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Research Article

Vaping, Smoking and Lung Cancer Risk

Bittoni MA, Carbone DP, Harris RE*

Colleges of Medicine & Public Health, and the Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio

***Corresponding author:** Harris RE, Colleges of Medicine & Public Health, and the Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio. Email: Harris.44@osu.edu

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Abstract

Nicotine exposure through the use of electronic delivery systems (vaping) has been found to elevate the risk of certain conditions of the lungs, e.g., vaping associated lung injury, EVALI). However, the potential impact of vaping on lung cancer risk remains unexplored. We, therefore, examined the association of vaping and cigarette smoking with lung cancer risk in a case control study conducted in central Ohio. The study design compared 4,975 individuals with recently diagnosed pathologically confirmed carcinoma of the lung to 27,294 controls without cancer that were group matched at a 5:1 ratio to the cases by age, gender, race and location of residence. Odds ratios (OR) adjusted for gender, age and race revealed a fourfold higher risk of lung cancer among individuals who vaped in combination with chronic smoking (OR=58.9, 95% CI=47.3-70.5) versus individuals who only smoked cigarettes (OR=13.9, 95% CI=12.7-15.3, P<0.001). Further adjustment for prevalent comorbidities, chronic obstructive pulmonary disease and coronary artery disease, reduced the magnitude of the OR, but the risk for vaping and smoking (OR=38.7, 95% CI =31.5-47.6) remained fourfold higher than for smoking alone (OR=9.6, 95% CI= 8.7-10.6, P<0.001). This finding was consistent for men and women, with adjustment for pack-years of smoking, and for the main histological cell types of lung cancer. Our results suggest that the addition of vaping to smoking accelerates the risk of developing lung cancer.

Simple Summary: We compared cigarette smoking and use of electronic cigarettes (vaping) among 4,975 cases with lung cancer to 27,294 control subjects without cancer. The control subjects were from the same general location as the cases and had the same distribution of age, gender and race as the cases. We found that vaping combined with cigarette smoking was eight times more common in the cases with lung cancer than the control subjects, and the risk of developing lung cancer was four times higher among those who combined vaping and cigarette smoking than those who only smoked. These findings were consistent for men and women and for all major cell types of lung cancer. Our results suggest that vaping in combination with cigarette smoking accelerates the rate of developing lung cancer compared to smoking alone.

Keywords: Lung Cancer; Smoking; Vaping; Electronic Cigarettes

Introduction

Lung cancer is the leading cause of cancer deaths worldwide killing 1.8 million people in 2020 (1.19 million men and 607,000 women), more than the combined number of deaths from the next four high ranking cancers (breast, prostate, colorectal cancer and pancreatic cancer caused 1.5 million deaths in 2020). In the same year, 2.09 million new cases of lung cancer were diagnosed (1.37 million in men and 725,000 in women). The persisting high ratio of deaths to incident cases (~0.90) reflects the high case fatality of lung cancer, irrespective of the developmental status of countries [1]. Thousands of published independent studies underscore the dominant role of cigarette smoking in the genesis of lung cancer. Estimates of attributable risk suggest that approximately 87% of lung cancers develop due to chronic tobacco smoking [2].

In the 1970s, the tobacco industry promoted the misconception that smoking filtered cigarettes was “safer” than smoking unfiltered cigarettes [3]. Indeed, the advent of filter cigarettes has now become the norm among those addicted to the smoking habit, but unfortunately, the transition of unfiltered to filtered cigarettes only resulted in a change of the histological cell type of lung cancer, e.g., pulmonary adenocarcinomas of the lower bronchi arise predominantly in filtered cigarette smokers whereas squamous cell carcinomas of the upper bronchi are more likely to arise in unfiltered cigarette smokers [4]. The overall impact of smoking

filtered versus non-filtered cigarettes has thus had negligible impact on overall lung cancer mortality [5].

