the highest prevalence of all cancers.(13) This also supports our findings about patients with a gynecologic malignancy having a significantly higher probability of continuing to smoke despite the diagnosis of a tobacco-related cancer. It is plausible that this could be related to the fact that gynecologists deal with cervical cancer, which represents a cluster of patients with higher-risk health behavior, and it might be harder to counsel this particular group against tobacco use because of their unfavorable socioeconomic and educational status.(26) (27) Another possible explanation might be the perception of disease both by the patient and the specialist. Both urology and gynecology specialties have an important proportion of endoscopic outpatient procedures compared to other specialties. These short endoscopic procedures, such as transurethral resection of the bladder or cervical conization, are usually low-complexity procedures, which do not leave any visible scars, and patients have a speedy recovery, often being discharged on the same day to their homes. This fast treatment and the shorter interaction with the physician could, in part, create fewer opportunities for counseling and explain the difference in the smoking rates in the survivors of these specialties.

We found that malignant hematology patients had the highest rate of tobacco cessation among the specialties in the current study. Importantly, out of all studied specialties in this study, hematologists were the only ones who had an internal medicine background compared to all other surgical specialties. Shaer et al. found that internists had the highest rates of implementation of arranging for follow-up for tobacco

cessation(24). Another possible reason could be that leukemia treatment usually lasts several months, and patients are admitted to hospitals for long periods creating more opportunities to discuss tobacco cessation with patients.

The importance of tobacco cessation in cancer survival has been widely studied and associated with a positive impact to a great extent. Some studies show that quitting smoking is associated with better tolerance of treatments and improvement in treatment outcomes,(28) (29) (30) (31) (32) (33), as well as fewer treatment complications.(34) Additionally, there is robust evidence that quitting smoking is associated with a substantial reduction in the risk of recurrence and progression.(4) (5) (6) (35) (36) Foerster et al. examined in a systematic review and meta-analysis the association between smoking status and the risk of biochemical recurrence, metastasis, and cancer-specific mortality among patients with localized prostate cancer undergoing treatment. Within the median follow-up of 72 months, current smokers had a 40% higher risk of biochemical recurrence, a significantly higher risk of metastasis (HR, 2.51; 95% CI, 1.80-3.51), and an 89% higher risk of cancer-specific mortality(37) Furthermore, smoking cessation reduces the risk of a second primary malignancy,(38) (39) (40) and is associated with better quality of life and longer survival.(8) (41) (7) (42) (43) This highlights the importance of providing extra support to those high-risk cancer populations.

Our results have implications for clinical practice, as they identify the characteristics of those patients who might require a special tobacco-cessation approach during their follow-up. Clinicians must obtain the necessary training to provide comprehensive tobacco cessation counseling to every patient and more intense counseling to cancer survivors and encourage them to engage in a tobacco cessation

program.(44) It was established that the best time to encourage a patient to quit smoking is at the time of the cancer diagnosis; this is known as “the teachable moment,” opportunity healthcare professionals should take advantage of.(45) (46) (47) A multidisciplinary approach to these patients must be offered to grasp this unique opportunity. The difference in tobacco cessation observed among specialties could serve as a call to action for societies and physicians to reflect on current tobacco cessation approaches offered to their patients.

Our paper has some limitations. First, this was a cross-sectional study, and we did not consider temporality; therefore, causality cannot be established. We do not know if some patients quit smoking before the cancer diagnosis. Nevertheless, this may not be a major drawback when investigating differences in smoking prevalence between patients that have ever been in contact with a physician of a particular specialty. Second, the BRFSS database is constructed by self-reported retrospective information that might be affected by recall and nonresponse bias. Nonetheless, the “guilt and shame” of patients who had tobacco-related cancer and continue to smoke might affect their report rates, underestimating the real prevalence of tobacco use in this population.(48) Third, we do not measure the number of packs/years, so we cannot determine whether participants were light or heavy smokers. However, for both questions regarding previous and current smoking status, the participant had the possibility to respond, “Don’t Know/Not Sure.” Fourth, even though we were able to do an analysis comparing different specialties, we could not examine differences among physicians’ characteristics. We believe certain factors, such as time since graduating from medical school, working in an academic hospital, and treating high-volume tobacco-related cancer patients, among others, might

be associated with different smoking cessation counseling rates. Further research focusing on physician education and practice on smoking cessation is warranted. Fifth, our study may have been affected by right-censoring due to the potential underrepresentation of severe cancer cases related to certain specialties, which could be linked to higher smoking rates and quantity. Nevertheless, this is data from the most extensive national survey available, providing a comprehensive overview of cancer survivors' current situation that can be used to identify key areas for improvement and opportunities for tobacco cessation counseling. Sixth, we could not adjust for all other potentially influential factors, such as comorbidities and household smoking, which might impact smoking continuation among cancer survivors. The lack of adjustment for these factors might limit our findings' generalizability. However, our study still provides valuable insights into the differences in smoking prevalence among cancer survivors by specialties and can help inform targeted interventions for tobacco cessation counseling. Seventh, the BRFSS database only contains data from participants living in the United States, which may limit our study's generalizability. Our findings may not apply to other countries with differing healthcare systems and smoking cessation policies. Additionally, the BRFSS only includes individuals with access to landlines or cell phones and may exclude some populations, such as homeless or institutionalized individuals.

In conclusion, this comprehensive examination found that one in four cancer survivors were current smokers and demonstrated a different rate of continued smoking among cancer survivors by specialties. These findings may aid societies in focusing on tobacco cessation counseling in guidelines and recommendations. It will also help physicians identify patients with a higher risk of continuing smoking after cancer diagnosis

and who might need personalized tobacco cessation counseling.

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TABLES & FIGURES

Table 1. Comparison of sociodemographic characteristics of lifetime smoking cancer survivors by medical specialty.
(n=19,855)

