Are e-Cigarette Users at an Increased Risk of Bladder and Lung Cancer?

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Research Article

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Abstract

Purpose

Electronic cigarette (e-cigarette) smoking and similar novel smoking modalities have raised questions about their impact on various cancers compared with traditional forms of tobacco smoking. Tobacco smoking has been proven to increase the risk of many cancers, including lung (LCa) and bladder (BCa) cancer. Currently, there is little data on how e-cigarette smoking impacts the incidence of these cancers. We investigated whether any disparities exist in the prevalence of LCa and BCa between various smoking histories using a US nationally representative data source.

Methods

This cross-sectional survey-based US study included men and women aged 18+ from the National Health Interview Survey (NHIS) database between 2016-2018. Primary endpoint was self-reported occurrence of LCa and BCa diagnosis. Multivariable logistic regression analyses assessed possible association of various covariates with diagnosis of these cancers.

Results

Prevalence of BCa and LCa was higher in all smoking histories compared to never smokers. Patients with a history of e-cigarette smoking vs. no history of e-cigarette smoking were significantly younger at BCa diagnosis (56.87 [±9.86] vs. 65.00 [±12.60] years, p=0.001). Multivariable logistic regression models showed that a history of cigarette smoking and e-cigarette smoking individually and exclusively was associated with increased ORs of 2.476 (p=<0.001) and 1.577 (p=<0.001) for BCa diagnosis, respectively, and 4.589 (p=<0.001) and 1.614 (p=0.007) for LCa diagnosis, respectively.

Conclusion

Compared to never smokers, e-cigarette smoking history was associated with increased risk of LCa and BCa development. Additional studies are needed to better define the public health effects of these novel and unregulated products.

Introduction

Tobacco smoking has been unequivocally proven to increase the risk of many cancers, especially lung (LCa) and bladder (BCa) cancer [1–3]. Smoking has been identified as the main known cause of cancer-related death worldwide, causing up to 30-40% of cancer deaths [1–2]. Of these cancer deaths, at least 85% of LCa are attributable to smoking [4]. Smoking is also the most important risk factor for BCa with an attributable risk of approximately 50% [5].

The introduction of electronic cigarettes (e-cigarettes) and other novel smoking modalities has resulted in questions being raised regarding their impact on cancer in comparison with traditional forms of smoking (i.e., cigarette smoking, cigar smoking, pipe smoking, and smokeless tobacco usage). E-cigarettes are nicotine delivery devices that are designed to look and feel like a traditional cigarette. They are often marketed as tobacco-free nicotine delivery devices that are safer than tobacco-containing traditional smoking methods [6–8]. For a typical device, instead of burning tobacco, a user draws air through the device; a physical power button, or sometimes an airflow sensor, activates a battery which powers an atomizer to produce an aerosol from liquid that contains nicotine, solvents such as glycerol and/or propylene glycol, and flavorings. Users inhale this aerosol into their lungs. While traditional smoking modalities are heavily regulated, e-cigarette smoking has seen little regulation – especially as e-cigarette smoking products are widely available to purchase on the internet [9–10]. Furthermore, e-cigarette smoking products are aggressively marketed as a “safer” alternative to traditional smoking modalities and as a smoking cessation aid, neither of which have been proven to be true [6–8, 11–12]. While certain carcinogens are less prevalent in e-cigarette smoking products when compared to traditional cigarettes [12–13], studies have found that e-cigarette smoking vapor can potentially damage DNA, cause point mutations in genes, and contain heavy metals and other carcinogens that can raise cancer risk [13–18]. Additionally, nicotine itself directly increases activity of the sympathetic nervous system and consequently may contribute to the potentiation of carcinogenesis and tumor growth [19]. As a cessation aid, results are mixed regarding their effectiveness [11, 18]. Additionally, e-cigarette smoking has increasingly gained popularity among never-smokers, especially adolescents [20]. Studies have shown strong and consistent evidence of an association between initial e-cigarette smoking and subsequent cigarette smoking initiation, which could further increase cancer risk [21–22].

The collection of e-cigarette smoking history has relatively recently been included in a limited number of federal and state health surveillance surveys, allowing the production of population-based information about the health of these individuals. While the volume of e-cigarette smoking data has been increasing, published studies on this population are limited in number and scope, especially with regards to their impact on cancer incidence and prevalence. To address this important knowledge gap, we investigated disparities between different smoking histories and the prevalence of LCa and BCa, using a US nationally representative data source.

Methods

Data Source and Study Design

Data for this study were retrieved using the National Health Interview Survey (NHIS) to identify all men and women living in the US who were included in the annual national survey from the 2016-2018 yearly cycles (January 2016 – December 2018). Prior cycles were not included, as questions assessing our outcomes of interest were not present or were phrased differently. The NHIS is the principal source of information on the health of the civilian noninstitutionalized population residing within the 50 states and the District of Columbia of the United States and is one of the major data collection programs of the National Center for Health Statistics (NCHS), a part of the Centers for Disease Control and Prevention (CDC). The NHIS is regarded as the

“gold standard” for U.S. health survey data [23]. The data supporting the findings of this study are openly available (https://cdc.gov/nchc/nhis/) and are routinely collected with the main objective to monitor the health of the United States population through the collection and analysis of data on a broad range of health topics. All data were previously de-identified and publicly available, waiving the need for institutional review board approval.

Sampling and Survey

The NHIS target population includes residents of households and noninstitutional group quarters. Persons residing temporarily in student dormitories or temporary housing are sampled within the households that they reside in permanently. Persons excluded from the survey are those with no fixed household, active-duty military personnel and civilians living on military bases, persons in long-term care institutions, persons in correctional facilities, and U.S. nationals living in foreign countries. While active-duty Armed Forces personnel cannot be sampled for inclusion in the survey, any civilians residing with Armed Forces personnel in non-military housing are eligible to be sampled [23].

To keep survey operations manageable, cost-effective, and timely, the NHIS uses geographically clustered sampling techniques to select the sample of dwelling units for the NHIS [23]. The sample is designed in such a way that each month’s sample is nationally representative. Data collection on the NHIS is continuous, i.e., from January to December each year. The sampling plan is redesigned after every decennial census. Commercial address lists are used as the main source of addresses, supplemented by field listing.

The U.S. Census Bureau, under a contractual agreement, is the data collection agent for the NHIS. Data are collected continuously throughout the year by Census interviewers. The NHIS is conducted using computer-assisted personal interviewing. Face-to-face interviews are conducted in respondents’ homes, but follow-ups to complete interviews may be conducted over the telephone.

Inclusion Criteria and Endpoints

The inclusion criteria were limited to all respondents, male and female, above the age of 18 who reported smoking histories, both positive and negative. The primary outcomes of the study were self-reported occurrence of BCa and LCa diagnosis in the last 10 years.

Covariates

We collected all available a priori determined demographic variables thought to be relevant in assessing prevalence of cancer diagnosis. These included: current age, age at cancer diagnosis, gender, race (White, Black, American Indian / Native Indian (AI/NI), Asian, and Other), US geographical region (Northeast, Midwest, South, West), marital status, and year of survey (2016-2018). Health-related covariates were also collected which included smoking status (history of ever cigarette smoking, ever e-cigarette smoking, ever cigar smoking, ever pipe smoking, and ever smokeless tobacco usage). Importantly, smokers were defined as men and women who reported any history of smoking, even if currently not smoking. Non-smokers were defined as those who had no history of any type of smoking.

Missing Data and Statistical Analyses

According to data published in the NHIS survey website, hot-deck imputation was used for missing data of race and Hispanic origin to improve the overall quality of the data [24]. In this data processing procedure, every case with a missing value is assigned the corresponding value of a “similar” case in the same imputation class. Descriptive analyses included medians and interquartile range for continuous variables and proportions for discrete variables. For comparison of discrete and continuous variables, the chi-squared test and the Kruskal-Wallis test were employed, respectively. Multivariable logistic regression analyses assessed association of a priori selected covariates with the prevalence of having been diagnosed with BCa and LCa. These included survey year, current age, gender, race, US region, marital status, and history of exclusive regular cigarette smoking history, exclusive e-cigarette smoking history or no smoking history at all. All statistical tests were two-tailed and a p-value of <0.05 was considered significant. Statistical analyses were performed using SPSS® statistical software version 23.0 (SPSS Inc., Chicago, IL).

Results

The responses of 85,187 adults, with 38,489 (45.18%) men and 46,417 (54.49%) women, were analyzed. The overall sample adult survey response rate varied slightly each year, with 80.9% in 2016, 80.7% in 2017, and 83.9% in 2018. A total of 34,176 (40.12%) reported a history of ever smoking cigarettes (cigarette smoking), 12,422 (14.58%) of ever smoking e-cigarettes (e-cigarette smoking), 24,077 (28.26%) of ever smoking cigars (cigar smoking), 11,760 (13.80%) of ever smoking pipes (pipe smoking), 9,052 (10.63%) of ever using smokeless tobacco (Smokeless tobacco usage), and 39,856 (46.79%) of never smoking at all.

Demographic characteristics of the analyzed study cohort stratified by smoking histories is presented (Table 1). Mean age was highest in the people with a cigarette smoking history (54.79 [±17.15] years) and lowest in those with an e-cigarette smoking history (41.21 [±15.63] years) compared to people with other smoking histories (cigar smoking at 49.15 [±17.70] year, pipe smoking at 50.02 [±19.79] years, and Smokeless tobacco usage at 46.91 [±16.54] years, p= <0.001). There was a significantly larger proportion of men vs. women for all smoking histories, especially for cigar smoking, pipe smoking, and Smokeless tobacco usage, (p=<0.001).

The reported prevalence rates for BCa and LCa stratified by smoking history are depicted in Figure 1. Prevalence of both BCa and LCa was higher in all smoking histories compared to never smokers. Within each respective ever smoking history of cigarette smoking, cigar smoking, and pipe smoking the rate of BCa was significantly higher than in never smokers. Cigarette smoking, e-cigarette smoking, and pipe smoking smokers had a significantly higher rate of LCa than never smokers. As shown in Table 2, individuals with an e-cigarette smoking history were significantly younger at BCa diagnosis compared to those who were non-e-cigarette smoking (56.87 [±9.86] vs. 65.00 [±12.60] years, p=0.001). All other smoking modalities had no significant difference in the age of BCa and LCa diagnosis between smokers and non-smokers.

Table 2
Mean age of bladder and lung cancer diagnosis for various smoking histories

	Ever smoked cigarettes?			Ever used e-cigarettes?			Ever smoked cigars?			Ever smoked pipes?			Ever used s tobacco?
	Yes	No	P value	Yes	No	P value	Yes	No	P value	Yes	No	P value	Yes
Mean Age of...													
...Bladder cancer diagnosis	64.01 (±12.41)	63.47 (±13.14)	0.788	**56.87 (±9.86)**	**65.00 (±12.60)**	**0.001**	63.77 (±12.85)	63.90 (±12.85)	0.939	64.52 (±11.17)	63.57 (±13.19)	0.606	63.32 (±12.43)
...Lung cancer diagnosis	53.10 (±25.32)	51.11 (±22.51)	0.597	51.80 (±22.07)	53.04 (±25.40)	0.738	52.09 (±24.79)	53.20 (±24.90)	0.710	56.11 (±21.94)	51.80 (±25.57)	0.201	50.25 (±24.83)

Lastly, a sensitivity analysis of a multivariable logistic regression was conducted comparing only three types of patients: cigarette smoking single-users, e-cigarette smoking single-users, and never smokers (Table 3). After adjusting for all known and available confounders, histories of only e-cigarette smoking and only cigarette smoking (compared to never smokers) had a significantly increased risk to develop LCa with ORs of 3.831 (95% CI 2.593-5.660, p=<0.001) and 7.870 (95% CI 2.596-23.860, p=<0.001), respectively. Exclusive cigarette smoking was associated with a significantly increased risk for BCa (OR 1.990, 95% CI 1.291-3.065, p=0.002).

Table 3
Sensitivity analysis of a multivariable logistic regression analysis for patients with exclusive regular cigarette, e-cigarette, or no smoking history examining possible associations with bladder and lung cancer:

	Bladder cancer		Lung cancer	
	OR (95% CI)	P value	OR (95% CI)	P value
Survey year (2016 reference)				
2017	1.003 (0.601-1.675)	0.991	1.046 (0.680-1.607)	0.839
2018	0.951 (0.562-1.607)	0.850	0.933 (0.599-1.453)	0.759
Current age	**1.034 (1.013-1.056)**	**0.020**	1.007 (0.992-1.023)	0.363
Gender (Male vs. Female)	**2.991 (1.918-4.664)**	**<0.001**	1.107 (0.740-1.658)	0.620
Race (White reference)				
Black	0.151 (0.021-1.101)	0.062	1.456 (0.776-2.731)	0.242
Asian	0.618 (0.148-2.580)	0.509	**2.826 (1.262-6.331)**	**0.012**
Other	0.627 (0.149-3.560)	0.602	2.188 (0.774-6.192)	0.140
Region (Northeast reference)				
Midwest	0.662 (0.318-1.377)	0.269	0.901 (0.497-1.632)	0.730
South	0.963 (0.526-1.764)	0.903	1.288 (0.775-2.141)	0.328
West	1.262 (0.676-2.357)	0.465	0.791 (0.433-1.446)	0.446
Martial status (With vs. Without partner)	1.223 (0.778-1.922)	0.384	1.042 (0.711-1.527)	0.834
Smoking status (Never smoked reference)				
Exclusive regular cigarette smoker	**1.990 (1.291-3.065)**	**0.002**	**3.831 (2.593-5.660)**	**<0.001**
Exclusive E-cigarette smoker	3.831 (0.494-29.701)	0.199	**7.870 (2.596-23.860)**	**<0.001**

Discussion

In this nationally representative US survey-based study of self-reported cancer prevalence in adults, more than 40% of men and women reported a history of cigarette smoking, with 14.6% of surveyed people reporting smoking e-cigarette smoking. These are consistent with estimates of US adults that 42.5% have a history of cigarette smoking and 14.9% have a history of e-cigarette smoking [25–26]. Unadjusted comparisons demonstrated that individuals with e-cigarette smoking history compared to those with no e-cigarette smoking history were significantly younger at BCa diagnosis. Cigarette, cigar, and pipe smokers had a significantly higher rate of BCa than never smokers. Cigarette, e-cigarette, and pipe smokers had a significantly higher rate of LCa than never smokers. Sensitivity analysis of a multivariable logistic regression for never smoker patients and those with an exclusive history of cigarette or e-cigarette smoking showed that a history of exclusive cigarette smoking was associated with an increased risk of developing LCa and BCa, but a history of exclusive e-cigarette

smoking was associated with an increased risk of LCa. These data suggest that e-cigarette smoking might be associated with an increased risk to develop LCa.

Traditional tobacco smoking is an established risk factor for many cancers including breast, lung, bladder, liver, colorectal, and head and neck cancers [3–5]. Because of its relatively recent introduction, not much is known about the effects of e-cigarette smoking and other electronic nicotine delivery system usage on various cancer diagnoses. Studies have found certain carcinogens to be less prevalent in e-cigarette smoking products and e-cigarette smoking users [13–14, 18, 27]. In contrast, others have found that e-cigarette smoking vapor can potentially damage DNA, cause point mutations in genes, and contain heavy metals and other carcinogens potentially raising cancer risk [13–18]. Of note, there are hundreds of different flavors for e-cigarette smoking products, some of which have been found to pose potential inhalation toxicity (e.g., benzyl alcohol, formaldehyde, benzaldehyde, vanillin, tobacco-specific nitrosamines (NNN and NNK), and other toxicants) or induce oxidative stress, inflammation, epithelial barrier dysfunction, and DNA damage in lung cells [10, 18, 28–29]. Furthermore, some reports add that dual use of cigarette smoking and e-cigarette smoking decreases cigarette smoking intake, but total nicotine use and dependence increases, consequently increasing carcinogen exposure and making cessation efforts potentially less effective [30].

LCa is both the most common cancer (11.6%) and the most common cause of cancer death (18.4%) worldwide, with tobacco smoking responsible for upwards of 85% of LCa cases [4, 31]. As e-cigarette smoking products increase the chance of smoking tobacco in the future [21–22], and are introducers of inhaled toxicants themselves [13–18, 28–29], they may be strong drivers of LCa risk. In contrast, while BCa is not as common a cancer (3.0%) or as common a cause of cancer death (2.1%), smoking is the most common risk factor for the development of BCa [5, 31]. Similar bladder carcinogens found in the urine of tobacco users have been found in the urine of e-cigarette smoking users, raising the possibility that e-cigarette smoking could increase the risk for BCa [27, 32]. Exposure time is important in the development of BCa [5]. E-cigarette smoking products have been shown to raise the risk of cigarette smoking usage and are increasingly used by younger persons and never smokers [20–22]. It is therefore possible that BCa risk could be high for e-cigarette smoking users, making them more prone to develop BCa at a younger age, as our data have shown.

This is the only study we are aware of that has looked at the risk of specific cancers for e-cigarette smoking compared to other smoking modalities. Most studies on e-cigarette smoking have thus far focused on the toxicological and carcinogenic properties of the various components in e-cigarettes, their association with quitting traditional-smoking modalities such as cigarette smoking, subsequent cigarette smoking use for e-cigarette smoking users, and risks to adolescents. This is unsurprising as e-cigarette smoking products are relatively novel and the cumulative effects of e-cigarette smoking, with regards to cancer diagnosis, take years to manifest.

The current study has several limitations. Firstly, the data is retrospective consisting of inherent biases, with possible inaccurate or unreported data entry. As a survey-based study, it is prone to recall bias among responding subjects. Additionally, while this database accounts for many significant socio-economical and clinical factors, direct ascertainment of other relevant clinical information is lacking, such as known malignancy risk factors, including family history, personal genetic risk factors, detailed history of medical comorbidities, diet, and occupational history. Another important limitation is the lack of data on the timing of smoking, and when exactly did it occur before the cancer diagnosis (if a cancer diagnosis exists). Importantly, all analyses were based on self-reported outcomes without confirmation of type, timing of cancer diagnosis, and cancer grade. Lastly, we had no socioeconomical data available to include in our analyses.

Despite these limitations, our study represents a large and nationally representative cohort of US men and women providing recent self-reported cancer prevalence and history of various smoking modalities, including e-cigarette smoking. These data suggest that, compared with never smokers, and after adjusting for all histories of other smoking modalities, a history of e-cigarette smoking by itself is independently associated with an increased risk of LCa and BCa development. Despite being marketed as a smoking cessation aid and as a safer alternative to tobacco smoking, e-cigarette smoking might be associated with an increased risk of some smoking related cancers. Our data warrant additional studies to examine the public health effects of these relatively novel and unregulated smoking products, which are more common among younger individuals, potentially putting them at an increased risk.

Declarations

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Conflict of Interest Statement:

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions:

Study conception and design, material preparation, data collection, and analysis were performed by Michael J. Herriges Jr and Hanan Goldberg. The first draft of the manuscript was written by Michael J. Herriges Jr, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability:

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Table

Table 1 is available in the Supplemental Files section.

Figures

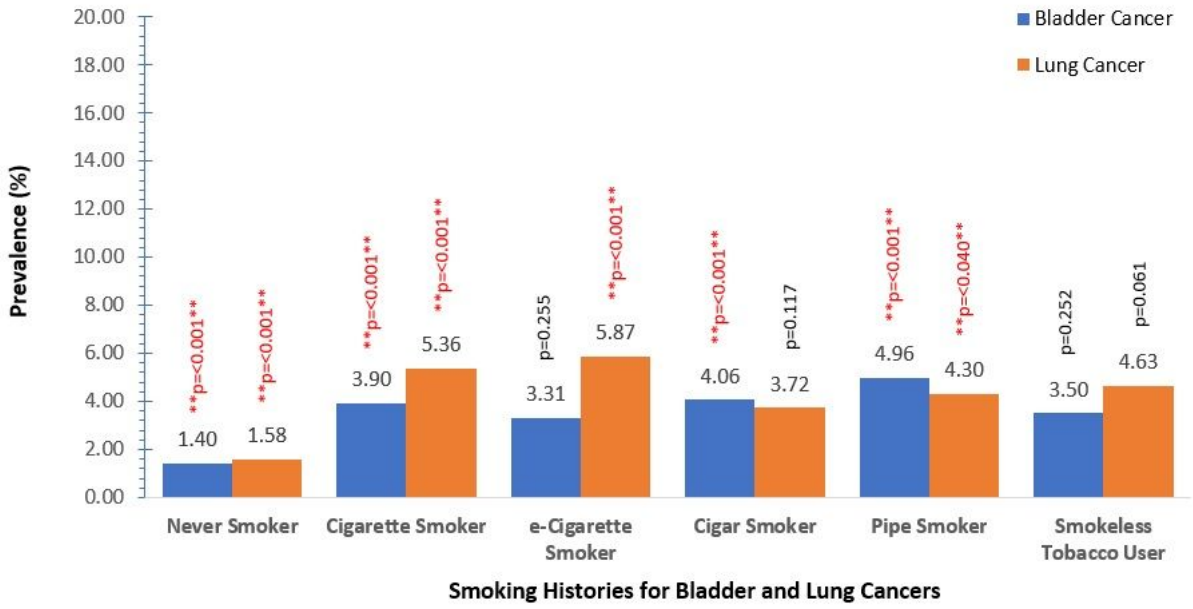

Figure 1

Unadjusted prevalence rates of bladder and lung cancers for various smoking histories.

Fig. 1 depicts unadjusted prevalence rates of bladder and lung cancers for various smoking histories. The X-axis shows various smoking histories from left to right including never-smokers, cigarette smokers, e-cigarette smokers, cigar smokers, pipe smokers, and smokeless tobacco users. The Y-axis shows the prevalence, in percent, of bladder and lung cancers for each of the smoking histories.

Supplementary Files

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