Early in the 21st century, the tobacco industry began promoting the use of electronic cigarettes to replace cigarette smoking to satisfy cravings for nicotine. The premise was that e-cigs were "safer" than cigarettes, for the primary reason that vaping involves inhalation of an aerosolized liquid and does not involve combustion of tobacco. The industry universally proposed that vape aerosol, while efficiently delivering nicotine into the lungs, contains lesser amounts of toxic and/or carcinogenic substances than tobacco smoke and is thus "safer" [6, 7].

The first commercially acceptable electronic cigarette was invented in China in 2003 and was marketed by the name "Ruhan". These devices were introduced in Europe and the USA in 2006 and 2007, respectively, and in recent years, the vaping epidemic has revolutionized the tobacco industry [6]. Scores of investigations have reported that "vaping" has replaced cigarette smoking, particularly among teenagers and young adults. Studies in the United States, China, Great Britain, France, Spain, Germany, Brazil, Russia and elsewhere provide unequivocable evidence that the majority of young people who take up the nicotine habit, do so by virtue of vaping as opposed to cigarette smoking. Studies in the US, Western Europe, China and Russia suggest that approximately 1 in 5 teenagers and 1 in 3 adults are currently vaping [8, 9]. Worldwide, it was estimated that nearly 70 million people were using electronic cigarettes in the year 2020 [10].

Use of electronic cigarettes has also been proposed and advertised as a method for smoking cessation among chronic cigarette smokers. However, the results of studies that have examined vaping as a smoking cessation tool are mixed and findings have generated much controversy [11]. Some studies suggest that electronic nicotine delivery reduces craving for nicotine and may be beneficial for those who want to quit smoking [12-14], whereas others have observed negligible effects [15]. Reviews and meta-analyses of the existing literature suggest that e-cigarettes may help some smokers quit or reduce cigarette smoking, however, results are limited by short follow-up times (<2 years) and additional studies are urgently needed to establish the long-term cessation effects of e-cigarettes [16, 17].

The popularity of e-cigarette use has arisen in the absence of convincing evidence that acquiring nicotine by vaping is any safer than smoking cigarettes. In 2019-2020, an outbreak of e-cigarette/vaping product use-associated lung injury (EVALI) occurred in the USA resulting in thousands of hospitalizations and 68 fatalities. Results of studies of lung specimens from afflicted patients suggest that EVALI is associated with inhalation of aerosolized vape liquid containing Vitamin E acetate and tetrahydrocannabinol (THC), but vaping-related exposure to nicotine and other toxic compounds has not been ruled out in the pathogenesis of EVALI [18, 19].

Nicotine itself is extremely addictive and a powerful vasoconstrictor that acutely increases blood pressure and heart rate, depresses respiratory function, and suppresses the immune system as well as having toxicological effects on fetal development during pregnancy [20, 21]. Pulmonary function studies show that e-cigarette use causes an immediate increase in airway resistance and inflammation, and exposure to other components of vape liquid (humectants, flavoring agents, metals, etc.) markedly increase the secretion of proinflammatory cytokines in the upper airways and lungs thereby heightening the risk of infection and pneumonia [22, 23]. These and other health consequences of using electronic cigarettes have been extensively studied and documented clearly revealing that vaping is not free of harm. Nevertheless, there is general consensus that vaping is associated with some harm reduction by lessening dependence on nicotine delivery by cigarette smoking [24]. Albeit, follow-up studies of individuals who regularly vape for many years have not yet been conducted to determine the incidence and severity of long-term deleterious effects. We are aware of no studies that have examined the risk of lung cancer in cigarette smokers compared to those who vape. In the current study, we, therefore, focus on the risk of lung cancer in association with cigarette smoking and vaping.

