

Impact of Electronic Cigarettes on the Upper Aerodigestive Tract: A Comprehensive Review for Otolaryngology Providers

Joanne Soo, MD , Meena Easwaran, MS, and Elizabeth Erickson-DiRenzo, PhD 

OTO Open
 2023, Vol. 7(1):e25
 © 2023 The Authors. OTO Open
 published by Wiley Periodicals LLC
 on behalf of American Academy of
 Otolaryngology-Head and Neck
 Surgery Foundation.
 DOI: 10.1002/oto.2.25
<http://oto-open.org>
 WILEY

Abstract

Objective. The use and effects of electronic (e)-cigarettes (e-cigs) are particularly relevant for otolaryngology providers as tobacco plays a major role in benign and malignant diseases of the upper aerodigestive tract. This review aims to (1) summarize the recent policies regarding e-cigs and important patterns of use and (2) serve as a comprehensive resource for clinical providers on the known biologic and clinical effects of e-cigs on the upper aerodigestive tract.

Data Sources. PubMed/MEDLINE.

Review Methods. We conducted a narrative review on (1) general information on e-cig use and informative findings in the lower respiratory system and a comprehensive review on (2) the effects of e-cigs on cell and animal models and the clinical implications of these products on human health as is relevant to otolaryngology.

Conclusions. Although e-cigs are likely less harmful than conventional cigarettes, preliminary research on e-cigs suggest several deleterious effects including in the upper aerodigestive tract. Due to this, there has been increased interest in restricting e-cig usage, particularly among the adolescent population, and caution in recommending e-cigs to current smokers.

Implications for Practice. Chronic e-cig use is likely to have clinical implications. It is critical for otolaryngology providers to be aware of the rapidly changing regulations and use patterns regarding e-cigs and how e-cigs influence human health, particularly with regards to the upper aerodigestive tract, to accurately counsel patients regarding potential risks and benefits of use.

Keywords

aerodigestive, e-cigarettes (e-cigs), electronic nicotine delivery systems, head and neck, otolaryngology, vaping

Received October 11, 2022; accepted December 2, 2022.

Tobacco has been implicated in 70% to 80% of head and neck malignancies^{1,2} as well as benign diseases of the head and neck.³ The morbidity of tobacco-related head and neck disorders is immense; patients are often left with deficits in voice and articulation, dysphagia, and disfigurement. There are over 60 well-established carcinogens in tobacco^{4,5} and a number of toxins, including ones not seen in combustible cigarettes, have been also found in electronic (e)-cigarettes (e-cigs).^{6,7}

In response to the rapid rise in youth nicotine use as a result of e-cigs,⁸ also known as electronic nicotine delivery systems, as well as growing evidence of the substantial harm of e-cigs, numerous government agencies have initiated policies to reduce the incidence of nicotine addiction including the banning of many flavors in “cartridge-based” products as well as imposing limitations on nicotine content.⁹⁻¹³ Nevertheless, the prevalence of e-cig use remains high,¹⁴ in large part due to the exemption of disposable e-cigs and flavor enhancers from these policies.¹⁵ The growing use of e-cigs has prompted a commensurate increase in research on their effects. On PubMed alone, the number of published articles on e-cigs has increased from 372 in 2014 to 1132 in 2021 and there are hundreds of review papers on various aspects of e-cig use. Significant headway has been made in assessing the effect of e-cig components on the respiratory and cardiovascular systems,¹⁶⁻²² and the number of studies exploring the effects of e-cigs on other organ systems has also recently grown.²³⁻⁴⁶

Despite the increase in research on the effect of e-cigs on cellular biology and human health, reports on e-cigs as they directly pertain to the upper aerodigestive tract remain limited, particularly for benign disorders. Furthermore, the

Department of Otolaryngology-Head & Neck Surgery, Stanford University School of Medicine, Stanford, California, USA

Corresponding Author:

Elizabeth Erickson-DiRenzo, PhD, Department of Otolaryngology-Head & Neck Surgery, Stanford University School of Medicine, 801 Welch Road, Palo Alto, CA 94304, USA.
 Email: edirenzo@stanford.edu

current rate of relevant research on e-cigs outpaces the ability of most practicing clinical providers to review. To provide a comprehensive review of e-cigs as it is most relevant for providers who manage the upper aerodigestive tract, the review serves two main objectives. First, we provide a broad overview on the latest policies regarding e-cigs, patterns of use in the general and adolescent populations, and highlight important insights on e-cigs from the lower respiratory system. Second, we detail the current findings on the effects of e-cigs on preclinical models and clinical outcomes in otolaryngology and identify areas and topics that require further research.

Methods

To address our two distinct goals of (1) providing a broad up-to-date overview of e-cigs and (2) comprehensively reviewing the direct impact of e-cigs on the upper aerodigestive tract, we performed our review in two phases.

To address our first goal, we evaluated recent statements and resources regarding e-cigs from the CDC, FDA, and the AAO-HNS to determine which topics would be of greatest interest and relevance to the otolaryngology practitioner. Based on these, we decided to include in the review information regarding regulatory policies, use patterns, toxicities, and major known biological effects on human health. We then searched PubMed and Ovid Medline for articles published on e-cigarettes in the last 10 years related to these topics. We additionally searched Google for rulings, policy statements, and news reports regarding e-cigs.

Subsequently, to provide a comprehensive review of preclinical and clinical studies pertaining specifically to the upper aerodigestive tract and address our second goal, we performed a structured review of the preclinical and clinical studies by using a combination of the following search terms: e-cigarette and/or otolaryngology and/or ENT and/or head and neck and/or oral and/or mouth and/or hypopharynx and/or oropharynx and/or nasal and/or nose and/or sinus and/or larynx and/or throat and/or voice and/or ear and/or otology. In addition, the reference lists of selected articles as well as review papers resulting from these searches were evaluated for additional studies not originally found. We included all primary literature that utilized cells, animal models, or clinical samples to evaluate the biological effects of e-cigs in the upper aerodigestive tract. Studies were excluded if one of the following applied: not available in English, did not contain original data, or aims not relevant to biologic consequences of e-cigs on the upper aerodigestive tract or ear (eg, articles assessing perceptions, policy, behavior, bronchial effects) including studies specific to dental health. All searches were performed in September 2021. Further details regarding searches conducted for goal 1 and goal 2 can be found in Supplemental Tables 1 and 2 and Figure 1, available online.