Cancer Survivors Characteristics	Non- Tobacco- Related- Cancers (15,370)		Gynecology (998)		Urology (957)		Colorectal Surgery (913)		Thoracic Surgery (875)		Malignant Hematology (259)		Head & Neck Surgery (252)		Surgical Oncology (231)		Chi2	DF
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE		
Age																		
< 40	3.7	0.3	30.8	2.6	2.3	1.2	4.8	2.1	3.6	1.5	11.5	3.1	10.5	5.5	13.0	5.0	99.0	5
40 - 49	6.2	0.3	24.3	2.5	4.7	1.2	6.9	1.6	3.7	0.9	7.4	3.1	6.2	3.1	10.4	3.5		
50 -59	15.3	0.5	18.3	1.8	12.9	1.6	18.0	2.2	16.1	2.8	19.4	4.3	19.9	5.0	16.3	4.5		
60 -69	28.8	0.6	13.3	1.4	31.9	2.3	26.4	2.2	26.8	2.3	27.7	4.2	27.7	4.4	31.6	4.7		
70 -79	30.6	0.6	6.8	1.0	27.6	2.0	26.5	2.5	35.0	2.7	27.6	5.8	24.4	4.3	21.4	3.7		
> 80	15.4	0.4	6.5	3.5	20.6	2.0	17.4	1.8	14.8	2.0	6.4	1.5	11.3	2.9	7.3	1.9		
Gender																		
Female	49.2	0.6	100	0	27.7	2.1	42.1	2.7	50.8	2.9	44.0	5.7	27.8	4.7	43.0	5.3	115.1	1
Male	50.8	0.6	-	-	72.3	2.1	57.9	2.7	49.2	2.9	56.0	5.7	72.2	4.7	57.0	5.3		
Marital Status																		
Single	38.2	0.6	56.5	2.9	38.2	2.3	42.3	2.8	53.5	2.9	35.8	4.9	41.5	5.4	42.8	5.4	28.3	1
Married or Partner	61.8	0.6	43.5	2.9	61.8	2.3	57.7	2.8	46.5	2.9	64.2	4.9	58.5	5.4	57.2	5.4		

Insurance																		
Yes	96.4	0.2	84.3	2.1	97.2	1.0	97.0	1.2	97.3	1.4	96.1	2.3	88.1	5.5	90.0	4.0	75.6	1
No	3.6	0.2	15.7	2.1	2.8	1.0	3.0	1.2	2.7	1.4	3.9	2.3	11.9	5.5	10.0	4.0		
Education Level																		
< High School Diploma	11.5	0.5	20.3	3.5	18.1	2.3	17.3	2.7	21.5	3.1	17.4	6.3	29.6	6.2	27.1	5.9	58.4	2
High School Diploma	64.6	0.6	71.4	3.4	65.9	2.4	69.3	2.7	66.5	3.0	58.9	5.7	52.5	5.8	60.3	5.6		
College Graduate	23.9	0.5	8.3	1.0	16.0	1.4	13.4	1.4	12.0	1.2	23.7	3.5	17.9	3.3	12.6	2.8		
Race																		
White	88.5	0.4	85.0	1.7	88.5	1.4	78.6	2.8	81.5	2.5	88.5	2.7	77.8	5.6	73.3	4.7	6.9	3
Black	5.8	0.3	4.6	1.0	6.7	1.2	12.8	2.6	10.0	2.0	4.6	2.0	12.6	5.1	16.9	3.9		
Hispanic	0.9	0.1	2.7	0.6	0.4	0.1	1.4	0.4	1.7	0.5	2.4	1.2	1.3	0.6	0.4	0.2		
Other	4.8	0.3	7.7	1.1	4.4	0.8	7.2	1.5	6.8	1.7	4.5	1.4	8.3	3.5	9.4	3.4		
Income (USD)																		
< 25,000	26.2	0.6	51.5	3.0	31.2	2.3	33.0	3.1	39.1	3.5	34.1	6.5	37.8	6.3	44.6	5.8	59.6	2
25,000 - 50,000	26.9	0.6	27.0	2.5	33.2	2.4	32.3	2.9	32.8	3.7	23.1	4.0	26.2	4.5	23.2	4.9		
> 50,000	46.9	0.7	21.5	2.0	35.6	2.3	34.7	2.7	28.1	2.8	42.8	5.6	36.0	5.7	32.2	5.1		

Note. Estimates reflect weighted data.

Table 2. Smoking Prevalence in Cancer Survivors by Specialty. (n=19,855)

Cancer Survivors by Specialty type	Distribution		Prevalence	
	%	SE	%	SE
- <u>Non-Tobacco-Related Cancers</u>	74.8	0.5	19.6	1.2
- <u>Tobacco-Related Cancers</u>				
Gynecology	6.9	0.4	51.8	0.9
Surgical Oncology	1.4	0.1	34.2	0.4
Urology	4.7	0.2	26.2	0.5
Head & Neck Surgery	1.4	0.1	25.8	0.4
Thoracic Surgery	4.6	0.2	25.8	0.6
Colorectal Surgery	4.6	0.2	21.8	0.5
Malignant-Hematology	1.2	0.1	19.3	0.2

Note. All estimates reflect weighted data.

Table 3. Modified Poisson Multivariate regression-based association of patient sociodemographic characteristics in continuing to smoke among cancer survivors with a smoking history. (n=19,855)

Factors Associated with Continuing to Smoke	Relative Risk	95% CI	p-value
Age (years)			
< 40	9.92	(7.46 - 13.19)	< 0.001
40 - 49	9.23	(6.97 - 12.23)	< 0.001
50 -59	7.26	(5.52 - 9.55)	< 0.001
60 -69	5.58	(4.25 - 7.32)	< 0.001
70 -79	3.22	(2.43 - 4.27)	< 0.001
> 80	(Ref)		
Gender			
Male	1.00	(0.92 - 1.08)	0.975
Female	(Ref)		
Marital Status			
Single	1.36	(1.26 - 1.48)	< 0.001
Married or Partner	(Ref)		
Insurance			
No	1.25	(1.13 -1.39)	< 0.001
Yes	(Ref)		
Education Level			
< High School Diploma	2.09	(1.80 - 2.42)	< 0.001
High School Diploma	1.67	(1.47 - 1.88)	< 0.001
College Graduate	(Ref)		
Race			
White	1.10	(0.96 - 1.27)	0.142
Black	1.27	(1.06 - 1.53)	0.009

Hispanic	1.47	(1.17 - 1.86)	0.001
<i>Other</i>	<i>(Ref)</i>		
Income (USD)			
< 25.000	1.46	(1.31 - 1.64)	< 0.001
25.000 - 50.000	1.30	(1.14 - 1.47)	< 0.001
> 50.000	<i>(Ref)</i>		

Note. Estimates reflect weighted data.

Table 4: Comparison of the likelihood of continuing to smoke between non-tobacco-related cancers and tobacco-related cancer, by cancer specialty, among lifetime smokers: a modified Poisson multivariate regression-based analysis disaggregated by non-elderly (<65) and elderly (>65) populations (n=19,855).