Methods

We utilized a case-control study design to examine the risk of lung cancer associated with cigarette smoking versus e-cigarette aerosol inhalation (vaping). During 2013-2021, we ascertained computerized medical records of 4,975 cases of newly diagnosed lung cancer at the James Cancer Hospital at The Ohio State University Wexner Medical Center. All cases were confirmed by pathological examination of lung tissues from the patients. Only those with confirmed carcinoma of the lung were included and other types of malignancy (lymphoma, sarcoma, carcinoid tumors, and metastatic cancer) were excluded from the sample of cases. During the same time period, we ascertained medical records of 27294 control subjects without cancer that were group-matched to the cases at an approximate 5 to 1 ratio by age (five-year age categories), gender, race, year of ascertainment, and location (county) of residence. All control subjects were accessed through outpatient clinics for routine annual checkups. Variables of interest, in addition to age, gender, race and county of residence, included reported comorbid conditions (coronary artery disease, chronic obstructive pulmonary disease), cigarette smoking, and use of e-cigarettes (vaping). Daily current cigarette smoking and vaping were self-reported at the time of patient intake. No personal health information was retrieved in the study, thereby retaining anonymity of all study participants, and the study protocol was approved by the Human Subjects Review Board of The Ohio State University Medical Center (Protocol Number 2019C0105).

Unconditional logistic regression analysis was conducted to estimate odds ratios with 95% confidence intervals and P-values for cigarette smoking, vaping and other potential risk factors. Estimates for smoking and vaping were adjusted for age as a continuous variable, gender, and race. Separate estimates were compared for men and women, and for distinct histologic cell types (pulmonary adenocarcinoma, squamous cell carcinoma, small cell and large cell carcinoma). Prevalent comorbid conditions, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), were added to regression models in order to test for effect modification. To further adjust estimates for smoking intensity and duration, we analyzed a subset of 4,637 cases and 24,055 controls frequency matched by age, gender, and race for whom we had more detailed information on cumulative cigarette smoking history (pack-years of smoking). In this analysis, we estimated effects of vaping status and smoking for those with 40 or more pack-years of cumulative cigarette smoking compared to those with lesser pack years of smoking. We also conducted a logistic regression analysis with smoking amount in pack-years (<30, 30-39, 40-49, 50-59, >59) treated as an independent variable to estimate the adjusted odds ratios for vaping plus smoking com-pared to smoking alone.

Results

Table 1 shows the distributions of age, gender, race and selected comorbid conditions (COPD and CAD), among the 4,975 cases and 27,294 controls. Over half of the individuals were male in both groups, over 88 percent were White and 11% Black, and the mean age was 62 years. As expected, age, gender and race were closely matched, and adjustment did not cause significant effect modification. Frequencies of COPD and CAD were higher among cases than controls (P<0.01) and effects were assessed in separate regression models (see Table 3).

Variable	**Cases (n=4,975)**		**Controls (n=27,294)**	
Age at Entry	**n**	**%**	**n**	**%**
<50	284	5.7	3193	11.7
50-59	1070	21.5	7751	28.4
60-69	1791	36	9663	35.4
70-79	1428	28.7	5623	20.6
>79	402	8	1065	3.9
Gender				
Men	2714	54.6	14858	54.4
Women	2261	45.4	12436	45.6
Race				
White	4405	88.5	24079	88.2
Black	556	11.2	3150	11.5
Asian	2	0.1	9	0.1
Other	12	0.2	56	0.2
Comorbidities*				
COPD	3747	75.3	6397	23.4
CAD	3197	64.3	9122	33.4

*Chronic Obstructive Pulmonary Disease (COPD), Coronary Artery Disease (CAD). Frequencies were significantly higher among cases, P<0.01.

Table 1: Characteristics of 4,975 lung cancer cases and 27,294 controls.

Table 2 shows the distributions of e-cigarette use (vaping) and cigarette smoking among cases and controls with estimated odds ratios (OR) and 95% confidence intervals. Based on a subset of nearly 10,000 individuals who reported daily frequency and duration of smoking, smokers had a median level of exposure of 40 pack-years with interquartile range of 20-60 pack-years. Cigarette smoking was reported by 89.3% of cases versus 37.6% of controls. Reciprocally, almost two thirds (62.4%) of controls reported never smoking versus only 10.7% of cases. Reported vaping was nearly eight-fold higher among the cases compared to controls (6.3% versus 0.80%, P<0.001) and over 97% of those who vaped also reported being smokers.