Discussion

Part One: Overview of E-cigarettes

History and Marketing of E-cigs

E-cigs and other vaping products work by heating nicotine-containing “e-juice” or “e-liquid” into an aerosol which is inhaled by the user. E-juice is primarily made up of glycerin and propylene glycol into which nicotine, flavoring, and a range of other minor components are dissolved. These products not only go by several names but also come in a wide range of shapes and sizes (**Figure 1A**). Early “cig-a-likes,” introduced to the US market in 2006, simulated the size and shape of conventional cigarettes. Subsequently, cartridge/pod devices became more popular, particularly with the introduction of JUUL in 2015. Over the last few years, partially in response to government regulation on pod devices such as JUUL, disposables (eg, Puff Bar), and high-powered advanced personal vaporizers or MODs have seen a dramatic increase in use.^{47,48}

E-cigs are produced by both startup companies as well as major international tobacco companies and have been marketed as being different from conventional cigarettes, including with claims that e-cigs are safe and benign.⁴⁹ The perception among the general public is that e-cigs use results in limited or no health consequences,⁵⁰⁻⁵³ particularly flavored e-cigs.⁵⁴

Toxic Constituents in E-cigs

Tobacco is known to have over 60 well-described carcinogenic agents and hundreds more under study.^{4,5} Although e-juice has fewer known carcinogens as compared to combustible cigarettes, studies have proven the presence of toxic constituents in e-cigs.^{55,56} These constituents include but are not limited to carbonyl compounds,⁵⁷ thiocyanate,⁵⁸ heavy metals,^{7,59,60} silicate particles,⁶⁰ diacetyl,⁶¹ and the known carcinogens formaldehyde^{62,63} and *N*-nitrosornicotine^{56,64} (**Figure 1B**). Many of these components of e-cigs come from the flavoring additives or devices themselves and thus vary widely between products.⁶⁵⁻⁷¹ Several of these toxins have not been notably associated with traditional cigarette smoke. Bystanders can also be exposed to toxins in secondhand and thirdhand smoke from e-cigs.⁷²⁻⁷⁵

Regulation of E-cigs

The largest concern regarding e-cigs is the rise in new smokers, particularly adolescents, and relapsed former-smokers.^{8,76-79} Once addicted to nicotine via e-cigs, many adolescents explore other tobacco products and are more likely to use traditional combustible cigarettes.⁸⁰⁻⁸² Due to the increased prevalence of e-cig use, there has been progress in regulatory oversight for e-cigs including the banning of many flavors in pods by the FDA^{9,10} and capping of nicotine at 20 mg/mL in Europe.¹¹ Most recently, the FDA has denied market authorization to the largest cartridge-based producer, JUUL,¹² though this

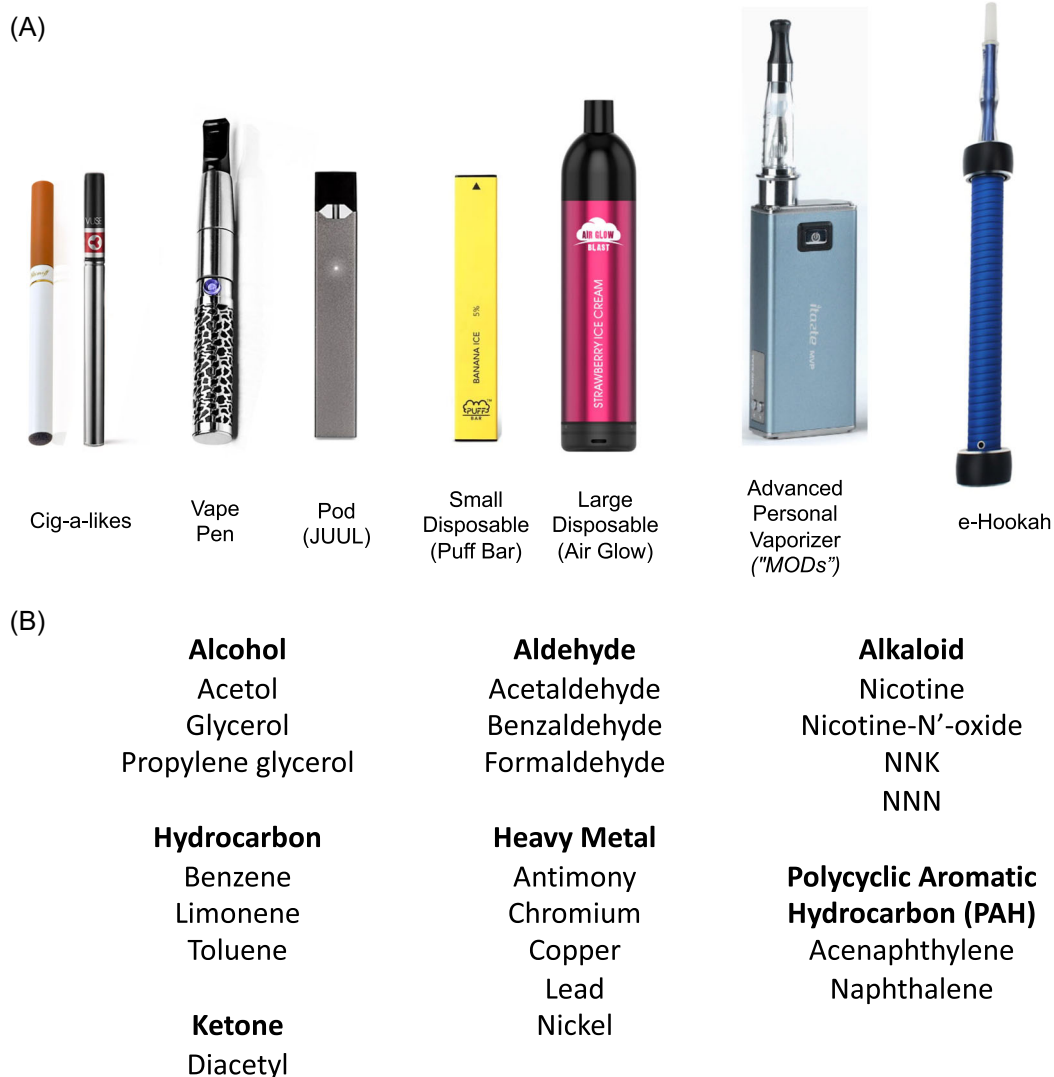


Figure 1. Common e-cigarette (e-cig) products and associated toxins. Representation of the (A) range of popular e-cig devices and (B) known toxins found in e-cigs.

has been stalled by a federal appeals court.¹³ Nevertheless, many methods including disposable and refillable e-cigs remain largely unregulated.¹⁵ There is no production standard among manufacturers and thus the contents and potential toxicities can vary widely.⁵⁵⁻⁷¹ Furthermore, users are increasingly creating their own device modifications, many of which pose an increased risk for elevated nicotine and carcinogen consumption and combustion.⁸³⁻⁹⁴

Evaluating Patterns of Use

E-cigs now make up the majority of nicotine use in teenagers and young adults⁹⁵ and the largest portion of non-cigarette or cigar use in older adults.⁹⁶ In order to adequately counsel at-risk patients about e-cigs, medical providers rely on patients' self-reported nicotine use. Studies have shown that the majority of users of alternative nicotine products including e-cigs will answer

“no” if asked about a smoking history but will affirm use of a particular alternative product when asked specifically.^{97,98} While e-cigs make up the largest share of alternative nicotine product use, there is a wide range of both traditional and modern alternative nicotine products including heated tobacco (HT) and oral nicotine products (ONP) (Figure 2).⁹⁹⁻¹⁰¹ Use patterns also vary based on nationality and culture.^{102,103} It is important, then, to ask about specific forms of tobacco consumption, both inhaled and smokeless, when assessing a patient's tobacco history. This is relevant for assessing both disease and surgical risk; an association with e-cig exposure and poor wound healing and flap failure has been reported in both animal models and surgical patients.^{97,104-111} Unfortunately, due to the variable nicotine content of e-cig products, it can be difficult to obtain a quantitative estimate of usage (ie, pack year equivalent).

