Electronic Cigarette Use and Oral Human Papillomavirus Infection Among US Adult Population: Analysis of 2013–2016 NHANES

BACKGROUND

There has been growing public health concern of harms associated with electronic cigarettes (e-cigarette). E-cigarette use is associated with molecular changes in oral epithelium, which may be linked to oral cancer development.[1] Similar to combustible cigarette smoking, e-cigarette use could have some negative effects on the oral mucosa and may impair immune defense, increasing susceptibility to infections.[2, 3] Oral human papillomavirus, particularly type 16 (HPV-16) is thought to infect epithelial cells and induce malignant transformation inside of the mouth.[4] Smoking increases the risk of HPV infection; however, whether e-cigarette use is associated with oral HPV infection is unknown. We examined the association between e-cigarette use and oral HPV infection among the US adult population.

METHODS

This was a cross-sectional study of the National Health and Nutrition Examination Survey (NHANES). The NHANES uses a stratified multistage probability sample design to be representative of the US population.[5] This study used data from the 2013–2016 NHANES with a response rate of 63.6% and included 9266 participants aged 18 to 69 years with complete oral HPV DNA testing and tobacco use data. A detailed description of the data collection is available elsewhere.[5] Briefly, participants' oral rinse samples were collected at a mobile examination center and analyzed for 37 types of HPV using the Roche Linear Array HPV Genotyping tests. Participants who currently used conventional cigarette or e-cigarette in the past 30 days were considered as current users, and self-reported smoking status was categorized into four mutually exclusive groups: conventional current smokers only ($n = 1744$), e-cigarette only ($n = 163$), dual conventional cigarette and e-cigarette use ($n = 219$), or non-current smokers (never or former smokers; $n = 7140$). Self-reported sexual behaviors, HPV vaccination, other substance use, and demographic information were also included.

Multivariable logistic regression models were used to compare the predicted probability of having oral HPV infection across the four groups, while adjusting for confounding and other risk factors.[2, 6] A sensitivity analysis was performed by including conventional cigarette smoking and e-cigarette use as separate independent variables. Interactions between conventional cigarette smoking and e-cigarette use were also tested in each model. All analyses were conducted using SAS 9.4 to account for the complex NHANES design. This study was deemed exempt from review by the University of Florida institutional review board.

RESULTS

Among 9265 mobile examination participants (representing 198,122,720 US adults), 6.9% (95% CI, 6.0–7.7%) had any oral HPV and 0.9% (95% CI, 0.7–1.1%) had oral HPV-16 detected. Dual users and current smokers had a higher predicted probability of any oral HPV (9.5% and 9.2%, respectively), compared with e-cigarette users (5.6%) or non-current smokers (5.3%). The predicted probability of oral HPV-16 was highest among dual users (1.4%), followed by e-cigarette users (1.2%), current smokers (0.6%), and non-current smokers (0.4%) (Fig. 1).