The odds ratio for vaping in combination with smoking (OR=57.8 95% CI=47.4-70.5) was fourfold higher (P<0.001) than the estimate for smoking alone (OR=13.9, 95% CI=12.7-15.3). It is notable that nearly all individuals who reported vaping also smoked cigarettes, and thus we have no estimates of vaping per se following chronic cigarette smoking. Nevertheless, it is clear from these data that vaping in combination with cigarette smoking significantly increased the risk of lung cancer compared to smoking alone.

Status	**Cases**	**Controls**	**OR (95% CI)***
Vaping & Cigarette Smoking	314	219	57.8 (47.4-70.5)
Cigarette Smoking	4130	10036	13.9 (12.7-15.3)
Nonsmoking	531	17039	1
Totals	4975	27294	--
*ORs are adjusted for matched variables of age, gender and race. Nonsmoking is the reference category for all estimates. OR estimate for vaping and cigarette smoking was significantly higher than the estimate for smoking, P<0.001.			

Table 2: Odds Ratios and 95% confidence intervals for vaping combined with cigarette smoking and cigarette smoking alone among lung cancer cases and controls.

Table 3 shows estimates of OR after further adjustment for prevalent comorbid conditions: chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD). Both conditions had significant independent effects (OR=4.5 for COPD, OR=2.3 for CAD) and the addition of each in logistic regression models reduced the OR estimates for smoking/vaping and smoking alone compared to the estimates of Table 1. Nevertheless, the 3-4-fold increase in lung cancer risk due to vaping and smoking compared to smoking alone persisted after adjustment for each individual comorbidity.

Comorbidity	**Condition**	**Vaping & Cigarette Smoking**	**Cigarette Smoking**
COPD	4.5 (4.2-4.9)	29.3 (23.7-36.2)	7.2 (6.5-8.0)
CAD	2.3 (2.1-2.5)	48.3 (39.5-59.2)	12.3 (11.2-13.6)
COPD & CAD	4.3 (3.9-4.8)	38.7 (31.5-47.6)	9.6 (8.7-10.6)
*ORs are adjusted for matched variables: age, gender and race; and comorbid conditions: Chronic Obstructive Pulmonary Disease (COPD) and Coronary Artery Disease (CAD). OR estimates for vaping and cigarette smoking were significantly higher than corresponding estimates for smoking, P<0.001.			

Table 3: Odds Ratios with 95% confidence intervals for comorbid conditions and lung cancer, and adjusted estimates for Vaping/ Cigarette smoking versus cigarette Smoking.*

Table 4 shows the distribution of cases by gender and distinct histologic cell types of lung cancer with separate estimates of odds ratios and 95% confidence intervals. Among the 4975 cases, 55% were male and 45% female. Adenocarcinomas were the most common cell type (51.6%) followed by squamous cell carcinomas (32.4%), small cell carcinomas (15.0%) and large cell carcinomas (1%). The OR estimates for adenocarcinoma were significantly less than the corresponding estimates for squamous cell carcinoma, e.g., 20.2 versus 46.0 for vaping/smoking and 4.7 versus 10.8 for smoking alone, P<0.05), whereas the estimates for small cell and large cell types, which are based on much small sample sizes, were similar to squamous cell carcinoma. Nevertheless, all of the OR estimates consistently reflect 3-4-fold higher lung cancer risk for men and women who vape in combination with cigarette smoking compared to those who only smoke, regardless of cell type.

Cases	n (%)	Vaping & Cigarette Smoking	Cigarette Smoking
Men	2714 (54.6)	30.8 (22.9-41.4)	6.8 (5.8-8.0)
Women	2261 (45.4)	22.1 (16.1-30.2)	6.9 (6.0-7.9)
Non-small Cell			
Adenocarcinoma	2556 (51.6)	20.2 (15.7-26.0)	4.7 (4.2-5.4)
Squamous Cell	1622 (32.4)	46.0 (32.9-64.3)	10.8 (8.8-13.4)
Small Cell	744 (15.0)	56.8 (36.6-88.2)	13.7 (10.2-18.6)
Large Cell	53 (1.0)	60.5 (12.9-282.5)	11.5 (3.4-38.3)
*ORs are adjusted for matched variables: age, gender and race and comorbid conditions, Chronic Obstructive Pulmonary Disease (COPD) and Coronary Artery Disease (CAD); OR estimates for vaping and cigarette smoking were significantly higher than corresponding estimates for smoking, P<0.001.			