	Total Distribution		Less than 65 years old			65 years or older		
	%	RR	%	RR	95% CI	%	RR	95% CI
Non-Tobacco Related cancers (Reference)	74.8	1.00	29.5	1.00		45.3	1.00	
Malignant Hematology	1.3	0.85	0.7	0.93	(0.63 - 1.38)	0.6	0.83	(0.38 - 1.80)
Colorectal Surgery	4.7	1.00	2.2	0.90	(0.73 - 1.11)	2.5	1.13	(0.79 - 1.61)
Head & Neck Surgery	1.4	1.02	0.7	1.13	(0.79 - 1.62)	0.7	0.96	(0.56 - 1.65)
Thoracic Surgery	4.7	1.12	1.8	0.98	(0.78 - 1.22)	2.9	1.36	(1.07 - 1.73)
Surgical Oncology	1.5	1.21	0.8	1.22	(0.93 - 1.61)	0.7	1.65	(0.93 - 2.85)
	F ₅		0.8			2.0		
	Prob > F ₅ =		0.567			0.078		
Gynecology	6.9	1.25	5.7	1.41	(1.27 - 1.57)	1.2	1.22	(0.64 - 2.33)
Urology	4.7	1.30	1.7	1.26	(1.05 - 1.52)	3.0	1.19	(0.93 - 1.53)
	F ₂		23.2			1.1		
	Prob > F ₂ =		< 0.001			0.324		
	F ₇		7.5			1.6		
	Prob > F ₇ =		< 0.001			0.610		

Note. Estimates reflect weighted data.

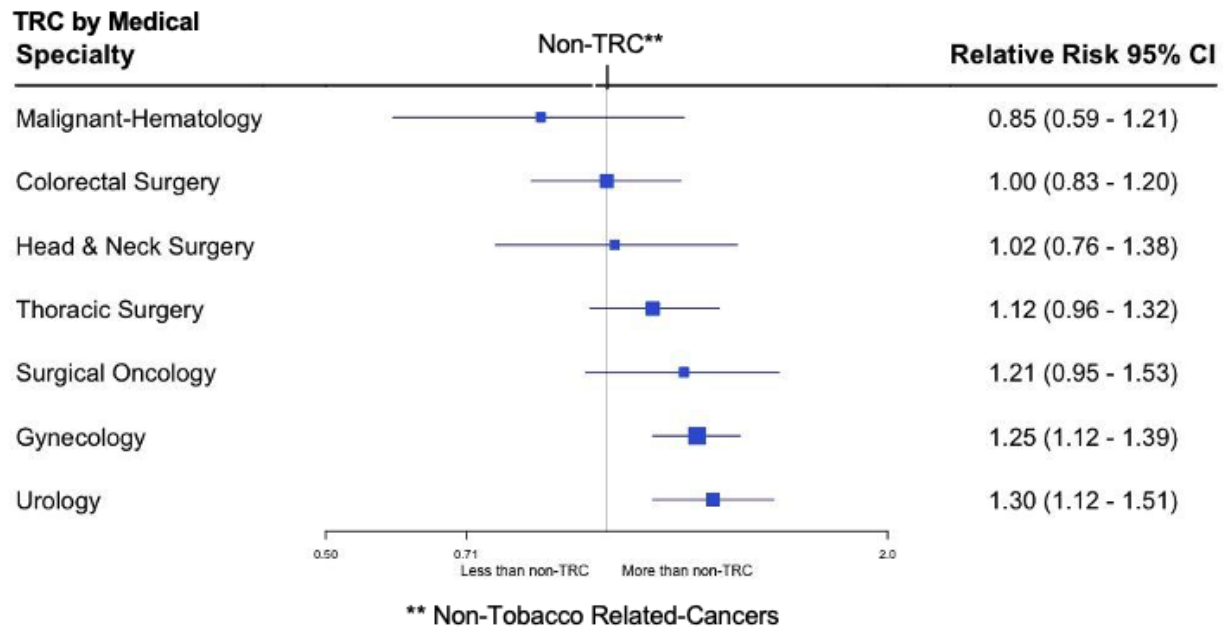
Table 5: Comparison of the likelihood of continuing to smoke between non-tobacco-related cancers and tobacco-related cancer, by cancer specialty, among lifetime smokers: a modified Poisson multivariate regression-based analysis disaggregated by education (< High-school diploma and High-school graduate or more) (n=19,855).

	Total Distribution		Less Than High-School			High-School graduate		
	%	RR	%	RR	95% CI	%	RR	95% CI
Non-Tobacco Related cancers (Reference)	74.8	1.00	8.6	1.00		66.2	1.00	
Malignant Hematology	1.3	0.85	0.2	0.54	(0.25 - 1.17)	1.1	0.96	(0.66 - 1.39)
Colorectal Surgery	4.7	1.00	0.9	0.77	(0.54 - 1.10)	3.8	1.11	(0.90 - 1.38)
Head & Neck Surgery	1.4	1.02	0.4	0.92	(0.64 - 1.34)	1.0	1.07	(0.66 - 1.72)
Thoracic Surgery	4.7	1.12	1.0	1.15	(0.89 - 1.49)	3.7	1.12	(0.93 - 1.36)
Surgical Oncology	1.5	1.21	0.5	0.82	(0.56 - 1.10)	1.0	1.49	(1.15 - 1.93)
	F ₅			1.44			2.23	
	Prob > F ₅ =			0.204			0.048	
Gynecology	6.9	1.25	1.4	1.01	(0.83 - 1.21)	5.5	1.36	(1.21 - 1.53)
Urology	4.7	1.30	0.8	1.2	(0.85 - 1.71)	3.9	1.35	(1.15 - 1.60)
	F ₂			0.56			18.5	
	Prob > F ₂ =			0.570			< 0.001	
	F ₇			1.23			6.19	
	Prob > F ₇ =			0.284			< 0.001	

Note. Estimates reflect weighted data.

FIGURE 1:

Comparison of the likelihood of continuing to smoke between non-tobacco-related cancers and tobacco-related cancer, by cancer specialty, among lifetime smokers. (n=19,855)



Note. Estimates reflect weighted data.

Supplementary Material

Supplementary Table A.

Smoking Status Assessment

SMQ100 Have you ever smoked more than 100 cigarettes in your life?		
1	Yes	Smoking History
2	No	Never Smokers
SMOKDAY2 Do you now smoke cigarettes every day, some days, or not at all?		
1	Every day	Current Smokers
2	Some days	Current Smokers
3	Not at all	Past Smokers

Note. Patients who report being “Never Smokers” were excluded from the analysis. Patients who had smoked at least 100 cigarettes in their lives were considered “Ever Smokers.” Those who ever smoked were further divided into current and former smokers according to the question SMOKDAY2.

Supplementary Table B.

Tobacco-Related Cancers, from National Cancer Institute (NIH)

Tobacco-Related Cancers

Lung
Larynx (voice box)
Mouth
Esophagus
Throat
Bladder
Kidney
Liver
Stomach
Pancreas
Colon
Rectum
Cervix
Acute Myeloid Leukemia

Note. Adapted from the National Cancer Institute (NIH) website. <https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco#:~:text=Tobacco%20use%20causes%20many%20types,well%20as%20acute%20myeloid%20leukemia>

Supplementary Table C.