When analyzing the models having conventional cigarette smoking and e-cigarette use as independent variables, current conventional smoking was associated with any oral HPV infection (OR, 1.95; 95% CI, 1.15–3.33) but not e-cigarette use ($P = 0.48$). For oral HPV-16 infection, e-cigarette use had a higher likelihood (OR, 2.95; 95% CI, 1.41–6.17) than non-users. Current smoking was not associated with oral HPV-16 ($P = 0.47$). These associations remained consistent after adjusting for other risk factors (Table 1). Interaction terms between current smoking and e-cigarette use were not significant, suggesting that the main effect of e-cigarette use on HPV-16 did not differ by concurrent cigarette smoking.
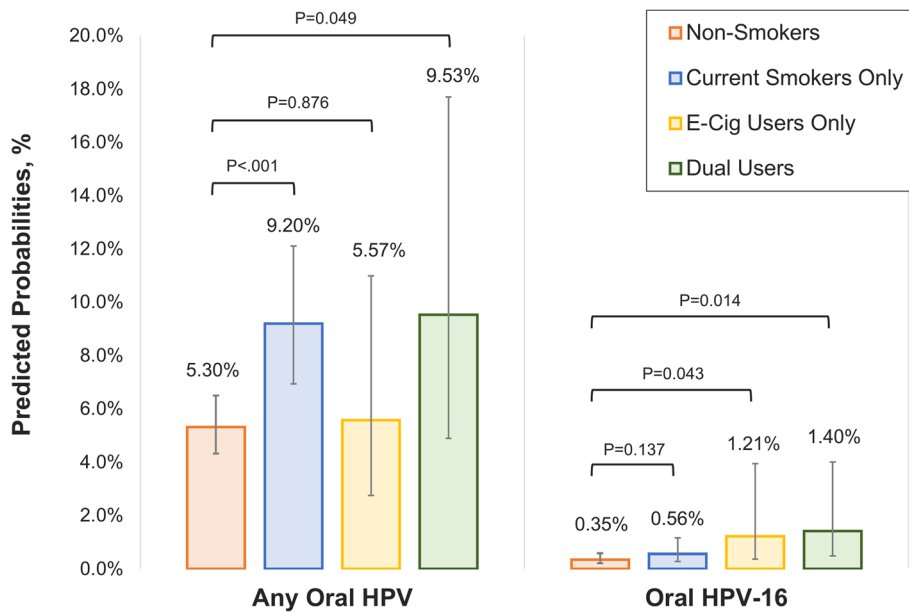
Figure 1 Predicted estimates of any oral HPV and HPV-16 infection among US adults aged 18–69 years, by smoking behaviors. Predicted estimates were calculated using multivariable logistic regression models adjusting for age (as a linear term), sex, education, marital status, marijuana use, HPV vaccination, and the number of recent oral sex partners (in the past 12 months). Important to note that estimates for dual users and e-cigarette users have a relative standard error greater than 30%. Caution is advised in interpreting these estimates.

DISCUSSION

This population-based study found a statistically significant association between e-cigarette use and oral HPV-16 infection, which was independent of conventional cigarette smoking. Dual use had increased risks for both any oral HPV and high-risk HPV-16 infections. While specific biological mechanisms that may explain these observed associations are unknown, e-cigarette use may influence DNA damage[1, 3] and make oral tissues more susceptible to a high-risk HPV genotype. HPV-16 causes more than 80% of oropharyngeal cancer cases.[4]

These results may suggest a potential role of high-risk HPV infection in the pathway between e-cigarette and oral carcinogenesis. However, long-term epidemiological studies are needed to accurately determine risks associated with e-cigarette use and subsequent progression to oral cancer. Study limitations include self-reported cigarette use, possibility of unmeasured confounding, and low prevalence of other HPV subtypes. Nevertheless, the study findings are useful for hypothesis-generating for future studies on e-cigarette use and oral cancer.

Table 1 Association of Smoking Behaviors with Any Oral HPV and HPV-16 Infections

	Any oral HPV infection				Oral HPV-16 infection			
	Crude OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value	Crude OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P* value
Conventional cigarette								
Non-users	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Current smokers	1.95 (1.15–3.33)	0.016	1.80 (1.05–3.09)	0.036	1.36 (0.58–3.22)	0.467	1.33 (0.57–3.08)	0.497
Electronic cigarette								
Non-users	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Current e-cig users	1.14 (0.79–1.64)	0.479	1.05 (0.69–1.58)	0.824	2.95 (1.41–6.17)	0.005	2.97 (1.25–7.06)	0.016
$P_{interaction}$	0.547		0.977		0.694		0.770	

Estimated from multivariable logistic models including current smoking, e-cigarette use, age, sex, education, marital status, marijuana use, HPV vaccination, the number of recent oral sex partners (in the past 12 months), and interaction terms: current smoking × e-cigarette use

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Compliance with Ethical Standards:

This study was deemed exempt from review by the University of Florida institutional review board.

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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