Table 4: Distributions of men, women and histologic cell types among 4975 cases of lung cancer with corresponding odds ratios and 95% confidence intervals for vaping and cigarette smoking.*

Table 5 shows odds ratios and 95% confidence intervals by vaping and smoking status for a subset of 4,637 cases and 24,055 controls for whom we had more detailed information on cumulative cigarette smoking history (pack-years of smoking). Estimates were 3.5 times higher for chronic smokers with greater cumulative exposure (40 or more pack years) who reported vaping than for those who smoked but did not vape (OR = 68.1 versus 19.8, P<0.001) as well as for chronic smokers with less cumulative exposure (<40 pack-years) who reported vaping versus those who smoked but did not vape (30.9 versus 8.8, P<0.001). We also conducted a logistic regression analysis of these data with smoking amount (pack-years) treated as an independent confounder to estimate the adjusted odds ratios for vaping plus smoking compared to smoking alone. Consistent with other results, the adjusted odds ratio for vaping plus smoking (OR=21.2, 95% CI=15.3-29.3) was four times higher than the odds ratio for smoking alone (OR=5.3, 95% CI=4.1-6.7, P<0.001). These results adjusted for levels of cumulative cigarette smoking history therefore provide additional evidence that vaping plus smoking elevates lung cancer risk 3-4 times higher than smoking only. Figure 1 is a forest plot of the 3-4-fold increases in risk estimates of lung cancer for cigarette smokers who also reported using electronic cigarettes (vaping) compared to those smokers who did not vape.

Vaping & Smoking*	Cases	Controls	Odds Ratio (95% CI)†
Vaper (≥40 pack-years)	175	78	68.1 (51.4-90.8)
Vaper (<40 pack-years)	117	115	30.9 (23.5-40.5)
Smoker (≥40 pack-years)	2310	3538	19.8 (17.9-21.0)
Smoker (<40 pack-years)	1540	5307	8.8 (7.9-9.8)
Nonsmoker	495	15017	1
Totals	4637	24055	--
* 40 pack-years: smoked the equivalent of 1 pack of cigarettes per day for 40 years. Nonsmokers: reference category for all estimates. †OR estimates for vaping and smoking by strata of pack-years were significantly higher than corresponding estimates for smoking, P<0.001.			

Table 5: Odds Ratios and 95% Confidence Intervals for lung cancer cases and controls by strata of vaping status and cumulative history of cigarette smoking (pack-years of smoking).