Medical Specialty Variable

Specialty	Cancer Site
Colorectal Surgery	Colon, and Rectum
Gynecology	Cervical
Head & Neck Surgery	Oral, Pharyngeal, and Larynx
Malignant Hematology	Leukemia
Surgical Oncology	Liver, Pancreas, and Stomach
Thoracic Surgery	Lung, and Esophageal
Urology	Kidney, and Bladder

Note. Medical Specialties according to the site of the Tobacco-Related cancer

PAPER 2

Impact of Smoking Status on Health-Related Quality of Life (HRQoL) in Cancer Survivors

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Impact of smoking status on Health-related Quality of Life (HRQoL) in Cancer Survivors.

Unstructured Abstract

This cross-sectional study examined the relationship between smoking status and health-related quality of life (HRQoL) among cancer survivors. We used data from the Behavioral Risk Factor Surveillance System (BRFSS) for 2016-2020, encompassing 39,578 adults with a history of cancer. A multidimensional composite outcome was constructed to capture HRQoL by integrating the four dimensions of general health, mental health, physical health, and activity limitations. Considering the complex survey design, a logistic regression model was used, adjusting for various demographic, socioeconomic, and health-related factors. The findings revealed that 13.9% (5,507) of cancer survivors exhibited compromised HRQoL. Current smokers manifested a significantly diminished HRQoL compared to never smokers (odds ratio:1.65; 95% CI:1.40-1.93). Furthermore, former smokers demonstrated a poorer HRQoL than never smokers, albeit to a lesser extent than current smokers (odds ratio:1.22; 95% CI:1.09-1.38). These observations underscore the adverse consequences of smoking on HRQoL in cancer survivors, accentuating the imperative for healthcare professionals to prioritize smoking cessation and provide tailored interventions to encourage patients to abandon this harmful habit.

Key Words: Smoking, Health-Related Quality of Life, Cancer

INTRODUCTION

Cancer is a leading cause of death globally, with well-established physical and psychological ramifications for affected individuals.(1) The significance of evaluating health-related quality of life (HRQoL) in cancer research has been increasingly acknowledged. HRQoL is a multifaceted construct encompassing various aspects of an individual's well-being.(2)(3) Numerous studies have established a robust correlation between elevated HRQoL and improved survival outcomes for cancer patients.(4)(5)(6) Interestingly, many patients regard enhanced HRQoL as more desirable than prolonged survival duration.(7) However, despite its significance, HRQoL often declines among cancer survivors due to a variety of factors, including physical symptoms like pain, fatigue, nausea, psychological distress, and social isolation.(8)

Remarkably, smoking continues to be a common practice among cancer survivors and is linked to adverse treatment consequences, including reduced treatment effectiveness, heightened risk of recurrence, increased complications, toxicity, and lower survival rates.(9)(10)(11) A systematic review and meta-analysis revealed a 17.2% prevalence of current smoking among cancer survivors, a rate slightly higher than the 15.0% observed in the general population. This prevalence was elevated in survivors of specific cancers, such as lung cancer (34.6%) and head and neck cancer (27.2%).(12) Nevertheless, there remains a limited understanding of the specific factors influencing health-related quality of life (HRQoL) in cancer survivors, particularly regarding smoking status. Although prior studies have demonstrated an association between smoking and poor HRQoL in diverse populations, (13)(14) few have investigated the association

between smoking and HRQoL among cancer patients. Uncovering this relationship is essential to improve the overall HRQoL of these individuals. Consequently, this study aimed to examine the relationship between smoking status and HRQoL among cancer survivors.

MATERIAL & METHODS

Study Population:

This study utilized data from the Centers for Disease Control and Prevention's (CDC) Behavioral Risk Factor Surveillance System (BRFSS) for the years 2016-2020, a cross-sectional, state-based telephone survey of non-institutionalized individuals aged 18 years or older residing in the United States.(15) The questionnaire contained sections addressing demographics, healthcare access, and health-related behaviors. Cancer survivors were identified through self-reported diagnoses, and those without cancer were excluded from further analyses. The resulting cohort comprised 39,578 adult cancer survivors living in the U.S. with at least one self-reported HRQoL proxy (general health, mental health, physical health, and activity limitations). The included cancers were brain, bladder, bone, breast, colon, cervical, endometrial, esophageal, gastric, Hodgkin's lymphoma, leukemia, liver, lung, melanoma, non-Hodgkin's lymphoma, oral, ovarian, pharyngeal, pancreatic, prostate, rectal, renal, testicular, thyroid, and other skin cancers. Due to the small sample size (fewer than 100 cases), laryngeal, heart, and neuroblastomas were excluded from the study.

Exposure Variable:

The exposure variable was defined as smoking status. Participants were categorized into one of three distinct groups (never smokers, former smokers, or current smokers) based on their responses to two self-reported questions. (a) "Have you smoked at least 100 cigarettes in your entire life?" Respondents who answered "no" were classified as never smokers. Those who answered "yes" to this question were further divided based on their response to a second question: (b) "Do you now smoke cigarettes every day, some days, or not at all?" Participants who replied "not at all" were classified as former smokers, while those who answered "every day or some days" were designated as current smokers.

Outcome and Variables:

The primary composite outcome measure was HRQoL. Participants' self-reported HRQoL was assessed using the core section of the survey, which included questions on four domains: general health, mental health, physical health, and activity limitations (Supplementary Table 1). These validated questions have previously been used to provide reliable HRQoL estimates.⁽¹⁶⁾ The self-assessed general health status was dichotomized into "fair/poor" and "excellent/very good/good." The other three HRQoL variables were dichotomized based on their frequency of occurrence in the preceding 30 days, with those reporting fewer than 14 (good) and 14 days or more (poor) following the approach used in earlier studies on this topic.⁽¹⁷⁾⁽¹⁸⁾

The composite outcome was created by first evaluating the reliability of the measurement instrument using Cronbach's alpha coefficient.(19) An alpha score > 0.6 was considered indicative of a valid instrument for measuring HRQoL.(20) The resulting Cronbach's alpha was 0.658, suggesting that the composite outcome was appropriate for the HRQoL assessment. We calculated the row mean of the four dichotomized domains to create the composite outcome "HRQoL." Patients were divided into two groups to assess their HRQoL: those with an HRQoL score below 0.5 were classified as having "poor HRQoL" ($\text{HRQoL} < 0.5$), while those with a score of 0.5 or above were categorized as "good HRQoL" ($\text{HRQoL} \geq 0.5$). This cut-off value was chosen to better identify patients with poorer quality of life, following the approach of dichotomizing the composite outcome into better and poorer halves, as employed by other researchers. (20)

Exploratory variables included smoking status, demographic factors (age, gender, race/ethnicity, and marital status), socioeconomic factors (healthcare insurance, employment status, education level, and income), and comorbidities [body mass index (BMI), cardiovascular disease (myocardial infarction, stroke, or coronary heart disease), diabetes, asthma, and type of cancer]. All these variables were considered during the analysis to assess HRQoL outcomes among cancer survivors.

Statistical Analysis:

Descriptive statistics, comprising frequencies and percentages, were utilized to concisely present the categorical variables, and chi-square tests were employed to examine the differences between the two groups by evaluating the distribution of these variables. A complex survey design was considered by adjusting for stratification and

clustering at the primary sampling unit using sampling weights to compute nationwide representative frequencies and proportions. Multiple imputations were conducted using the predictive mean-matching method to address missing values, with $k = 5$ imputations.

A logistic regression model was used to calculate the odds of having poor HRQoL among cancer survivors based on their smoking status (never, former, and current smokers), adjusting for multiple potential confounders, including age, body mass index, gender, race, education, income, marital status, insurance, employment status, cardiovascular disease, diabetes, asthma, and type of cancer. The predictive probability of poor HRQoL for each smoking exposure group was calculated. Secondary analyses were conducted to further understand the association between smoking and HRQoL in the context of tobacco-related cancers and non-TRCs, as well as to evaluate potential interactions between HRQoL, age, and gender. Statistical significance was determined at $\alpha < 0.05$, with data analyzed using STATA/BE version 17.0.

Sensitivity Analysis:

Several sensitivity analyses were performed to ensure the robustness of the findings. First, an analysis that excluded missing data was conducted to evaluate the potential influence of incomplete information on the results. Subsequently, two alternative HRQoL dichotomizations were examined. The first dichotomization classified participants as having "good health" if they scored 1 in all self-reported dimensions, while those with a score lower than 1 were considered "poor HRQoL." The second dichotomization categorized participants with an HRQoL score of 0 as having "poor HRQoL" (Table 3).

RESULTS

Study Population:

The sample consisted of 2,193,981 participants surveyed between 2016 and 2020, of which 39,578 were cancer survivors. The weight of this sample was estimated to represent 13,836,840 cancer survivors. Regarding exposure status, 9.76% were current smokers, 36.64% were former smokers, and 53.60% had never smoked. Table 1 shows the differences between these groups according to their demographic and health-related characteristics. Compared to never smokers, current smokers were, on average younger, more likely to be single, have a lower education level, and have lower income. Furthermore, current smokers had a higher prevalence of comorbidities, such as CVD, diabetes, and asthma.

Additional details regarding the participant characteristics are presented in Table 1. Multiple imputations were used to address missing values, representing 16.80% for the income variable, 2.80% for diabetes, 1.80% for CVD, and less than 0.40% for employment status, asthma, insurance, education, gender, and marital status.

Smoking status and HRQoL

In our multivariate analysis, we found that smoking status was an independent predictor of HRQoL in cancer survivors. Our results indicated that being a current or former smoker was significantly associated with reduced HRQoL compared with never smokers. Furthermore, the relationship between smoking and HRQoL was even stronger among current smokers, who had 65% higher odds of having a poor HRQoL than never-

smokers OR of 1.65 (95% CI 1.40-1.93). Moreover, former smokers also exhibited a higher probability of poor HRQoL compared to never smokers, with an OR of 1.22 (95% CI 1.09-1.38). (Table 2) The predictive probabilities of poor HRQoL were 11,55% for never, 15.52%, and 21.43% for never smokers, former smokers, and current smokers, respectively. (Figure 1)

Impact of type of cancer: tobacco-related cancers (TRC) vs. non-tobacco-related cancers (non-TRC) in HRQoL.

We investigated the relationship between HRQoL and TRC and non-TRC groups. (Supplementary Table 2) We found that patients with a TRC had significantly greater odds of having a poor HRQoL than those with non-TRC, with an OR of 1.51 (95%CI:1.32-1.72; $p < 0.001$).

Interactions:

We evaluated the interactions between smoking status and tobacco-related cancers in predicting HRQoL. The results indicated no significant interaction between the two variables. Additionally, we examined potential interactions between gender and age; however, none were significant predictors of HRQoL.

Sensitivity Analysis.

In the sensitivity analysis, we excluded all the missing data and discovered that the outcomes were consistent with the initial analysis after multiple imputations. The odds of poor HRQoL were 80% higher for current smokers than never smokers, with an OR of

1.80 (95% CI 1.46-2.22) ($p < 0.001$). Former smokers exhibited a tendency toward lower HRQoL compared to never smokers, with an OR of 1.14 (95% CI 0.98-1.33), although this relationship was not statistically significant ($p = 0.082$). The results of our second sensitivity analysis involved dichotomizing HRQoL into two alternate categories. The first category was those with a score of 1 representing good health across all self-reported dimensions and those with a score lower than 1 (prevalence 25%), implying at least one impairment in any self-reported dimension, and was consistent with previous findings that both former and current smokers had higher odds of poorer HRQoL than non-smokers, as evidenced by the ORs being 1.21 (95% CI:1.10 -1.33) for former smokers and 1.73 (95% CI:1.51 -1.98) for current smokers ($p < 0.001$). We also explored another alternative classification, segregating participants with a score of 0 (prevalence 11.4%), which typified the poorest HRQoL, from those with a score higher than 0. Comparable results emerged as smoking was associated with a decline in HRQoL. This connection was evidenced by an OR of 1.22 (95% CI 1.07-1.39) for former smokers and an OR of 1.65 (95% CI 1.39-1.96) for current smokers ($p < 0.001$) (Table 3).

DISCUSSION:

This study found that smoking is strongly associated with poor HRQoL among cancer survivors. The prevalence of current smoking was approximately 9%, and that of former smokers was 36%, indicating that one-fourth of cancer survivors continue to smoke after a cancer diagnosis. The results demonstrated that smoking status is an independent predictor of HRQoL in cancer survivors. After adjusting for demographic,

socioeconomic, and health-related factors, we found that being a current smoker was associated with 65% higher odds of having a poor HRQoL, and being a former smoker was associated with a 22% increase in the odds of having a poor HRQoL compared to never smokers among cancer survivors.

As HRQoL is an essential aspect of cancer care and is closely linked with survival and treatment outcomes,(22)(23)(24)(25) comprehending the factors influencing HRQoL in cancer survivors is crucial to enhance their well-being and long-term health.(26)(27) Previous studies established an association between smoking and reduced HRQoL in the general population and patients with diverse medical conditions.(28)(29)(30)(31)(32) However, few studies have addressed the impact of smoking on cancer survivors' HRQoL. Our study adds to the literature by specifically examining the association between smoking and HRQoL in a large sample representative of the U.S. cancer survivor population.

Delving into the enigmatic nexus between smoking and HRQoL in patients with cancer is paramount to elucidating the precise mechanistic underpinnings. A conceivable rationale for the deleterious impact of smoking on HRQoL might be its association with concomitant health behaviors, encompassing physical inactivity, suboptimal sleep hygiene, and deficient dietary practices. These factors have been implicated in increased morbidity rates.(33) Emerging evidence suggests that smoking could attenuate the efficacy and tolerability of cancer therapies, conceivably owing to the propensity of cigarette smoke to provoke oxidative stress and modulate drug-metabolizing enzymes.(34)(35) A more comprehensive exploration of this intricate interplay is required to advance our understanding of these multifaceted associations.