Common Alternative Nicotine Products

Category	Possible Products and Alternative Names
Combustible Tobacco	Cigarette Bidi Kretek Cigar Cigarillo Pipe
Heated Tobacco	Heat-not-burn
E-cigarette	Vape Pod E-hookah Tank Electronic nicotine delivery system (ENDS)
Waterpipe	Hookah Shisha
Oral Tobacco	Chewing tobacco SNUS Snuff Paan Beta Quid Gutkha Lozenge Orb Toothpick/Stick Strip Pouches

Figure 2. Range of alternative nicotine products. Patients who use alternative forms of nicotine, such as those listed, often deny a smoking history but will report use when asked about specific methods of consumption.

E-cigs for Current Smokers: Weighing Benefits Against Risk of Dual Usage

One popularly cited benefit of e-cigs use is that they can reduce or eliminate the use of traditional cigarettes in current smokers. This potential benefit is the main reported driving factor for increased e-cig use among cancer patients.¹¹² There is indeed evidence that e-cigs are not as harmful as conventional cigarettes.¹¹³⁻¹¹⁶ However, the clinical impact of e-cig use in current smokers is complicated by additional factors. Although e-cig use has been shown to modestly reduce cigarette consumption,¹¹⁷⁻¹²⁷ about 40% to 50% of smokers who do try e-cigs become “dual-users” who continue to smoke cigarettes but use e-cigs in places smoking is prohibited, thus facilitating their addiction.¹²⁸⁻¹³² Dual users often have a higher consumption of nicotine and toxic byproducts and lower rates of smoking cessation.^{122,133,134} Furthermore, a large portion of e-cig users believe they are not addicted to nicotine despite regular use^{52,135} which can limit motivation to quit. Therefore, while e-cigs may be a useful tool for harm reduction in current smokers who are unwilling to otherwise reduce the use of combustible cigarettes or have failed other forms of smoking cessation, care should be taken to caution these patients about the risk of dual usage. This is reflected in the position statement by the AAO-HNS regarding e-cigs.¹³⁶

Biological Impact of E-cigarettes: Insights from the Lower Respiratory System

E-cigs have been studied extensively with regards to the lower respiratory system. Components of e-cig aerosol have been shown to cause oxidative damage,¹³⁷⁻¹³⁹ DNA breaks,¹⁴⁰ and inhibit DNA repair^{6,141} in human-derived lung cells which theoretically could lead to the development of oncogenic mutations (**Figure 3A**), though the effect size of mutagenic activity from e-cigs is still unclear.^{142,143} Several studies in lung-derived cell lines demonstrate that e-cig vapor results in gene expression changes similar to cigarette smoke and increases the risk of malignant transformation and metastasis.^{6,141,144,145} E-cigs have also been shown to cause mitochondrial dysfunction,^{140,146} alter the cellular metabolome and proteome,¹⁴⁷⁻¹⁴⁹ and reduce cellular viability,^{150,151} indicating that e-cigs may not only increase the risk of cancer but also lead to the development of benign disorders. Finally, e-juice and e-cig aerosols have been demonstrated to potentially increase the risk of infection by promoting inflammation while reducing innate immune activity and the production of antimicrobial proteins.¹⁵²⁻¹⁵⁴

The effect e-cigs have on cellular and tissue function has been confirmed in organoid and animal models (**Figure 3B**). Exposure to e-cig aerosol and e-juice has

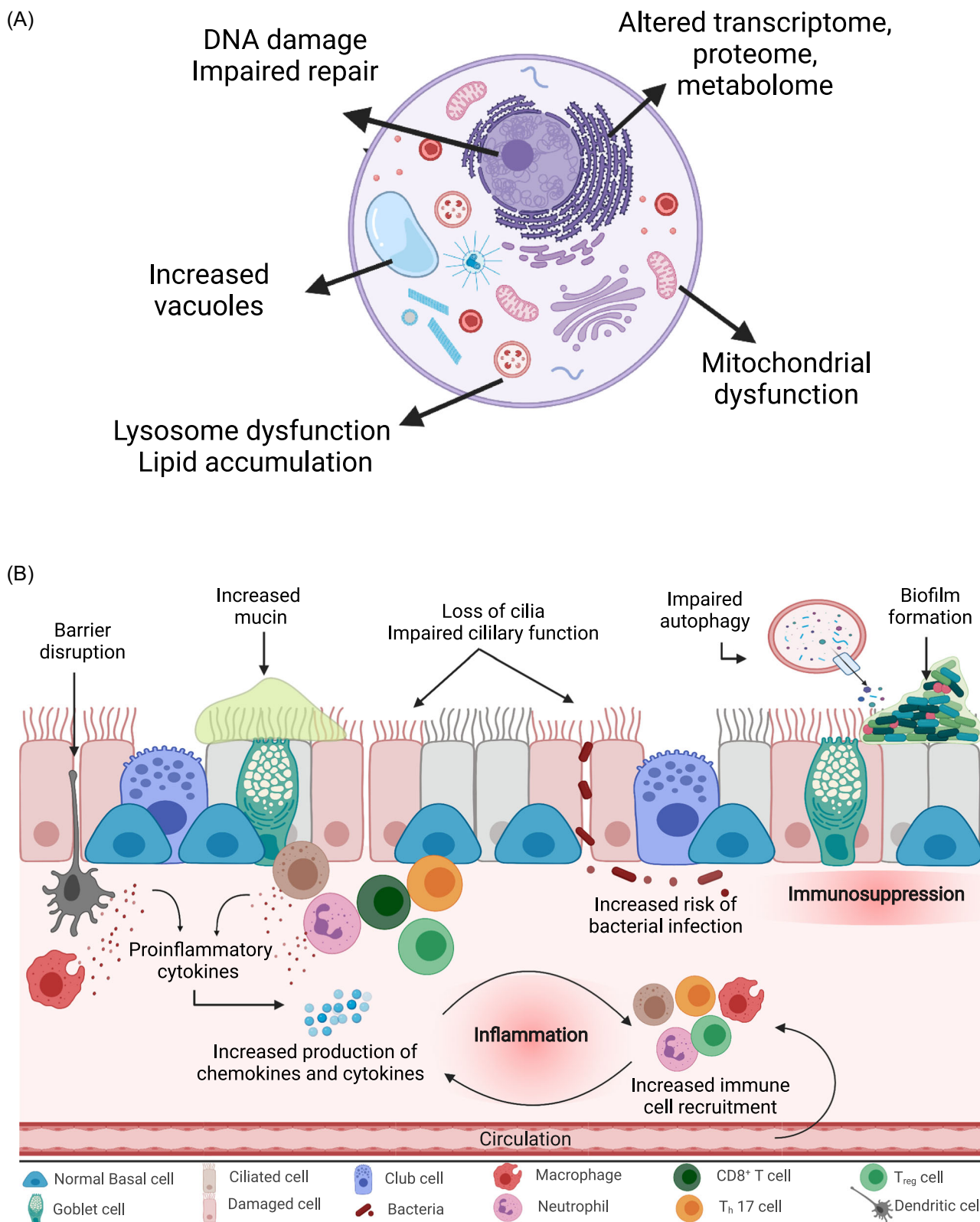


Figure 3. Cellular toxicity from e-cigarettes (e-cigs). (A) Example of pathways through which e-cigs cause cytotoxicity. (B) Changes noted cell and animal models after e-juice and e-cig aerosol exposure.