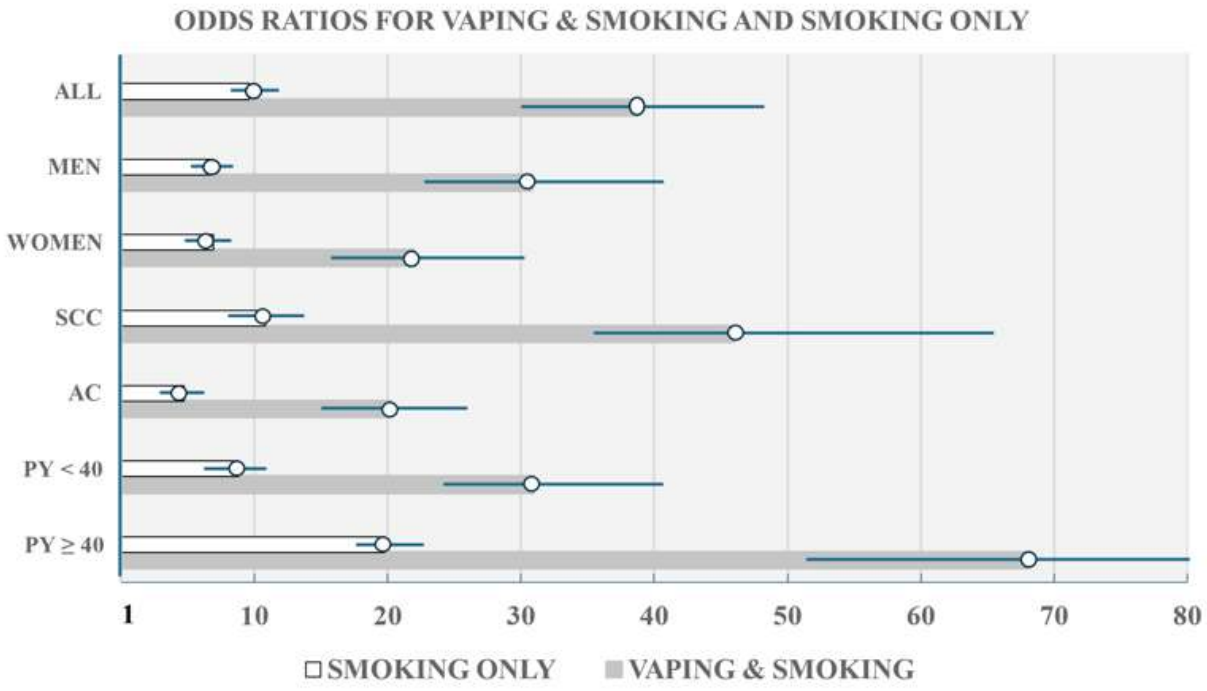

Figure 1: Odds Ratios (OR) of lung cancer in chronic smokers who vaped versus chronic smokers who did not vape by gender, histologic cell type (SCC: Squamous Cell Carcinoma, AC: Adenocarcinoma) and pack-years (PY) of cigarette smoking. ORs and 95% confidence intervals are adjusted for matched variables: age, gender and race; and comorbid conditions: Chronic Obstructive Pulmonary Disease (COPD) and Coronary Artery Disease (CAD).

Discussion

Our findings provide the first evidence that smoking in combination with vaping significantly increases the risk of lung cancer compared to smoking alone. Risk estimates reflect 3-4-fold higher risk of lung cancer among those who combine vaping with smoking cigarettes (OR=38.7) compared to those who only smoke (OR=9.6). Separate results for men and women, with adjustment for pack-years of smoking, and for the main histological cell types of lung cancer, were consistent in showing 3-4-fold higher lung cancer risk for vaping and smoking compared to cigarette smoking alone.

Our results are in agreement with a recent animal study in which exposure to nicotine from e-cigarette vapor was found to cause lung cancer in mice. The amount of smoke the mice were exposed to was similar to a person who had vaped for about three to six years [25].

Notably, two recent human epidemiologic studies found that vaping combined with smoking elevated the risk of developing chronic obstructive pulmonary disease (COPD) to a higher level than observed for smoking alone [26, 27]. Similar to our results for lung cancer, these findings for COPD reflect synergistic interaction between cigarette smoking and vaping that heightens the risk of lung disease.

Tobacco smoke contains multiple carcinogens that cause lung tumors in animals and humans [28]. Major carcinogenic components of tobacco smoke include polycyclic aromatic hydrocarbons, nitrosamines, heterocyclic aromatic amines, and carbonyl aldehydes. Of these compounds, certain carbonyl aldehydes, specifically acrolein, acetaldehyde and formaldehyde, are among the most powerful carcinogens in tobacco smoke since they efficiently impede DNA repair mechanisms while inducing mutagenesis and formation of DNA adducts [29]. Notably, thermal decomposition of humectants and flavoring chemicals in vape liquid has been found to increase formation of these highly carcinogenic carbonyl aldehydes [30]; and furthermore, elevated levels of these compounds have been observed in vape aerosol and in exhaled breath of e-cigarette users [31, 32].

