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Association between Electronic Cigarette Use and Asthma in Never-Smokers

To the Editor:

Electronic cigarettes (e-cigarettes) have gained significant popularity in the United States during the last few years, and particularly among people who have never been smokers (1). Despite their increasing popularity, there is a paucity of data about their effects on respiratory health and there are growing concerns

from health authorities regarding their safety (2, 3). These concerns are based on animal and *in vitro* studies that have shown that exposure to the e-juice, vapor, or vapor condensate produced during use triggers a response similar to that evoked by cigarette smoke (4–6). In addition, recent epidemiological studies have shown an association between e-cigarette use and asthma among children (7–9) and adults with respiratory disorders (10).

Our aim was to examine the association between the use of e-cigarettes and a self-reported diagnosis of asthma among never-smokers of conventional cigarettes in a large, nationally representative sample of the U.S. population. We hypothesized that e-cigarette use would be associated with the self-reported diagnosis of asthma after controlling for confounding factors

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in never-smokers. We also examined self-reported asthma by frequency of e-cigarette use (daily, some days, and former use).

Methods

Population. The 2016 ($N = 486,303$) and 2017 ($N = 450,016$) Behavioral Risk Factor Surveillance System (BRFSS) surveys were used for the analysis (11–13). Current or former cigarette smokers (>100 cigarettes) and participants who had a self-reported history of chronic obstructive pulmonary disease were excluded. The UConn Health Internal Review Board classified this analysis as nonhuman research.

Defining e-cigarette users and never-smokers. Respondents were first asked, “Have you ever used an e-cigarette or other electronic ‘vaping’ product, even just one time, in your entire life?” Those who responded “no” were considered never e-cigarette users. Those who answered “yes” were categorized as ever e-cigarette users, and then asked, “Do you now use e-cigarettes or other electronic ‘vaping’ products every day, some days, or not at all?” Ever e-cigarette users who responded “every day” were

characterized as current e-cigarette daily users, those who reported “some days” were categorized as current e-cigarette some-days users, and those who answered “not at all” were categorized as former e-cigarette users.

Participants were considered never-smokers of conventional cigarettes if they answered “no” to “Have you smoked at least 100 cigarettes in your entire life?”

Outcome. Participants were defined as currently having a diagnosis of asthma if they answered affirmatively to both “Has a doctor, nurse, or other health professional ever told you that you have asthma?” and “Do you still have asthma?”.

Statistical analysis. The 2016 and 2017 BRFSS data were combined and analyzed according to the published Centers for Disease Control and Prevention recommendations, using the proper weighting methodology to improve the representativeness of the data (14). Multivariable logistic regression was used to examine the association between e-cigarette use and asthma, adjusting for the covariates in Table 1. Participants with missing covariates were removed. Analyses were conducted using R 3.4.2 (15).

Table 1. Demographic characteristics of non-cigarette smokers stratified by electronic cigarette use*

	E-Cigarette Category		
	Never User ($n = 456,379$)	Current User ($n = 3,771$)	Former User ($n = 24,927$)
Male	42.7 (42.4–43)	66.9 (64.3–69.4)	56.5 (55.4–57.7)
Age groups, yr			
18–24	13.5 (13.2–13.7)	65.5 (63–68)	50.4 (49.3–51.6)
25–34	17.5 (17.3–17.8)	22.6 (20.3–24.8)	28.7 (27.6–29.7)
35–44	17 (16.8–17.3)	6.7 (5.4–7.9)	10.3 (9.6–11)
45–54	17.9 (17.6–18.1)	3.1 (2.3–3.9)	5.8 (5.4–6.3)
55–64	15.8 (15.6–16)	1.5 (1–1.9)	3.1 (2.8–3.4)
65 or older	18.3 (18.1–18.5)	0.7 (0.3–1)	1.7 (1.6–1.9)
Married	54.9 (54.6–55.3)	14.3 (12.5–16.1)	23.7 (22.7–24.6)
Body mass index [†]	27.8 (27.7–27.8)	26.3 (26–26.7)	26.6 (26.4–26.7)
Race and ethnicity			
White only, non-Hispanic	58.3 (58–58.6)	58.2 (55.4–61)	54 (52.8–55.1)
Black only, non-Hispanic	12.6 (12.4–12.8)	12.2 (10.3–14.2)	13.2 (12.4–14)
Other race only, non-Hispanic	8.5 (8.3–8.8)	8.8 (7–10.6)	8.1 (7.4–8.8)
Multiracial, non-Hispanic	1.1 (1.1–1.2)	2.5 (1.8–3.2)	2.3 (2–2.7)
Hispanic	19.5 (19.2–19.8)	18.3 (15.9–20.6)	22.4 (21.3–23.5)
Annual income			
Less than \$15,000	9.6 (9.3–9.8)	9.9 (8.2–11.6)	10.1 (9.3–10.9)
\$15,000 to less than \$25,000	15.3 (15.1–15.6)	18.6 (16.3–21)	16.2 (15.3–17.2)
\$25,000 to less than \$35,000	9.6 (9.4–9.8)	12.2 (10.3–14.1)	10.4 (9.6–11.1)
\$35,000 to less than \$50,000	12.6 (12.4–12.8)	13.6 (11.6–15.5)	14.1 (13.3–15)
\$50,000 or more	52.9 (52.5–53.2)	45.7 (42.7–48.7)	49.2 (47.9–50.4)
Education			
Did not graduate high school	11.9 (11.6–12.1)	9.9 (8.2–11.6)	7.2 (6.4–7.9)
Graduated high school	24.5 (24.3–24.8)	40 (37.3–42.8)	29.1 (28–30.1)
Attended college or technical school	29.1 (28.8–29.4)	37.6 (34.9–40.3)	39.1 (38–40.2)
Graduated from college or technical school	34.5 (34.2–34.8)	12.5 (11.2–13.8)	24.7 (23.8–25.5)
Currently uses smokeless tobacco	2.1 (2–2.2)	7.1 (5.9–8.3)	5.2 (4.7–5.7)
History of diabetes	9.5 (9.3–9.7)	2.9 (2–3.8)	2.5 (2.2–2.7)
History of heart attack	2.5 (2.4–2.6)	0.7 (0.2–1.1)	0.7 (0.5–0.9)
History of angina or coronary disease	2.6 (2.5–2.7)	0.3 (0.1–0.5)	0.7 (0.5–0.9)
History of stroke	2.2 (2.1–2.2)	0.6 (0.2–1.1)	0.6 (0.5–0.7)