been shown to cause a wide variety of biological changes in the airway including increased production and decreased clearance of mucin,¹⁵⁵⁻¹⁵⁷ reduction in ciliary function,^{157,158} increase in cytokines,¹⁵³ and impaired

immune cell function.^{154,159} In respiratory models, e-cigs have additionally been shown to increase alveolar-capillary barrier permeability¹⁶⁰ and increase airway hyperreactivity.^{156,157} Finally, early data in mouse lung

models demonstrates that prolonged e-cig exposure can directly induce malignancy.¹⁶¹

Clinically, e-cigs have been shown to directly impact lower airway epithelial cells in a similar manner as conventional cigarettes resulting in functional changes such as increased airway resistance and airway obstruction, symptomatic immune suppression, mucin production, irritation and inflammation, and lung disease exacerbation.^{16,21,22,162,163} While the risk of cancer in e-cig users has not been fully studied due to the relatively short time e-cigs have been on the market, preliminary experimental in vivo human data has demonstrated epigenetic changes in the airway after even brief e-cig aerosol exposure including changes in the p53 pathway.¹⁶⁴ In addition, over 2600 cases of e-cig or vaping product use associated lung injury have been reported secondary to vaping in the United States alone,^{18,19} largely due to the presence of vitamin E acetate in aerosolized cannabis oils.¹⁶⁵

Part Two: Biological and Clinical Endpoints in the Upper Aerodigestive Tract

Basic Research on E-cigs in Otolaryngology

Several studies have evaluated the effect of e-cigs in cell, organoid, and animal models of the upper aerodigestive tract (**Table 1**). The largest volume of primary literature on the effects of e-cigs on the upper aerodigestive tract is in relation to oral and dental health.^{26-29,166-169} As expected, e-cigs do not appear to be as harmful as conventional cigarette smoke in cell and animal models.^{170,171} Nevertheless, numerous studies have demonstrated biological disruption as a result of even brief e-cig exposure.²⁹ Liquid nicotine has been shown to promote the migration of dysplastic oral keratinocytes, suggesting a contribution of nicotine alone to oral carcinogenesis.^{172,173} In the larynx, rats exposed to e-cig aerosols showed early evidence of hyperplasia and metaplasia of the mucosa,¹⁷⁴ although the results were not statistically significant in this limited study, and increases in IL-4.¹⁷⁵ In addition, both nicotine-containing and nicotine-free e-juice have been found to cause biologic disruptions including oxidative stress, DNA breakage, metanuclear anomalies, liposomal dysfunction, and solvent and lipid accumulation, and cytotoxicity in human gingival fibroblasts,^{67,176-180} vocal fold epithelial cells and fibroblasts,^{181,182} head and neck squamous cell carcinoma cell lines,^{67,183-185} noncancerous oral and oropharyngeal epithelial cells,^{139,178,186-192} middle ear epithelial cells,¹⁹³⁻¹⁹⁵ nasal epithelial cells,^{196,197} and organotypic cultures/organoids.^{178,182,197} Interestingly, a recent study found that oral cancer cells exposed to e-cig aerosols increased cell resistance to cisplatin through changes in drug transporters, suggesting a mechanism for e-cig-induced chemotherapy resistance.¹⁹⁸ Therefore, the potential mutagenic and functional effects of e-cigs and

other noncombustible nicotine products on various cell types throughout the head and neck should not be underestimated.

Translational Research on E-cigs in Otolaryngology

A smaller number of studies have looked at the effects of e-cigs in human users (**Table 2**). In a preliminary study looking at the oral transcriptome of e-cig users and cigarette smokers as compared to nonsmokers, e-cig users showed a disruption of multiple molecular pathways that have been implicated in carcinogenesis, many of which overlapped with smokers but some of which were unique.¹⁹⁹ Consistent with previous research in cells, an increase in inflammatory markers and changes in the gene expression and metabolome can be detected from saliva and mucosa collected from e-cig users compared to nonsmokers.^{200,201} Another study found evidence of inflammation and immune suppression in the oral mucosa of e-cig users¹⁸⁵ which is consistent with separate studies with similar findings in the nasal mucosa.^{202,203} Finally, analysis of the saliva of e-cig users has revealed the presence of carcinogens,^{58,64} metanuclear abnormalities in oral cells,²⁰⁴ changes in antimicrobial properties,²⁰⁵ and possibly the oral microbiome.^{185,206} The generalizability and clinical applicability of these results will become more evident as additional studies are performed.

Clinical Research on E-cigs in Otolaryngology

E-cig use has also been associated with a wide range of self-reported upper aerodigestive symptoms including throat irritation and discomfort, cough, tongue pain, nasal congestion, and sinus infections.^{53,207-217} Although research on the effects of e-cigs on human oral, oropharyngeal, and laryngeal health is still in its early stages, findings thus far are consistent with effects of e-cigs in other organ systems and include immune suppression and inflammation (**Table 3**). Due to their effect on the immune system and oral microbiome, e-cigs may additionally promote the risk of oral infection.²¹⁸ Consistent with this, are multiple reports of inflammatory and infectious processes in the mouth and throat including uvulitis and epiglottitis which appear to be secondary to e-cig use,^{219,220} although interestingly there is a single case study reporting resolution of recurrent tonsillitis in a nonsmoker after e-cig use.²²¹ Finally, there are multiple reports of gingival and dental disease resulting from e-cig use.^{26-29,209,222-224}

A few studies have demonstrated an increase in mucosal lesions in e-cig users as compared to controls and former smokers.²²⁵⁻²²⁷ Two case studies have linked necrotic palatal ulcers with e-cig use.^{228,229} Importantly, multiple cases of oral carcinoma in the setting of prolonged e-cig use in the absence of other risk factors have been reported.^{230,231} Aside from effects of the toxic and carcinogenic contents of aerosolized e-juice on the

Table 1. Primary Studies on the Effects of E-Cigarettes on the Upper Aerodigestive Tract and Ear in Cell and Animal Models

References	Subject of interest	Study design	Exposure time (method)	Outcome(s)
Alanazi et al ¹⁷⁷	Primary human gingival fibroblasts	Ex vivo	1 hour a day for 1, 3, 5, and 7 days (extract in media)	Changes in morphology, decreased viability, increased apoptosis, delayed migration/wound closure
Carson et al ¹⁹⁷	Primary human nasal epithelial cell 3D model	Ex vivo	100 seconds (puffs over air-liquid interface)	Reduction in ciliary beat frequency, development of fibrillar mesh-like debris
Duggar et al ¹⁸⁷	Oral keratinocytes	In vitro	24 hours a day for 1, 2, and 3 days (extract in media)	Decreased growth, increase in cytotoxin expression
Ganapathy et al ¹³⁹	Human oral keratinocyte cell line (POE9n), human oral SCC cell line (UM-SCC-1)	In vitro	1 hour every other day for 2 weeks (extract in media)	Increased oxidative DNA damage
Go et al ¹⁸⁵	Human middle ear epithelial cell line (HMEEC)	In vitro	24 hours (extract in media)	Decreased viability, increased autophagy and apoptosis, increased cytokines, increased mucin production, dysregulation of water channels
Ha et al ¹⁷⁵	Murine model (C57BL/6)	In vivo	31 minutes and 40 seconds a day, 5 days a week, for 16 weeks (whole body chamber)	Differential inflammatory cytotoxin levels
Iskandar et al ¹⁷⁰	Human buccal epithelial (EpiOral) 3D model	In vitro	28 minutes (puffs over culture)	No significant histopathologic changes, significant differential gene expression (especially inflammatory pathways)
Ji et al ¹⁸⁸	Human oral epithelial cell line (NHOK)	In vitro	24 hours (extract in media)	Increased cytotoxicity, increased oxidative stress
Ji et al ¹⁸⁹	Human oral epithelial cell line (NHOK)	In vitro	4 hours (extract in media)	Differential gene expression (especially unfolded protein response)
Lungova et al ¹⁸²	Human induced pluripotent stem cell (hiPSC) —derived engineered vocal fold mucosae	In vitro	24 hours a day for 7 days (extract in media)	Changes in mucosal structure, increased mucin clots, dysregulated cytokine production, lipid deposition within cytoplasm and intercellular spaces causing epithelial injury and remodeling
Martinez et al ¹⁸¹	Human vocal fold fibroblast cell line (hVFF)	In vitro	24 hours (extract in media)	Increased cytotoxicity, no significant differences in gene expression
Manyanga et al ¹⁹⁸	Human oral and pharyngeal epithelial cell lines (UM-SCC-1, WSU-HN6, WSU-HN30)	In vitro	24 hours a day for 2 and 4 days (extract in media)	Increased viability in setting of cisplatin exposure due to increased cisplatin resistance
Pushalkar et al ¹⁸⁵	Human hypopharyngeal SCC (FaDu) and leukoplakia (MSK-Leuk-1) cell lines	In vitro	40 minutes (puffed over culture)	Increased inflammatory cytokines in setting of infection, increased infection efficiency
Rouabhia et al ¹⁹⁰	Primary human gingival epithelial cells	Ex vivo	15 minutes a day for 1, 2, and 3 days (puffs over culture)	Change in morphology, increased apoptosis, increased DNA fragmentation
Rouabhia et al ¹⁹⁶	Primary human nasal epithelial cells and 3D model	Ex vivo	15 minutes twice a day for 1, 2, and 3 days (puffs over culture)	Changes in morphology, decreased viability, changes in mucosal structure, increased inflammatory cytokines
Sancilio et al ¹⁷⁶	Primary human gingival fibroblasts	Ex vivo	6 and 24 hours a day for 1, 2, and 3 days (extract in media)	Changes in morphology, decreased viability, increased apoptosis, increased ROS formation

(continued)

Table 1. (continued)

References	Subject of interest	Study design	Exposure time (method)	Outcome(s)
Sancilio et al ¹⁷⁹	Primary human gingival fibroblasts	Ex vivo	3 and 24 hours a day for 1 and 2 days (extract in media)	Changes in morphology, increased cytotoxicity, changes in collagen release, increase in lysosomes, increased LC3 IIB/LC3 expression
Salturk et al ¹⁷⁴	Murine model (Wistar albino, female)	In vivo	60 minutes a day for 4 weeks (whole body chamber)	Nonsignificant trend toward increased squamous metaplasia and hyperplasia, no difference in Ki67 expression
Song et al ¹⁹³	Human middle ear epithelial cell line (HMEEC-1)	In vitro	24 hours (extract in media)	Decreased viability
Song et al ¹⁹⁴	Human middle ear epithelial cell line (HMEEC-1)	In vitro	24 hours (extract in media)	Decreased viability, increased inflammatory cytokines, differential gene expression
Sun et al ¹⁹¹	Human oral leukoplakia cell line (MSK-Leuk1)	In vitro	16 hours (extract in media)	Increased metabolism of polycyclic aromatic hydrocarbons to genotoxic products
Sundar et al ¹⁷⁸	Human gingival epithelium cell line (HGEPP) and 3D model (EpiGingival)	In vitro	15 minutes (puffed over culture)	Increased protein carbonylation, increased inflammatory cytokines, increased DNA damage
Tellez et al ¹⁸⁶	Human oral epithelial (MOE1A, MOE1B) and leukoplakia (MSK-Leuk1) cell lines	In vitro	20 minutes (puffed over culture)	Increased cytotoxicity, increased DNA damage
Tsai et al ¹⁸⁴	Human oral SCC cell lines (Ca9-22, CAL-27)	In vitro	24 hours (extract in media)	Altered cell invasion, increased RAGE expression, differential cytokine expression
Ureña et al ⁶⁷	Human oral SCC (SCC-25) and gingival fibroblast cell lines (HGF-1)	In vitro	3 minutes total—1 minute every 3 hours (puffed over culture)	Decreased viability, increased oxidative stress
Vermehren et al ¹⁸⁰	Human gingival fibroblast cell line (HFIB-G)	In vitro	15 minutes (puffed over culture)	Decreased proliferation, increased metabolic activity, no significant difference in apoptosis or ROS formation
Welz et al ¹⁹²	Primary human pharyngeal organoid	Ex vivo	24 and 2.5 hours per day for 5 days (extract in media)	Increased cytotoxicity, increased DNA fragmentation
Yu et al ¹⁸³	Human oral SCC cell lines (HN30, UMSSC10B)	In vitro	24 hours a day for 1 week (extract in media)	Increased DNA strand breaks, increased cell arrest, increased apoptosis and necrosis

Table 2. Primary Studies on the Biologic Effects of E-Cigarettes on the Upper Aerodigestive Tract and Ear in Human E-Cig Users

References	Subject of interest	Study design	Number of e-cig users	Outcome(s)
Alqahtani et al ²⁰⁰	Saliva	Cross-sectional	14	Elevated inflammatory cytokines, differential expression of metabolites
Bustamante et al ⁶⁴	Saliva	Cross-sectional	16	Elevated levels of carcinogen N'-nitrosonornicotine (NNN)
Cichońska et al ²⁰⁵	Saliva	Cross-sectional	40	Decreased lysozyme and increased lactoferrin, no difference in IgA
Flieger et al ⁵⁸	Saliva	Cross-sectional	8	Elevated levels of thiocyanate
Franco et al ¹⁷¹	Oral epithelial cells	Cross-sectional	22	No significant increase in micronuclei
Hamad et al ²⁰¹	Buccal cells and blood	Self-controlled	3	Differential gene expression
Martin et al ²⁰²	Nasal epithelial cells	Cross-sectional	12	Differential gene expression (especially suppression of immune-related genes)
Pushalkar et al ¹⁸⁵	Saliva	Cross-sectional	40	Altered oral microbiome, nonsignificant but considerable alterations in inflammatory cytokines
Rebuli et al ²⁰³	Nasal epithelial cell	Clinical trial	15	Suppression of IgA in setting of viral inoculation, differential gene expression, differential cytokine levels
Schwarzmeier et al ²⁰⁴	Oral epithelial cells	Cross-sectional	20	Increased metanuclear abnormalities
Stewart et al ²⁰⁶	Saliva and buccal swab	Cross-sectional	10	No significant differences in oral microbiome
Tommasi et al ¹⁹⁹	Oral epithelial cells	Cross-sectional	42	Differential gene expression

upper aerodigestive tract, e-cig devices have also been implicated in multiple reports of burns and trauma of the upper aerodigestive tract and maxillofacial structures^{83-94,232,233} and toxic ingestion.²³⁴⁻²³⁷

Studies pertaining to the clinical effect of e-cigs on the larynx and ear are particularly limited. One study evaluating acoustic voice changes in e-cig users found no significant difference between e-cig users and controls, however this study was limited by the small cohort size, short duration of e-cig use (1-3 years), and explicit exclusion of laryngeal pathologies for which cigarette and e-cig exposure is known to be a significant risk factor such laryngeal inflammation and irritation.²³⁸ A second limited study also showed no change in acoustic measures between e-cig users and nonsmokers but did find significant reduction in the vocal fold mucosal wave, irregularity of the free vocal fold edge, and abnormal phase closure as evaluated by videostroboscopy.²³⁹ While traditional cigarette smoke has been implicated in a number of otologic disorders,²⁴⁰ there is currently only one report regarding a case of sudden sensorineural hearing loss after ingestion of e-juice²⁴¹ with regards to the clinical effect of e-cigs on the ear.

Future Directions

Although there has been an exponential rise in basic and translational work regarding e-cigs in multiple organ systems, there are fewer studies pertaining specifically to the upper aerodigestive tract. Meta-analyses on existing studies are needed but complicated by significant variations between and within studies in e-cig brands, devices, and flavors used; exposure method; extract concentrations; and exposure durations; among other factors. Furthermore, the potential long-term health consequences remain unknown; many consequences of cigarette smoking develop only after chronic use, and no current laboratory experiment can truly emulate decades of exposure. Even less is known about other alternative nicotine products including HTs and ONPs, which have been gaining market share and will likely play an increasing role in tobacco- and nicotine-associated health concerns. While e-cigs appear less carcinogenic than conventional cigarettes, the data thus far suggests a negative impact of e-cigs across multiple organ systems including the upper aerodigestive tract. Given the outsized impact of smoking on diseases in otolaryngology, further work on e-cigs and other alternative nicotine products is urgently needed.

Researchers in otolaryngology can benefit from building upon the research performed in models of other organ systems, particularly the lower respiratory system, to determine how e-cig exposure interacts with the unique anatomy, physiology, and function of the various areas of the head and neck. In addition, the current reports on clinical diseases in e-cig users pertaining to the upper aerodigestive tract are largely

Table 3. Primary Studies on Clinical Symptoms and Findings in Patients Who Report E-Cig Usage

References	Study design	Number of e-cig users	Outcomes(s)
Andresen et al ²³³	Case report	1	Fall with e-cig in mouth resulting in pharyngeal and esophageal burns, diffuse supraglottic edema requiring tracheostomy and long-term percutaneous feeding
Bardellini et al ²²⁵	Case-control	45	Similar total prevalence of oral mucosal lesions in e-cig users compared to former smokers; increase in nicotine stomatitis, hairy tongue, and angular cheilitis compared to former smokers
Bartram et al ²²⁶	Case report	1	Lichenoid eruption after switching from cigarettes to e-cig with high propylene glycol content with near-resolution after switching to e-cig with low propylene glycol content
Bozzella et al ²²⁰	Case report	1	Epiglottitis in e-cig user without other risk factors or identifiable etiology; focal erosions/ulcerations and reactive/inflammatory changes on biopsy of arytenoid, soft palate, tongue
Brooks et al ⁹⁰	Case report	1	E-cig explosion resulting in extensive intraoral and facial injuries
Brownson et al ⁸⁵	Case series	15	E-cig explosion resulting in flame burns, chemical burns, and blast injuries
Cant et al ²²⁹	Case report	1	Necrotic palatal ulcer in setting of e-cig use
Cason et al ⁹¹	Case report	1	E-cig explosion resulted in extensive intraoral and facial injuries and inhalational injuries
Chen et al ²¹⁵	Observational	138,448	Wide range of self-reported symptoms from e-cig users, most commonly related to the respiratory system and mouth
Cho et al ²⁰⁹	Cross-sectional	216	Adolescent daily e-cig users report increased rate of oral pain and dental concerns compared to never users
Demir et al ²⁴¹	Case report	1	Pediatric sudden sensorineural hearing loss after accidental ingestion of e-liquid
Farinha et al ²²⁷	Case report	1	Lingua villosa nigra after switching from cigarettes to e-cig and resolution after switching back to cigarettes
Farsalinos et al ⁵³	Observational	19,414	Wide range of self-reported symptoms from e-cig users, most commonly sore/dry mouth and throat
Frossard et al ²¹⁹	Case report	1	Acute uvulitis after e-cig use without other risk factors or known etiology requiring intubation
Gill et al ²³⁵	Case report	1	Accidental ingestion of e-liquid resulting in nicotine poisoning
Harrison et al ⁸⁸	Case report	1	E-cig explosion resulting in extensive intraoral injuries
Huilgol et al ²²²	Cross-sectional	4957	Self-reported daily e-cig use associated with poor oral health compared to intermittent or no use
Hua et al ²⁰⁷	Observational	481	Wide range of self-reported symptoms from e-cig users, most commonly related to the respiratory system and mouth/throat
Hua et al ²⁰⁸	Observational	NA (41,216 posts)	Wide range of self-reported symptoms from e-cig users, most commonly related to the neurologic and respiratory symptoms and mouth/throat
Hughes et al ²³⁶	Observational	256	Of 256 calls to a poison center regarding e-cigs, majority involved children and the refill containers or fluid. Of pediatric patients who ingested e-liquid, initial symptoms present in 32%
Jankowski et al ²¹⁶	Observational	61	Wide range of self-reported symptoms from e-cig users, most commonly cough and sore throat
King et al ²¹⁰	Observational	1624	Wide range of self-reported symptoms from e-cig users, most commonly cough and dry/irritated mouth/throat
Klawinski et al ²³¹	Case report	1	Stage IV SCC in 19-year-old with no other risk factors
Kumral et al ²¹¹	Randomized control	42	SNOT-22 scores worse in patients who used e-cigs to quit smoking than those who quit without the use of e-cigs
Kumetz et al ⁹²	Case series	2	E-cig explosion resulting in extensive intraoral injury and burns

Table 3. (continued)

References	Study design	Number of e-cig users	Outcomes(s)
Li et al ²¹³	Cross-sectional	641	Adult e-cig users have increased wheezing and related respiratory symptoms compared to nonusers but less than current smokers
Luo et al ²¹⁴	Observational	NA (7927 posts)	Wide range of self-reported symptoms from e-cig users, most commonly respiratory and throat symptoms
Miler et al ²²¹	Case report	1	Resolution of chronic tonsillitis in a never-smoker after vaping
Mokeem et al ²¹⁸	Cross-sectional	30	Oral <i>Candida albicans</i> burden in e-cig users is significantly higher than never-smokers and similar to cigarette and waterpipe smokers
Moore et al ⁹³	Case report	1	E-cig explosion resulting in intraoral injuries
Morse et al ⁸⁴	Case report	1	E-cig explosion result in extensive oropharyngeal and palatal burns and associated right ear pain requiring intubation, Dobhoff tube, right SLN blocks, and extensive swallow and speech therapy
Nguyen et al ²³⁰	Case series	2	Oral basaloid SCC in two patients with no other risk factors
Norii et al ⁹⁴	Case report	1	E-cig explosion resulting in pharyngeal injury and C1 and C2 fracture
Reuther et al ¹⁰⁴	Quasi-experimental	10	5 minutes of vaping in prior nonusers resulted in temporary increase in capillary perfusion of buccal mucosa
Richmond et al ²³⁷	Observational	220	Of 220 cases of e-cig inhalation and ingestion in children presenting to pediatricians, majority of inhalation in male adolescents while majority of ingestion was in male children. Both inhalation and ingestion most commonly resulted in nausea/vomiting, cough, throat irritation, or acute toxicity
Rogér et al ⁸⁹	Case report	1	E-cig explosion resulting in extensive intraoral injuries and burns
Sample ²³⁹	Cross-sectional	7	E-cig users had raised vocal shimmer compared to nonusers and use was associated with abnormal mucosal wave, free edge, phase closure, vocal fold varices, and vocal fold edema
Seo et al ²³⁴	Case report	1	Death of a 15-month-old child from accidental ingestion of e-liquid
Soule et al ²¹²	Observational	49	Wide range of self-reported symptoms from e-cig users, most commonly dry throat/mouth
Tsiouma et al ²²⁸	Case report	1	Palatal ulceration in e-cig user which resolved with treatment after switching to conventional cigarettes
Tuhanoğlu et al ²³⁸	Cross-sectional	21	No significant difference in VHI-10 values or vocal quality between e-cig users and nonusers
Vaught et al ⁸⁶	Case report	1	E-cig explosion resulting in significant facial trauma
Walele et al ²¹⁷	Clinical trial	102	Prior smokers who switched from conventional cigarettes to e-cig noted headache, nasopharyngitis, sore throat as the most common adverse events, most of which were transient

case studies and case series, thus necessitating further investigation to determine if e-cigs are truly the causal agent. Finally, there are several avenues specific to otolaryngology that have been minimally explored, particularly the effects of e-cigs on the sinonasal cavity, larynx, and ear.

Implications for Practice

Otolaryngology providers are among the first clinicians that nicotine users encounter with a smoking-related disease process. Despite recent enhancement of policies to

reduce youth nicotine use, youth use of and addiction to nicotine products has increased dramatically as compared to the decade prior, and medical practitioners should expect to see the health effect of this increase in the coming decades. In current smokers, the evidence for the utility of e-cigs for overall risk reduction is heterogenous. While e-cigs have been demonstrated to have fewer carcinogenic agents than their traditional counterparts—a fact often advertised by tobacco companies—there is evidence that these products remain a significant factor in the development of disease. Therefore, it is critical for every otolaryngology provider to stay abreast regarding

the potential health consequences of e-cigs, particularly with regards to the upper aerodigestive tract.

Acknowledgments

We would like to thank Dr Robert Jackler for his comments and the Stanford Research into the Impact of Tobacco Advertising (SRITA) collection for providing the images for **Figure 1** (tobacco.stanford.edu). **Figure 3** was created with BioRender.com.

Author Contributions

Joanne Soo, study design, literature search and analysis, manuscript preparation, revisions, approval for final version; **Meena Easwaran**, literature analysis, manuscript preparation, revisions, approval for final version; **Elizabeth Erickson-DiRenzo**: study design, manuscript preparation, revisions, approval for final version.

Disclosures


Competing interests: None.


Funding sources: None.

Supplemental Material

Additional supporting information is available in the online version of the article.

ORCID iD

Joanne Soo  <http://orcid.org/0000-0001-7556-7157>

Elizabeth Erickson-DiRenzo  <http://orcid.org/0000-0002-9841-0184>

References

- Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet*. 2008;371(9625):1695-1709.
- Jethwa AR, Khariwala SS. Tobacco-related carcinogenesis in head and neck cancer. *Cancer Metastasis Rev*. 2017;36(3):411-423.
- Tavaluc R, Tan-Geller M. Reinke's edema. *Otolaryngol Clin North Am*. 2019;52(4):627-635.
- Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nat Rev Cancer*. 2003;3(10):733-744.
- NTP (National Toxicology Program). Report on carcinogens, fifteenth edition. 2021. Accessed February 10, 2022. <https://ntp.niehs.nih.gov/go/roc15>
- Canistro D, Vivarelli F, Cirillo S, et al. E-cigarettes induce toxicological effects that can raise the cancer risk. *Sci Rep*. 2017;7(1):2028.
- Hess CA, Olmedo P, Navas-Acien A, Goessler W, Cohen JE, Rule AM. E-cigarettes as a source of toxic and potentially carcinogenic metals. *Environ Res*. 2017;152:221-225.
- Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. *JAMA Pediatr*. 2017;171(8):788-797.
- Food and Drug Administration (FDA), HHS. Deeming tobacco products to be subject to the Federal Food, Drug, and Cosmetic Act, as amended by the family smoking prevention and tobacco control act; restrictions on the sale and distribution of tobacco products and required warning statements for tobacco products. 2016. Accessed September 7, 2021. <https://www.govinfo.gov/content/pkg/FR-2016-05-10/pdf/2016-10685.pdf>
- 111th Congress. Family smoking prevention and tobacco control act, H.R. 1256, Pub. L. No. 111-31, 123, 1776 Stat. 2009. Accessed September 7, 2021. <https://www.govinfo.gov/content/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf>
- European Commission. Directive 2014/40/EU of the European Parliament and of the Council of 4 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing directive 2001/37/EC. 2014. Accessed September 7, 2022. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014L0040>
- Food and Drug Administration (FDA), HHS. FDA denies authorization to market JUUL products. 2022. Accessed July 2, 2022. <https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products>
- The Washington Post. Court temporarily halts FDA ban on Juul e-cigarettes. 2022. Accessed July 2, 2022. <https://www.washingtonpost.com/business/2022/06/25/juul-vaping-cigarettes-fda-ban-appeal/>
- Yang Y, Lindblom EN, Salloum RG, Ward KD. The impact of a comprehensive tobacco product flavor ban in San Francisco among young adults. *Addict Behav Rep*. 2020;11:100273.
- Gaiha SM, Lempert LK, McKelvey K, Halpern-Felsher B. E-cigarette devices, brands, and flavors attract youth: informing FDA's policies and priorities to close critical gaps. *Addict Behav*. 2022;126:107179.
- Gotts JE, Jordt SE, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ*. 2019;366:l5275.
- Kalininskiy A, Kittel J, Nacca NE, Misra RS, Croft DP, McGraw MD. E-cigarette exposures, respiratory tract infections, and impaired innate immunity: a narrative review. *Pediatr Med*. 2021;4:5.
- Cherian SV, Kumar A, Estrada-Y-Martin RM. E-cigarette or vaping product-associated lung injury: a review. *Am J Med*. 2020;133(6):657-663.
- Kalininskiy A, Bach CT, Nacca NE, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. *Lancet Respir Med*. 2019;7(12):1017-1026.
- Kennedy CD, van Schalkwyk MCI, McKee M, Pisinger C. The cardiovascular effects of electronic cigarettes: a systematic review of experimental studies. *Prev Med*. 2019;127:105770.
- Chun LF, Moazed F, Calfee CS, Matthay MA, Gotts JE. Pulmonary toxicity of e-cigarettes. *Am J Physiol Lung Cell Mol Physiol*. 2017;313(2):L193-L206.

22. Thiri6n-Romero I, P6rez-Padilla R, Zabert G, Barrientos-Guti6rrez I. Respiratory impact of electronic cigarettes and “low-risk” tobacco. *Rev Invest Clin*. 2019; 71(1):17-27.
23. Martheswaran T, Shmunes MH, Ronquillo YC, Moshirfar M. The impact of vaping on ocular health: a literature review. *Int Ophthalmol*. 2021;41(8):2925-2932.
24. Miglio F, Naroo S, Zeri F, Tavazzi S, Ponzini E. The effect of active smoking, passive smoking, and e-cigarettes on the tear film: an updated comprehensive review. *Exp Eye Res*. 2021;210:108691.
25. Nicholson T, Scott A, Newton Ede M, Jones SW. The impact of E-cigarette vaping and vapour constituents on bone health. *J Inflamm*. 2021;18(1):16.
26. Almeida-da-Silva CLC, Matshik Dakafay H, O'Brien K, Montierth D, Xiao N, Ojcius DM. Effects of electronic cigarette aerosol exposure on oral and systemic health. *Biomed J*. 2021;44(3):252-259.
27. Sultan AS, Jessri M, Farah CS. Electronic nicotine delivery systems: oral health implications and oral cancer risk. *J Oral Pathol Med*. 2021;50(3):316-322.
28. Ebersole J, Samburova V, Son Y, et al. Harmful chemicals emitted from electronic cigarettes and potential deleterious effects in the oral cavity. *Tob Induc Dis*. 2020;18:41.
29. Yang I, Sandeep S, Rodriguez J. The oral health impact of electronic cigarette use: a systematic review. *Crit Rev Toxicol*. 2020;50(2):97-127.
30. Ruskiewicz JA, Zhang Z, Gonalves FM, Tizabi Y, Zelikoff JT, Aschner M. Neurotoxicity of e-cigarettes. *Food Chem Toxicol*. 2020;138:111245.
31. McGrath-Morrow SA, Gorzkowski J, Groner JA, et al. The effects of nicotine on development. *Pediatrics*. 2020;145(3):e20191346.
32. Jamshed L, Perono GA, Jamshed S, Holloway AC. Early life exposure to nicotine: postnatal metabolic, neurobehavioral and respiratory outcomes and the development of childhood cancers. *Toxicol Sci*. 2020;178(1):3-15.
33. Tzortzi A, Kapetanstrataki M, Evangelopoulou V, Behrakis P. A systematic literature review of e-cigarette-related illness and injury: not just for the respirologist. *Int J Environ Res Public Health*. 2020;17(7):2248.
34. Eltorai AE, Choi AR, Eltorai AS. Impact of electronic cigarettes on various organ systems. *Respir Care*. 2019;64(3):328-336.
35. Arany I, Taylor M, F6l6p T, Dixit M. Adverse effects of chronic nicotine exposure on the kidney: potential human health implications of experimental findings. *Int J Clin Pharmacol Ther*. 2018;56(11):501-506.
36. Tweed JO, Hsia SH, Lutfy K, Friedman TC. The endocrine effects of nicotine and cigarette smoke. *Trends Endocrinol Metab*. 2012;23(7):334-342.
37. M6nzel T, Hahad O, Kuntic M, Keaney JF, Deanfield JE, Daiber A. Effects of tobacco cigarettes, e-cigarettes, and waterpipe smoking on endothelial function and clinical outcomes. *Eur Heart J*. 2020;41(41):4057-4070.
38. Benowitz NL, Fraiman JB. Cardiovascular effects of electronic cigarettes. *Nat Rev Cardiol*. 2017;14(8):447-456.
39. Bergstrom HC, McDonald CG, French HT, Smith RF. Continuous nicotine administration produces selective, age-dependent structural alteration of pyramidal neurons from prelimbic cortex. *Synapse*. 2008;62(1):31-39.
40. Biyani S, Derkay CS. E-cigarettes: considerations for the otolaryngologist. *Int J Pediatr Otorhinolaryngol*. 2015; 79(8):1180-1183.
41. Biyani S, Derkay CS. E-cigarettes: an update on considerations for the otolaryngologist. *Int J Pediatr Otorhinolaryngol*. 2017;94:14-16.
42. Stobbs N, Lillis A, Kumar N. E-cigarettes in ENT: what do we need to know? *J Laryngol Otol*. 2016;130(6):512-515.
43. Flach S, Maniam P, Manickavasagam J. E-cigarettes and head and neck cancers: a systematic review of the current literature. *Clin Otolaryngol*. 2019;44(5):749-756.
44. Kar M, Emre IE, Bayar Muluk N, Cingi C. Effect of electronic cigarettes on the inner mucosa of the craniofacial region. *J Craniofac Surg*. 2019;30(3):e235-e238.
45. Born H, Persky M, Kraus DH, Peng R, Amin MR, