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Original Article

World J Oncol. 2022;13(1):20-26

Cancer Prevalence in E-Cigarette Users: A Retrospective Cross-Sectional NHANES Study

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Abstract

Background: It is well known that traditional smoking causes various types of cancer, leading to the current decline in traditional smoking among US adults from 20.9% in 2005 to 14.0% in 2019. Electronic cigarettes (e-cigarettes) are commonly marketed as a safe alternative and gaining popularity especially among never-smokers and adolescents. However, there is limited evidence of effects of e-cigarette on cancer. Hence, we aim to find the prevalence and association of e-cigarette and traditional smoking among cancer respondents.

Methods: We conducted a retrospective cross-sectional study using the NHANES database from 2015 to 2018. We assessed history of cancer (MCQ220), type of cancers (MCQ230a), and smoking status (e-cigarette: SMQ900 or SMQ905 and traditional smoking: SMQ020) using questionnaires. We performed multivariable logistic regression models to find the association of e-cigarette use, traditional smoking, and no smoking with cancer after adjusting for confounding variables.

Results: A total of 154,856 participants were included, of whom 5% were e-cigarette users, 31.4% were traditional smokers, and 63.6% were nonsmokers. There is a higher prevalence of e-cigarette use among younger participants, females (49 vs. 38) in comparison to traditional smokers (P < 0.0001). The e-cigarette users have lower prevalence of cancer compared to traditional smoking (2.3% vs. 16.8%; P < 0.0001), but they were diagnosed with cancer at a younger age. Among cancer subtypes, cervical cancer (22 vs. 2.6), leukemia (8.5 vs. 1.1), skin cancer (non-melanoma) (15.6 vs. 12.3), skin (other) (28 vs. 10) and thyroid (10.6 vs. 2.4) had higher prevalence of e-cigarette use compared to traditional smokers (P < 0.0001). Our regression analysis showed that e-cigarette users have 2.2 times higher risk of having cancer compared to non-smokers (odds ratio (OR): 2.2; 95% confidence interval (CI): 2.2 - 2.3; P < 0.0001). Similarly, traditional smokers have 1.96 higher odds of having cancer compared to non-smokers (OR: 1.96; 95% CI: 1.96 - 1.97; P < 0.0001).

Conclusion: In our study, e-cigarette users had an early age of cancer onset and higher risk of cancer. Hence, this is stepping stone for future research to evaluate the safety and effects of e-cigarettes in patients with cancer.

Keywords: E-cigarettes; Electronic nicotine delivery system; Smoking; Cancer; Traditional smoking

Manuscript submitted December 4, 2021, accepted January 19, 2022
Published online February 8, 2022

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doi: https://doi.org/10.14740/wjon1438

Introduction

Traditional smoking is the leading cause of preventable morbidity and mortality in the USA and worldwide. According to CDC 2019 estimates, nearly 40 million US adults aged 18 years or older are smokers and smoking is responsible for more than 480,000 deaths per year, including more than 41,000 deaths resulting from secondhand smoke exposure [1]. Approximately 16 million live with debilitating conditions due to smoking, including cancer, heart disease, stroke, lung diseases, and diabetes [1]. Every year, the US government spends nearly $170 billion as a direct cost on medical care, and indirectly around

$156 billion is lost due to premature death and exposure to secondhand smoking [1]. According to 2020 estimates of the Surveillance, Epidemiology, and End Results Program (SEER) database, there will be 1.8 million new cancer diagnoses and 606,520 cancer deaths in the USA [2]. Few adults might be using electronic cigarettes (e-cigarettes) as part of smoking cessation. Dual use of both e-cigarettes and traditional cigarettes is recently becoming common, and there is the continued use of e-cigarettes by many former smokers.

Various studies show that smoking causes cancer of the lung, oral cavity, pharynx, larynx, esophagus, pancreas, urinary bladder, and renal pelvis [3]. In addition, tobacco smoking-related mortality is due to atherosclerotic cardiovascular disease (CVD), lung cancer, chronic obstructive pulmonary disease (COPD), and smoking-related cancers almost anywhere in the body [1]. A study by Salloum et al, with 32,244 adult participants, reported 12.7% were current smokers, 32.9% were former smokers in cancer survivors compared with 18.5% and 19.0%, respectively, in non-cancer adults [4]. Thus, for many years, there has been robust literature that cancers can be attributed to smoking [1]. Since the information about the harmful effects of tobacco smoking is spreading, there is no surprise that the use of e-cigarette is increasing among the population as a safe alternative to the source of nicotine.

E-cigarettes are battery-operated devices that heat a liquid-containing nicotine, among other harmful and potentially harmful substances, producing an aerosol that the user inhales [5]. According to the CDC, e-cigarettes are sometimes called "e-cigs", "vapes", "e-hookahs", "vape pens", and "electronic nicotine delivery system (ENDS)". Some e-cigarettes look like regular cigarettes, cigars, or pipes. However, some look like USB flash drives, pens, and other everyday items [6]. Since their introduction in the market, they are gaining popularity among never-smokers and adolescents and smokers who want to reduce the health risks of smoking or would like to quit smoking, as they are commonly marketed as a safe alternative to traditional tobacco use [7]. This fact is documented by the National Youth Tobacco Survey (2011 - 2018) of US middle and high school students reporting the increased use of e-cigarettes in this group from 1.5% in 2011 to 20.8% in 2018 [7]. The prevalence of e-cigarettes in US adolescents ranges from less than 1% to 10% [8]. However, cancer-related effects caused by activation of the sympathoadrenal system, which is procured by the inhalation of nicotine, the main component of the e-cigarettes, are entirely overlooked.

To date, limited studies are evaluating the long-term health effects of e-cigarettes in humans [9, 10]. Current e-cigarette use was reported in 3.8% of cancer survivors compared to 5.7% of non-cancer adults. Less than 5% of cancer survivors used all other forms of tobacco [4]. E-cigarette and vape product sales are expected to reach more than $40 billion by 2023 [11]. Hence, we aim to evaluate the prevalence of e-cigarette and their association with cancer.

Materials and Methods

The National Health and Nutrition Examination Survey (NHANES) is a population-based, cross-sectional survey designed to assess the health of children and adults in the USA, administered by the CDC. NHANES data are released in 2-year cycles and utilize a multistage probability sampling design to create a nationally representative sample for each cycle. The sampling design and protocol of NHANES is reviewed by the US Department of Health and Human Services and approved by the National Center for Health Statistics Research ethics Review Board on a yearly basis. The NHANES surveys include demographic, socioeconomic, dietary, laboratory, and health-related questions. The examination component consists of medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained medical personnel. As in past health examination surveys, data will be collected on the prevalence of chronic conditions in the population. Estimates for previously undiagnosed conditions, as well as those known to and reported by respondents, are produced through the survey. Such information is a particular strength of the NHANES program.

The data have been taken from NHANES database sponsored by the CDC and is free publicly available database, so informed consent or IRB approval was not needed for the study. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

We conducted a retrospective cross-sectional study using the NHANES database from 2015 to 2018. The NHANES datasets were downloaded and combined using SAS software (version 9.4). Weighting procedures for 4 years of NHANES data were employed. We included participants aged ≥ 18 years, diagnosed with cancer and had complete data on smoking/cigarette and e-cigarette use in the questionnaires. Sociodemographic variables such as age, gender, race, annual household income, comorbid conditions, serum cotinine and hydroxycotinine were included. We have excluded participants with dual smoking use that is both e-cigarette and traditional smoking. Participants with missing information on age, gender or smoking were excluded.

Our primary aim of the study is to find the prevalence of e-cigarette and traditional smoking in respondents with cancer. Our secondary aim is to evaluate the association of smoking (traditional smoking and e-cigarette) with cancer while adjusting for the confounding variables.

Cancer

To assess the cancer diagnosis of participants, the following question was included in MCQ220: "Have you ever been told that you had cancer or malignancy"?

Smoking

The current smoking status of the participants was assessed by the following questions: SMQ020: "Smoked at least 100 cigarettes in life", SMQ040: "Do you now smoke cigarettes?"

E-cigarette

The e-cigarette use was assessed by the question: SMQ900:

"Have {you/SP} EVER used an e-cigarette?

Sociodemographic characteristics in the study analysis were age, sex, race and annual household income at the time of survey. These variables were obtained by asking the participants: Are you male or female? And, how old are you? Race/ethnicity was classified as Mexican American, Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, or others. The comorbidities like hypertension, high cholesterol, diabetes mellitus, stroke, coronary heart disease, liver disease, and anemia were assessed from those who answered yes to the questions: Have you EVER been told by a doctor or other health professional that you had… 1) Hypertension, also called high blood pressure +2 times, 2) High cholesterol, or 3) Diabetes or sugar diabetes? 4) Stroke, 5) Had coronary heart disease? 6) Had any kind of liver condition? 7) Taking treatment for anemia/past 3 months respectively. People who refused, were not asked, or did not know were coded as missing.

Statistical analysis

SAS software (version 9.4) was used for analyzing the data for the study. Univariate analysis to find association of smoking and e-cigarette with cancer and other sociodemographic variables using Chi-square for categorical variables and *t*-test/Wilcoxon for continuous variables was performed. Multivariable logistic regression models were conducted to find the association of e-cigarette use, traditional smoking, and no smoking with cancer after adjusting for confounding variables. The P value < 0.05 is considered to be statistically significant.

Results

In our study, we included 154,856 participants from 2015 to 2018. Out of these, 7,756 (5%) were e-cigarette users, 48,625 (31.4%) were traditional smokers and 98,475 (63.6%) were non-smokers. We found that e-cigarette users were younger (median age 25 years) compared to traditional smokers (median age 62 years). There was a higher prevalence of e-cigarette use among females compared to traditional smokers (49 vs. 38; P < 0.0001). Whites have lower utilization of e-cigarette (28%) compared to traditional smokers (42%) (P < 0.0001). On the other hand, Mexican American (20% vs. 13%) and Asian (12% vs. 7%) have higher frequency of e-cigarette use compared to traditional smokers (P < 0.0001). Respondents with depression (28% vs. 23%), alcohol use disorder (69 vs. 46%) and marijuana or hashish use (79% vs. 70.3%) have higher frequency of e-cigarette use compared to traditional smokers (P < 0.0001), respectively (Table 1).

As described in Table 2, respondents with cancer have a lower prevalence of e-cigarette compared to traditional smoking (2.3% vs. 16.8%; P < 0.0001). We found that e-cigarette users were diagnosed with cancer at a younger age (median age: 45) than traditional smokers (median age: 63). Among cancer subtypes cervical cancer (22 vs. 2.6), leukemia (8.5 vs. 1.1), skin cancer (non-melanoma) (15.6 vs. 12.3), skin (other) (28 vs. 10) and thyroid (10.6 vs. 2.4) had higher prevalence of e-cigarette use compared to traditional smokers (P < 0.0001).

Our multivariate logistic regression analysis showed that e-cigarette users have 2.2 times higher risk of having cancer compared to non-smokers (odds ratio (OR): 2.2; 95% confidence interval (CI): 2.2 - 2.3; P < 0.0001). Similarly traditional smokers have 1.96 higher odds of having cancer compared to non-smokers (OR: 1.96; 95% CI: 1.96 - 1.97; P < 0.0001) (Table 3).

Discussion

In our study, we found that the prevalence of e-cigarette users was 5%, 31.4% for traditional smokers, and 63.6% for non-smokers. Our study found that e-cigarette smokers had 2.2 times higher risk and traditional smokers had 1.96 times higher risk of having cancer compared to non-smokers. Interestingly, cancer respondents had a lower prevalence of e-cigarette use than traditional smoking (2.3% vs. 16.8%), and e-cigarette users were diagnosed with cancer at a younger age than respondents with traditional smoking (median age of 45 years vs. 63 years).

Recently, there has been an exponential increase in the use of e-cigarettes due to their widespread promotion as safer alternatives to traditional smoking. This dangerous threat is a public health risk. A study by Canistro et al demonstrated that e-cigarette vapor has cancer-initiating effects and co-mutagenic effects in rat lung cancer model [12]. In 2018, Staudt et al, showed that even short-term use of e-cigarettes induces tumor and metastasis promoting factors related to lung cancer in small airway epithelium [13]. Stephens et al showed that vaporized nicotine emissions from e-cigarettes contain carcinogens generally in lower concentrations with cancer potencies < 1% that of tobacco smoke [14]. Mean lifetime cancer risks decline from traditional smoking to e-cigarettes. Although smoking in any form is never safe, e-cigarettes can be recommended by clinicians as an alternative to traditional smoking in populations with a history of cancer who would otherwise continue to smoke or those who want to start smoking at all cost. This could dramatically decrease the risk of serious disease in nicotine users and other high-risk groups [15].

Tobacco smoke has multiple components which are carcinogenic. Polycyclic aromatic hydrocarbons (PAHs), nicotine and nicotine-derived nitrosamine ketone (NNK) play major roles in the pathogenesis of a wide range of cancers. These carcinogens can cause point mutations, deletions, translocations, and gene recombination and alter the expression of oncogenes, DNA repair, tumor suppressors, and apoptosis-related genes through several mechanisms [16]. Although the concentration of aerosol delivered by e-cigarettes is lower than traditional smoking, this does not render it harmless [17]. The particles in the aerosol are deposited in the alveoli, which generate free radicals that cause DNA damage [17]. Aerosols delivered by e-cigarette mainly contain tobacco-specific nitrosamines (TSNAs), N-nitrosonornicotine (NNN), glycidol, and polycyclic aromatic hydrocarbon (PAHS), which are highly carcinogenic [17]. The recent outbreak of e-cigarette vaping-associated lung injury (EVALI) in the USA suggests caution: EVALI is primarily attributable to vitamin E acetate in cannabis oils distributed through illicit channels [18]. A study has shown that the use

Table 1. Epidemiological Characteristics of Cancer Respondents

Variable	E-cigarette, N = 7,756 (5.01%)	Traditional smoking, N = 48,625 (31.4%)	No smoking, N = 98,475 (63.6%)	Total, N = 154,856 (100%)	P value
Age (median (Q1-Q3))	25 (20 - 31)	62 (50 - 71)	50 (34 - 64)		< 0.0001
Gender (%)					< 0.0001
Male	51	62	38	46	
Female	49	38	62	54	
Race (%)					< 0.0001
White	28	42	30	34	
African American	23	21	20	20	
Mexican American	20	13	17	16	
Other Hispanic	11	12	12	12	
Asian	12	7	18	14	
Other race	7	5	3	4	
Annual household income					< 0.0001
$0 - 24,999	27	32	24	27	
$25,000 - 64,999	32.2	38.6	34.5	35.7	
$65,000 - 99,999	17	14	17	16	
$100,000 and over	24	15.6	24.3	21.5	
Comorbidities					
Hypertension	68	80	80.3	80	< 0.0001
Diabetes mellitus	3.3	22.1	14.0	16.0	< 0.0001
Hypercholesterolemia	10.6	46	35	37	< 0.0001
Coronary heart disease	1.5	8.5	3.3	5.0	< 0.0001
Stroke	1.1	6.7	3.2	4.3	< 0.0001
Marijuana or Hashish	7	70.3	32.3	44.8	< 0.0001
Cocaine/heroin/methamphetamine	12.8	27.1	5.1	11.8	< 0.0001
Injectable illegal drug	1.1	4.2	0.4	1.5	< 0.0001
Alcohol use disorder	69.5	46.3	38.6	43.3	< 0.0001
Anemia	4.0	4.4	4.6	4.5	0.0012
Depression	28.1	23.5	20	22	< 0.0001
Liver disease	2.5	7.2	4.1	5.1	< 0.0001
Serum cotinine (ng/mL), mean ± SE	20.8 ± 0.9	67.2 ± 0.6	6.8 ± 0.17		< 0.0001
Serum hydroxy cotinine (ng/mL), mean ± SE	8.1 ± 0.43	27.4 ± 0.30	3.2 ± 0.1		< 0.0001

SE: standard error.

of e-cigarettes induces DNA-strand breaks in the human epithelial cell line HaCaT independent of nicotine, while there is evidence that e-cigarette vapor exaggerates the extent of nicotine-induced DNA damage [19]. In 2018, Schaal and colleagues found that e-cigarettes can enhance tumor-promoting properties similar to nicotine by expressing Sox2 and mesenchymal markers, increasing migration in non-small cell lung cancer [20]. Per Gronkiewicz et al, by switching from traditional cigarettes to e-cigarettes, nicotine exposure is unchanged. However, e-cigarettes have fewer carcinogens than conventional cigarettes. To date, the long-term safety of e-cigarettes is unknown [21].

We identified that respondents with e-cigarette use were diagnosed with cancer at a younger age than respondents with traditional smoking. Similar to our study, Kalkhoran et al reported current e-cigarette use is more likely in women cancer respondents compared to men [22]. E-cigarettes are used as a strategy to quit smoking in most cancer respondents. E-cigarette users were younger compared to dual and traditional smokers per our study. Per Sanford et al's study using NHIS survey database, it was found that younger age groups less than 50 years have higher odds of e-cigarette use compared to older [22]. No long-term population-based studies of e-cig-

Table 2. Univariate Analysis of Association of Smoking With Cancer

Variable	E-cigarette, N = 7,756 (5.01%)	Traditional smoking, N = 48,625 (31.4%)	No smoking, N = 98,475 (63.59%)	Total, N = 154,856 (100%)	P value
Cancer (%)	2.32	16.8	9.5	11.6	< 0.0001
Age at first cancer (median (Q1-Q3))	45 (40 - 62)	63 (52 - 72)	59 (47 - 69)	NA	< 0.0001
Types of cancer (prevalence %)					
Lung	0	3.0	0.6	1.7	< 0.0001
Bladder	0	4.8	2.2	3.4	< 0.0001
Breast	12.1	12.0	20.4	16.4	< 0.0001
Leukemia	8.5	1.1	1.7	1.5	< 0.0001
Cervical	22	2.6	2.6	2.8	< 0.0001
Colon	0	5.2	6.9	6.1	< 0.0001
Melanoma	3.5	7.5	6.0	6.7	< 0.0001
Skin (non-melanoma)	15.6	12.3	15.9	14.2	< 0.0001
Skin (other)	27.7	9.5	6.2	7.9	< 0.0001
Prostate	0	20.1	15.2	17.7	< 0.0001
Thyroid	10.6	2.4	2.6	2.6	< 0.0001
Uterus	0	2.6	4.8	3.7	< 0.0001
Lymphoma/Hodgkin's disease	0	1.7	2	1.9	< 0.0001
Kidney	0	2.0	2.0	2.0	< 0.0001

arette use and related health effects have been published, so it is unclear if switching to e-cigarettes from cigarettes improves morbidity and mortality. Additionally, a portion of the adult population who have never smoked cigarettes reported trying e-cigarettes (8.7% in 2013) [22] and the potential for negative health effects from exposure to nicotine or other chemicals in e-cigarettes among non-smokers is concerning.

Limitations and strength of the study

NHANES is the self-reported cross-sectional survey and study, so this survey is likely to get affected by recall bias and causal or temporal association could not be established. Tumor grading, severity and precise cancer details are missing. NHANES could not geographically represent the entire US population due to the cluster data collection methods. There is no information on onset of use, average frequency or duration hours per day of e-cigarette use or uniform unit like pack per day to correlate severity with disease. Despite the limitations, to our knowledge, this is the first large population-based study to find potential association between e-cigarette use and cancer in humans.

Conclusion

Our study found e-cigarette users had an early age of cancer onset as well as higher odds of having cancer compared to non-smokers. Females had higher prevalence of e-cigarette use and cervical, thyroid and skin cancers were more prevalent amongst the e-cigarette users. More prospective studies should be planned to mitigate the risk. The long-term effect of e-cigarettes is not known yet, since they are relatively new compared to traditional cigarette smoking. Furthermore, due to higher prevalence of certain types of cancers in e-cigarette use and unknown consequences of e-cigarette use, more guidelines are needed regarding the use of e-cigarettes and their association with cancer. E-cigarette should not be considered as a safe alternative to dual or traditional smoking without stronger clinical evidence on its safety.

Acknowledgments

None to declare.

Financial Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

Authors declare no conflict of interest.

Informed Consent

Not applicable.

Table 3. Adjusted Multivariate Analysis of Association Between Cancer and Smoking

Variable	Cancer (OR (95% CI); P value)
No smoking	Reference
E-cigarette	2.2 (2.2 - 2.3); P < 0.0001
Traditional smoking	1.96 (1.96 - 1.97); P < 0.001
Gender (%)	
Male	Reference
Female	1.67 (1.675 - 1.678); P < 0.001
Race (%)	
Mexican American	Reference
White	2.56 (2.56 - 2.57); P < 0.001
African American	1.51 (1.50 - 1.51); P < 0.001
Other Hispanic	1.92 (1.91 - 1.92); P < 0.001
Asian	1.81 (1.80 - 1.81); P < 0.001
Other race	0.48 (0.47 - 0.48); P < 0.001
Annual household income	
$0 - 24,999	Reference
$25,000 - 64,999	2.25 (2.24 - 2.25); P < 0.001
$65,000 - 99,999	0.67 (0.66 - 0.67); P < 0.001
$100,000 and over	1.72 (1.71 - 1.72); P < 0.001
Comorbidities	
Hypertension	1.44 (1.43 - 1.44); P < 0.001
Hypercholesterolemia	1.11 (1.11 - 1.12); P < 0.001
Diabetes mellitus	1.47 (1.43 - 1.44); P < 0.001
Anemia	3.74 (3.73 - 3.74); P < 0.001
Marijuana or Hashish	1.25 (1.24 - 1.25); P < 0.001
Cocaine/heroin/methamphetamine	0.46 (0.45 - 0.46); P < 0.001
Injectable illegal drug	1.45 (1.44 - 1.46); P < 0.001
Stroke	1.56 (1.56 - 1.57); P < 0.001
Alcohol use disorder	0.94 (0.94 - 0.94); P < 0.001

OR: odds ratio; CI: confidence interval.

Author Contributions

Conceptualization: Anusha Chidharla and Kriti Agarwal; Methodology: Deep Mehta; Acquisition of data: Deep Mehta, Salwa Abdelwahed, Anusha Chidharla and Kriti Agarwal; Formal analysis and investigation: Deep Mehta, Anusha Chidharla and Kriti Agarwal; Writing original draft preparation: Anusha Chidharla, Kriti Agarwal, Salwa Abdelwahed, Renu Bhandari, Abhishek Singh, Rizwan Rabbani, Kajal Patel, Priyanka Singh, Deep Mehta, and Pritika S. Manaktala; Writing review, critical feedback, and editing: Shreejith Pillai, Sachin Gupta, and Thoyaja Koritala; Resources and supervision: Thoyaja Koritala.

Data Availability

The dataset is available at CDC website https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. The information on datasets and user guide resources are available on NHANES website.

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