Our study also found that current smokers had a significantly higher likelihood of experiencing poor HRQoL than never smokers, with a predictive probability of 21.43% versus 11.55%, respectively. Moreover, former smokers had poorer HRQoL than those who never smoked but were not as bad as current smokers. These results highlight the significance of providing smoking cessation education to cancer survivors and emphasize that quitting is never too late. Given the increased risk of cancer progression, recurrence, second primary malignancies, and inferior treatment outcomes, smoking cessation should be a top priority in managing cancer patients who smoke.(36)(37)

While several factors like comorbidities, education, and income level are non-modifiable, smoking is a modifiable risk factor that offers a tangible area for supportive care interventions.(38) Therefore, healthcare professionals must prioritize smoking cessation counseling. These results suggest that healthcare professionals should be aware of the potential impact of smoking on HRQoL to provide better care for cancer patients. Notably, tailored smoking cessation interventions are recommended for patients with cancer as part of their cancer care by various organizations such as the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), US Preventive Services Task Force (USPSTF), and Centers for Disease Control and Prevention (CDC).(39)(40)(41)(42) These organizations suggest that healthcare providers should assess all cancer patients for tobacco use and provide evidence-based interventions, including pharmacotherapy and behavioral counseling, to improve overall health outcomes and quality of life.

A thorough understanding of the association between smoking and its impact on HRQoL in cancer survivors and an evaluation of the socioeconomic burden associated

with smoking-related health costs and loss of productivity can provide a comprehensive understanding of the detrimental effect of smoking on society and the healthcare system. This valuable insight can be utilized to create effective strategies and health policies to lessen this considerable burden, consequently improving HRQoL for cancer survivors and potentially abating the economic strain on the healthcare system.(43)(44)

Our study has notable strengths, including its large sample size of 39,578 cancer survivors and its use of the world's largest continuously conducted health survey by the CDC.(45) Additionally, we employed a composite outcome to analyze the multidimensional concept of HRQoL and conducted a Cronbach's test to ensure instrument measure validity and reliability. However, as with any other study, our study has some limitations. First, the cross-sectional design precluded the ability to establish a causal relationship between smoking status and HRQoL. It is necessary to conduct longitudinal investigations to obtain a more profound comprehension of this association. Second, our reliance on self-reported data was subject to potential misclassification due to participants' memory recall. Third, we must recognize that while our logistic regression model accounts for numerous demographic, socioeconomic, and health-related aspects, HRQoL remains a nuanced and multifarious notion. In this context, unmeasured confounders may influence the outcome. Fourth, our investigation is susceptible to right censoring, as excluding the most severe cancer cases, possibly attributable to mortality, may introduce a bias to the findings. Fifth, it is essential to recognize the restricted generalizability of our findings, given that our investigation concentrated on a cohort of cancer survivors residing in the United States. Consequently, the outcomes may not be seamlessly applicable to cancer survivor populations in other countries. Sixth, our

research did not consider temporality, thus rendering it impossible to determine whether cancer survivors had ceased smoking before or after their diagnosis. Seventh, by dichotomizing HRQoL into "good" and "not good" categories, our study loses granularity, potentially obscuring more subtle variations in the relationship between smoking status and HRQoL. Nevertheless, we opted for this approach to facilitate a simplified comparison between those with better and worse HRQoL, which can be valuable in offering an easily interpretable and accessible analysis for a broader audience.

In the current era of personalized medicine, there is an urgent need to assimilate patient-reported outcomes, social determinants of health, quality of life, nutrition, and behavioral data into cancer research. With a multitude of diverse and competing treatment strategies available, it is imperative to tailor indications to reflect the personalized needs of patients. Integrating these non-clinical data into the treatment decision-making process is crucial to realizing this objective. In light of this, healthcare providers must diligently evaluate and track HRQoL at an early stage and longitudinally. Further research endeavors should encompass a broader spectrum of HRQoL factors, including pain and social and emotional support, to gain deeper insights into their influence on treatment outcomes. Other investigators have also sought to understand and address the HRQoL of patients in clinical practice. For example, the National Comprehensive Cancer Network (NCCN) advises incorporating distress management and HRQOL interventions into routine practice. It suggests using the "Distress Thermometer tool" to screen for distress at every medical encounter. This instrument evaluates various domains, including physical symptoms, emotional well-being, family or

interpersonal issues, spiritual concerns, financial distress, and functional limitations.(46)(47)

In conclusion, our study shows a robust association between smoking status and the negative impact on cancer survivors' HRQoL. The practical implications of our findings cannot be understated, as it calls for prompt interventions to help cancer survivors quit smoking and improve their HRQoL. As such, healthcare providers must acknowledge the detrimental effect of smoking on HRQoL and take proactive steps to facilitate smoking cessation in this population. Nonetheless, the intricate relationship between smoking status and HRQoL among cancer survivors warrants further inquiry and exploration, and the onus remains on the research community to unravel this intricated association.

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Impact of smoking status on Health-related Quality of Life (HRQoL) in Cancer Survivors.

Tables

Table 1. Baseline Characteristics of Cancer Survivors by Smoking Status (n=39,578)

Cancer Survivors Characteristics	Never Smokers (n=20,733)		Former Smokers (n=14,756)		Current Smokers (n=4,089)		p-value
	No.	Column %	No.	Column %	No.	Column %	
Age (years)							<0.001
< 40	497	2.4	225	1.5	324	7.9	
40 - 49	982	4.7	464	3.1	406	9.9	
50 -59	2904	14.0	1423	9.6	865	21.2	
60 -69	5958	28.7	3909	26.5	1385	33.9	
70 -79	6324	30.5	5538	37.5	907	22.2	
≥ 80	4068	19.6	3197	21.7	202	4.9	
Gender							<0.001
Female	13276	64.0	7491	50.8	2558	62.6	
Male	7454	36.0	7262	49.2	1530	37.4	
Race							<0.001
White	18616	89.8	13249	89.8	3384	82.8	
Black	778	3.8	518	3.5	237	5.8	
Hispanic	257	1.2	209	1.4	125	3.1	
Other†	1082	5.2	780	5.3	343	8.4	
Marital Status							<0.001
Single	8063	38.9	6242	42.3	2322	56.8	
Married or Partner	12669	61.1	8514	57.7	1767	43.2	
Education Level							<0.001
< High School Diploma	659	3.2	816	5.5	434	10.6	
High School Diploma	10085	48.7	8451	57.4	2866	70.2	
College Graduate	9963	48.1	5461	37.1	781	19.1	

Employment status						<0.001
Yes	7860	38.1	4074	27.7	1474	36.2
No	12793	61.9	10633	72.3	2603	63.8
Income (USD)						<0.001
< 25.000	3105	18.3	2667	21.5	1522	42.8
25.000 - 50.000	4325	25.5	3658	29.5	995	28.0
> 50.000	9527	56.2	6084	49.0	1037	29.2
Insurance						<0.001
Yes	20284	98.0	14469	98.2	3788	92.9
No	410	2.0	268	1.8	291	7.1
Body mass index						<0.001
Underweight (< 18.5)	274	1.3	178	1.2	175	4.3
Normal (≥ 18.5 < 25)	6126	29.5	4001	27.1	1433	35.0
Overweight (≥ 25 < 30)	7346	35.4	5426	36.8	1276	31.2
Obese (> 30)	6987	33.7	5151	34.9	1205	29.5
CVD†						<0.001
Yes	114	0.6	188	1.3	70	1.8
No	20310	99.4	14272	98.7	3917	98.2
Diabetes						<0.001
Yes	3569	17.7	2975	20.8	707	17.9
No	16613	82.3	11359	79.2	3252	82.1
Asthma						<0.001
Yes	2806	13.6	2091	14.2	796	19.6
No	17883	86.4	12628	85.8	3275	80.4

Note.

† Consists of Asian, Alaskan, and Native Americans

‡ Self-reported cardiovascular disease (CVD), including (myocardial infarction, stroke, or coronary heart disease)

Table 2. Association between Smoking Status and Poor HRQoL: Univariate and Multivariate Analysis

	Univariate			Multivariate*		
Smoking Status	OR	CI	p-value	OR	CI	p-value
Never Smoker	Ref			Ref		
Former Smoker	1.43	1.27 -1.60	< 0.001	1.22	1.09 -1.38	< 0.001
Current Smoker	2.54	2.19 - 2.94	< 0.001	1.65	1.40 -1.93	< 0.001

Note: *Multivariate analysis adjusted by: age, gender, race/ethnicity, marital status, healthcare insurance, employment status, education level, income, and comorbidities [body mass index (BMI) cardiovascular disease (myocardial infarction, stroke or coronary heart disease), diabetes, asthma, and type of cancer].

CI = confidence interval

OR = odds ratio

Poor HRQoL was defined as a composite outcome of HRQoL with a score below 0.5, based on a validated measurement instrument using self-assessed general health status, mental health, physical health, and activity limitation domains.

Estimates reflect weighted data.

Table 3. Multivariate analysis of the association between smoking status and health-related quality of life at different cut-off points.

	HRQoL = 0 / HRQoL > 0			HRQoL <0.5 / HRQoL ≥ 0.5			HRQoL < 1 / HRqoL = 1		
Prevalence “poor HRQoL”	11.4%			13.9%			25.3%		
	OR	CI	p-value	OR	CI	p-value	OR	CI	p-value
Smoking Status									
Never Smoker	Ref			Ref			Ref		
Former Smoker	1.22	1.07 -1.39	< 0.001	1.22	1.09 -1.38	< 0.001	1.21	1.10 - 1.33	< 0.001
Current Smoker	1.65	1.39 -1.96	< 0.001	1.65	1.40 -1.92	< 0.001	1.73	1.51 - 1.98	< 0.001

Note: Multivariate analysis of the association between smoking status and health-related quality of life (HRQoL) at different cut-off points. HRQoL cut-offs: HRQoL = 0 or HRQoL > 0, HRQoL < 0.5 or HRQoL ≥ 0.5, HRQoL < 1 or HRQoL = 1.

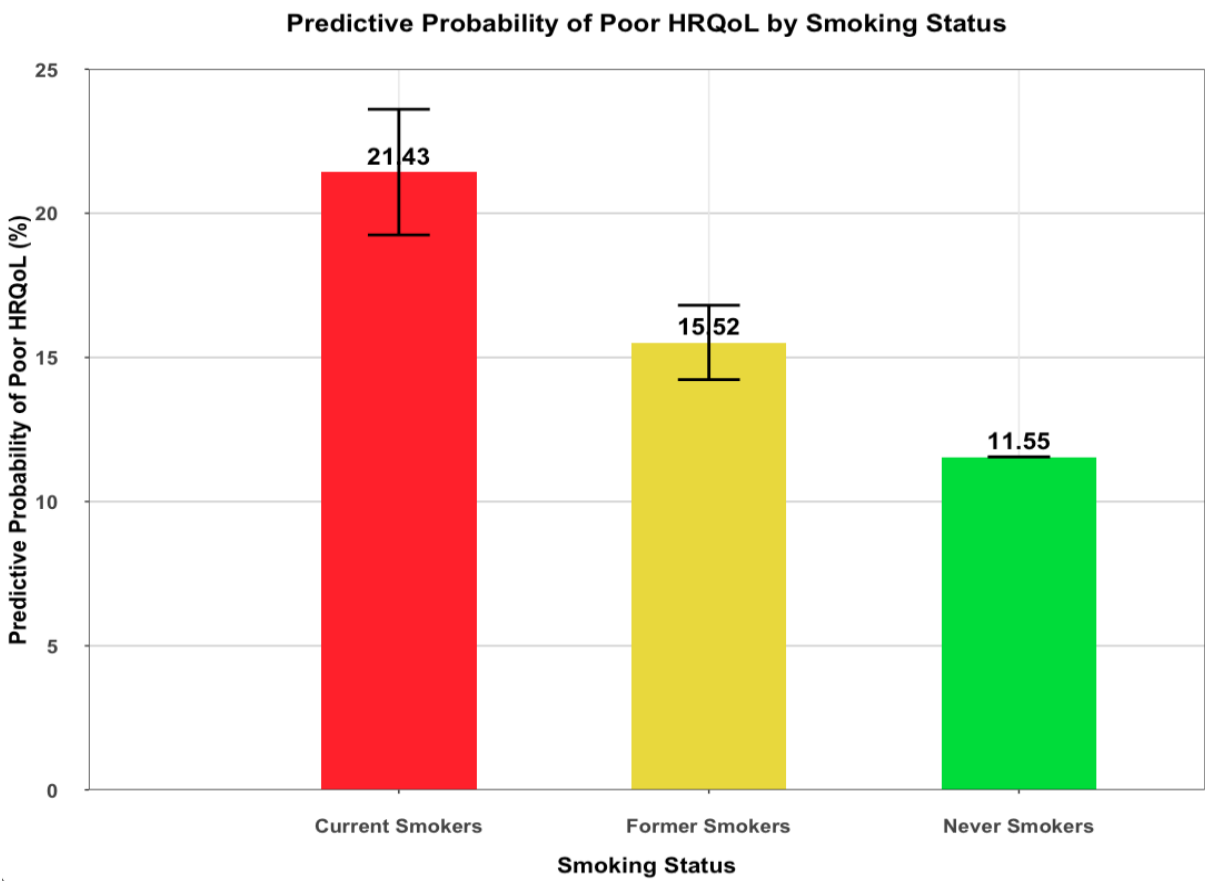
CI = confidence interval

OR = odds ratio

Estimates reflect weighted data.

FIGURE

Figure 1: Predictive Probability of Poor HRQoL by Smoking Status Among Cancer Survivors. (n=39,578)



Note: Predictive probability of Poor HRQoL among cancer survivors according to smoking status after adjusting for covariates (age, gender, race/ethnicity, marital status, healthcare insurance, employment status, education level, income, and comorbidities [body mass index (BMI) cardiovascular disease (myocardial infarction, stroke or coronary heart disease), diabetes, asthma, and type of cancer]).

HRQoL encompasses General Health, Mental Health, Physical Health, and Activity Limitations.

Estimates reflect weighted data.

Supplementary Materials

Supplementary Table 1. Health-Related Quality of Life (HRQoL) survey questions in the BRFSS.

HRQoL Outcome	BRFSS Question
General Health	“Would you say that in general your health is: excellent, very good, good, fair, poor?”
Mental Health	“Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?”
Physical Health	“Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?”
Activity Limitation	“During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as selfcare, work, or recreation?”

Supplementary Table 2. Tobacco-Related Cancers and Non-Tobacco-Related-Cancers

Tobacco-Related Cancers†	Non-Tobacco Related-Cancers
Lung	Breast
Laryngeal*	Endometrial
Mouth	Ovarian
Esophagus	Thyroid
Throat	Hodgkin Lymphoma
Bladder	Non-Hodking Lymphoma
Kidney	Prostate
Liver	Testicular
Stomach	Melanoma
Pancreas	Other skin Cancer
Colon	Bone
Rectum	Brain
Cervix	
Acute Myeloid Leukemia	

Note.

† TRC according to the National Cancer Institute (NIH) Adapted from the Nation Cancer Institute (NIH) website. <https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco#:~:text=Tobacco%20use%20causes%20many%20types,well%20as%20acute%20myeloid%20leukemia>

*Laryngeal cancer (heart and neuroblastoma) were excluded due to the small sample size.

SUMMARY OF PAPERS

In our *first paper*, we executed a comprehensive, nationally representative investigation to examine the association between the smoking behaviors of cancer survivors and the medical specialty engaged in their care. Our findings revealed that 26.3% of oncology patients with a previous smoking history continued their habit following their cancer diagnosis. The inquiry centered on tobacco-related cancers, which are those that necessitate additional efforts from healthcare practitioners and patients to attain tobacco cessation. We discerned that the persistence of smoking fluctuated among patients contingent upon the medical specialties administering their treatment. Notably, individuals with urological and gynecological cancers exhibited a significantly augmented rate of sustained smoking post-cancer diagnosis, potentially attributable to insufficient tobacco cessation counseling offered by their managing physicians. Conversely, patients diagnosed with malignant hematology manifested the highest tobacco cessation rate across the analyzed specialties. The insights derived from this investigation accentuate the significance of all-encompassing tobacco cessation counseling, particularly for high-risk cancer cohorts. Furthermore, the results call for reflection from specialists regarding the effectiveness of current tobacco cessation approaches and the need to adapt strategies to improve patient outcomes.

In our *second paper*, we explored the complex interplay between smoking habits and Health-related Quality of Life (HRQoL) within an extensive cohort of 39,587 cancer survivors. We analyzed HRQoL as a multidimensional composite outcome comprising four critical dimensions: General Health, Mental Health, Physical Health, and Activity

Limitation. After adjusting for various demographic, socioeconomic components, and health-related variables, our analysis disclosed a significant escalation in the risk of poor HRQoL for both current and former smokers relative to their non-smoking peers. Intriguingly, this association manifested more prominently in active smokers than in those who had quit. Present smokers had a 65% increase in the likelihood of poor HRQoL, while former smokers exhibited a 22% increase in the odds of poor HRQoL compared to never smokers. These revelations bear substantial implications for cancer patients, underscoring the urgency of integrating smoking cessation interventions into treatment regimens to bolster patients' most coveted outcome—their quality of life.

DISCUSSION AND FUTURE DIRECTIONS

Our investigation revealed disparate rates of smoking persistence among cancer survivors, contingent upon the medical specialty implicated in their oncological care. Initial examination revealed that survivors of tobacco-related urological and gynecological cancers exhibited the most pronounced rates of continued smoking across all analyzed medical specialties. Furthermore, our subsequent manuscript identified a substantial correlation between smoking and poor health-related quality of life (HRQoL) in oncology patients.

Our investigation's notable strengths encompass the utilization of the Behavioral Risk Factor Surveillance System (BRFSS) dataset, an assemblage of data from each state within the United States, representing the most comprehensive health survey on a global scale. This methodology enabled the application of sampling weights, thereby ensuring a nationally representative examination of paramount importance. By amalgamating data accumulated over the preceding half-decade, our rigorous analysis elucidates the intricate nexus between smoking propensities and health-related quality of life among cancer patients domiciled in the United States. To substantiate the robustness and validity of our findings, we meticulously conducted an array of sensitivity analyses, thereby augmenting the credibility and dependability of our results.

Our first study provides a novel and unique perspective by incorporating the medical specialty factor as a predictor of smoking persistence alongside previously identified patient-related factors. To the best of our knowledge, our secondary manuscript

represents the most extensive cohort, including 25 distinct cancers, that analyzes the impact of smoking on HRQoL in cancer survivors.

Nonetheless, our studies have several limitations. Primarily, the inherent constraints of their cross-sectional design delimit our conclusions. Although we identified correlations, we were unable to ascertain the causality. Second, the BRFSS database depends on telephonic surveys and self-reported data, potentially introducing recall and response bias. Third, we did not quantify the number of packs per year, and both smoking persistence and HRQoL may exhibit dose-dependent effects. Fourth, the absence of demographic data on medical specialists restricted us from correlating smoking rates with the medical specialty type without further dissection of distinct physician factors.

Future investigations should explore the influence of physician-related factors on the perpetuation of smoking habits among oncology patients. In addition, future research must probe the potential mechanisms through which smoking deleteriously impacts HRQoL in patients with cancer. Our findings provide pivotal insights that must be translated into innovative policies and guidelines. The focus should be directed toward raising patient education to avoid the pervasive issue of smoking continuation after a cancer diagnosis. Physicians across all specialties must undergo comprehensive training in tobacco cessation counseling. This instruction should be formally integrated into medical school curricula and residency programs, comprising a structured syllabus on the importance of smoking cessation and practical techniques for its implementation. By embracing such measures, we can cultivate a better-equipped healthcare environment to overcome the challenges of smoking persistence in cancer patients and promote enhanced health-related quality of life for this susceptible population.