Definition of abbreviation: CI = confidence interval.

*Results are reported as percentages (95% CI) unless otherwise stated.

[†]Mean and 95% CI.

Results

Among never-smokers of cigarettes, there were 456,379 never e-cigarette users, 3,771 current e-cigarette users, and 24,927 former e-cigarette users. Table 1 presents their demographic characteristics. The prevalence of asthma was 7% (95% confidence interval [CI], 6.8–7.1) among never e-cigarette users, 10.6% (95% CI, 9–12.2) among current e-cigarette users, and 8.9% (95% CI, 8.2–9.6) among former e-cigarette users. For the multivariable regression analysis, after participants with any missing covariates were removed, there were 351,327 never e-cigarette users, 2,851 current e-cigarette users, and 19,682 former e-cigarette users (see Table E1). Among never-smokers, the odds ratio [OR] of reporting asthma was 1.36 (95% CI, 1.11–1.68) for current e-cigarette users and 1.11 (95% CI, 1.00–1.23) for former e-cigarette users compared with never e-cigarette users. Daily e-cigarette users had a statistically significant OR for asthma compared with never e-cigarette users. There was no statically significant difference in the OR of some-days users compared with never e-cigarette users (Table 2).

Discussion

This study shows an association between the use of e-cigarettes and asthma in a large representative cohort of adults who were never smokers of conventional cigarettes. Similar findings were obtained by Wills and colleagues in an adult population (10), and in other studies in pediatric populations (7–9). Furthermore, wheezing, a common symptom in asthma, was recently reported to be more common among e-cigarette users than among non-e-cigarette users (both adolescents and adults) (16, 17).

Our findings suggest that e-cigarette use may be associated with asthma among never-smokers, despite other reports (18). This is critical information, as the prevalence of e-cigarette use among younger adults and adolescents is rising quickly (19, 20) while the prevalence of conventional cigarette smoking in this age group has declined (21, 22).

A major strength of our approach is the large, representative sample of the U.S. population we used to test our hypothesis. By selecting never cigarette smokers, we removed the confounding effect attributed to dual use of conventional cigarettes. There are also limitations to these analyses. BRFSS is a cross-sectional survey, so a causal relationship between e-cigarette use and asthma cannot be evaluated. However, animal studies and *in vitro* studies do support a causal association (6, 23, 24). Another potential limitation is recall bias and residual confounding; however, the self-reported diagnosis of asthma by a healthcare provider is commonly used by government agencies and scientists in general, as it has been shown to correlate well with the diagnosis of asthma (25, 26).

Table 2. Association between the frequency of e-cigarette use and reported asthma diagnosis for never cigarette smokers ($n = 373,860$)

	Odds Ratio (95% Confidence Interval)
Never e-cigarette user	Reference
Daily e-cigarette user	1.81 (1.23–2.66)
Some days e-cigarette user	1.26 (0.99–1.60)
Former e-cigarette user	1.11 (1.00–1.23)

In conclusion, adult e-cigarette users who were never smokers of conventional cigarettes had higher odds of reporting a diagnosis of asthma than those who did not use e-cigarettes.

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Fulvestrant for the Treatment of Pulmonary Arterial Hypertension

To the Editor:

Postmenopausal women and men with pulmonary arterial hypertension (PAH) have higher circulating estrogen levels than respective control subjects, and higher levels of estrogen are associated with worse hemodynamics and lower 6-minute-walk distance (6MWD) in PAH (1, 2). We have shown increased expression of estrogen receptor α (ER α) in the small muscular pulmonary arteries of women with PAH (3). In PAH, hematopoietic progenitor cells (HPCs) are increased in the bone marrow, and estradiol increases HPC proliferation and circulation via ER α leading to lung microvessel growth (4, 5). The link between ER α signaling and HPCs has not been well studied in PAH.