Several investigations have compared levels of nicotine and its metabolite, cotinine, as well as toxic and carcinogenic compounds in e-cigarette users with levels in cigarette smokers. In one highly cited study, 28 e-cigarette users who vaped an average of one ml of

vape liquid per day with an average nicotine concentration of 12.5 mg/ml were compared with subgroups of cigarette smokers who smoked on average over 20 cigarettes per day. Results showed that urinary levels of nicotine and cotinine levels were significantly higher in one comparison group of cigarette smokers, but were similar in another. In contrast, urinary levels of several toxicants and carcinogens (metabolites of polycyclic aromatic hydrocarbons, nitrosamines, mercapturic acids, acrolein, propylene oxide, and benzene) were significantly lower in e-cigarette users compared to cigarette smokers. Nevertheless, urinary levels of the toxic and carcinogenic compounds were detectable in all urine samples of the e-cigarette users and their mean values were significantly elevated above zero [33].

Other studies have also found similar levels of urinary nicotine and lower levels of toxicants, carcinogens and volatile organic compounds in e-cigarette users compared to cigarette smokers; however, when dual users of e-cigarettes and combustible cigarettes were examined, they were found to have elevated levels of nicotine, toxicants and carcinogenic compounds compared to those who only smoked cigarettes [34, 35]. Based on these findings coupled with our current results, it is plausible to hypothesize that the added use of e-cigarettes by chronic cigarette smokers may have increased rather than decreased exposure to certain lung carcinogens thereby heightening their lung cancer risk.

It is clear from the scientific literature that a variety of toxic compounds besides nicotine are present in aerosolized e-liquid. Compounds with both carcinogenic and toxic potential therefore contaminate the ultrafine nicotine laced particles that are routinely inhaled deep into the lungs by those who chose to vape [36]. Furthermore, all of these inhaled compounds are foreign to the microenvironment of the lungs and chronic exposure to any of them is capable of inciting sustained activation of the cyclooxygenase and lipoxygenase inflammatory cascades and the inflammogenesis of lung cancer [37].

Results of the current study are in sharp contrast to reports that propose vaping as "harm reduction" compared to cigarette smoking [20, 24, 38]. Our findings suggest that rather than creating a microenvironment that is less favorable for the growth and development of lung tumors, exposure to aerosolized e-liquid may in fact promote lung carcinogenesis. A limitation of our study is that the derived risk estimates pertain to vaping as a substitute for or in combination with cigarette smoking as a source of nicotine. The study was also limited by the nature of the electronic medical record data whereby we were not able to quantify vaping and smoking as detailed as we had planned. Though we were able to stratify estimates by vaping status for a subset of individuals according to the cumulative history of cigarette smoking (pack-years of smoking), we did not have consistent information on duration of smoking cessation or the levels of continued cigarette smoking among those who reported vaping. We were also not able to quantify vaping levels and the timing of vaping relative to smoking. Nevertheless, we found large differences in the risk of lung cancer between those who reportedly vaped and smoked versus those who smoked only. Given the current pandemic of vaping among young people and the burden of lung cancer worldwide, well-designed studies are urgently needed to further examine the associations of vaping, smoking and lung cancer risk, and, in particular, the carcinogenic potential of using electronic nicotine delivery systems.

Conclusions

In a case control study of 4975 lung cancer cases and 27294 controls without cancer, we found that the risk of lung cancer among those who combined vaping with cigarette smoking (OR=38.7) was fourfold higher than for those who only smoked (OR=9.6). Findings were similar for men and women, with adjustment for pack-years of smoking, and for the main histologic cell types of lung cancer. Results suggest that the addition of vaping to smoking accelerates the risk of lung cancer. Future studies with well-quantified estimates of smoking and vaping are needed to confirm these results.

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Human Subjects Review: No personal health information was retrieved in the study, thereby retaining anonymity of all study participants, and the study protocol was approved by the Human Subjects Institutional Review Board of The Ohio State University Medical Center (Protocol Number 2019C0105, 2/5/2021).

Data Available: The Ohio State University Comprehensive Cancer Center, https://cancer.osu.edu

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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