Fulvestrant is a U.S. Food and Drug Administration (FDA)-approved intramuscularly administered ER α inhibitor for the treatment of metastatic breast cancer and for combination use. Fulvestrant blocks dimerization of ER α , decreases ER α expression, and limits nuclear translocation of transcriptional activating factors. We aimed to determine if fulvestrant would improve right ventricular function, reduce HPCs and other biomarkers, and increase 6MWD in PAH.

Methods

We performed a proof-of-concept open-label pilot study of fulvestrant in PAH. The trial protocol (*see online supplement*) was approved by the institutional review board and registered at

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clinicaltrials.gov before enrollment (NCT02911844). We enrolled five postmenopausal women with PAH. We excluded patients using hormone therapy or warfarin, with a history of breast cancer, or with World Health Organization class IV functional status or Child-Pugh C liver disease (*see clinicaltrials.gov* for complete criteria and online supplement). Endpoints included changes from baseline to follow-up (~ 9 weeks) in 6MWD, plasma N-terminal pro-brain natriuretic peptide, HPCs, estradiol levels and other blood biomarkers, and echocardiographic measures (right ventricular systolic pressure, stroke volume, and tricuspid annular plane systolic excursion). The lung uptake of ^{18}F -fluoroestradiol (^{18}F -FES), an established probe for estradiol binding to ER, was measured using positron emission tomography–computed tomography imaging before and after treatment with fulvestrant under a distinct protocol and informed consent (NCT02899533) and under an investigational new drug application (FDA #126041) (6).

For flow cytometry, peripheral blood mononuclear cells (PBMCs) were isolated by density-gradient centrifugation and washed to remove platelet contamination. PBMCs (10^6 cells) were labeled with PeCy5.5 anti-CD45 (Invitrogen; cat# MHCD4518), fluorescein isothiocyanate anti-CD34 (BD Biosciences; cat# 555821), and allophycocyanin anti-CD133 (Miltenyi Biotech; cat# 130-90-826) or with appropriate isotype controls and were analyzed on a MacsQuant 10 (Miltenyi Biotech). HPCs were defined as CD34 $^{+}$ CD133 $^{+}$ cells, which were CD45dim (expressed as percentage of PBMCs) (7). Estradiol and other estradiol metabolites were measured in plasma using liquid chromatography–mass spectrometry (8).

Fulvestrant was administered in a 500-mg dose intramuscularly on Days 0, 14, 28, and 56 by study personnel. Research assessments were performed at baseline (Day 0) before the first dose of fulvestrant and at 9 weeks (Day 63).

Sign-rank tests and Spearman rho were used as appropriate. The analysis plan included reporting *P* values, but they were not used for inference. A data-sharing statement is provided online.

Results

The median age of the study subjects was 55 years (range, 52–66 yr), three were non-Hispanic white, two were non-Hispanic black, and

Online Data Supplement

Association of Electronic Cigarette Use and Asthma in Never Smokers

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Table E1. Results of the Multivariable Logistic Regression Model Showing the Association Between Current E-Cigarette Use and Asthma for Never Cigarette Smokers.

	Odds ratio	95% Confidence Interval
Never E-cigarette user	Reference	
Current E-cigarette user	1.36	1.11 - 1.68
Former E-cigarette user	1.11	1.00 - 1.23
18 to 24	Reference	
25 to 34	0.75	0.68 - 0.84
35 to 44	0.67	0.60 - 0.75
45 to 54	0.68	0.61 - 0.76
55 to 64	0.62	0.55 - 0.69
65 or older	0.46	0.41 - 0.52
Not married	Reference	
Married	0.83	0.78 - 0.88
Male	Reference	
Female	1.87	1.77 - 1.99
Body Mass Index	1.04	1.03 - 1.04
Less than \$15,000	Reference	
\$15,000 to less than \$25,000	0.87	0.78 - 0.98
\$25,000 to less than \$35,000	0.80	0.71 - 0.90
\$35,000 to less than \$50,000	0.82	0.72 - 0.93
\$50,000 or more	0.87	0.78 - 0.97
Did not graduate High School	Reference	
Graduated High School	1.08	0.93 - 1.25
Attended College or Technical School	1.23	1.06 - 1.43
Graduated from College or Technical School	1.26	1.08 - 1.46
History of heart attack	1.26	1.07 - 1.49
Currently use smokeless tobacco	0.86	0.73 - 1.02
History of diabetes	1.34	1.23 - 1.47
White only, Non-Hispanic	Reference	
Black only, Non-Hispanic	1.03	0.94 - 1.12
Other race only, Non-Hispanic	0.64	0.55 - 0.75
Multiracial, Non-Hispanic	1.60	1.32 - 1.94
Hispanic	0.69	0.62 - 0.76
History of Angina or coronary disease	1.21	1.05 - 1.41
History of stroke	1.58	1.31 - 1.92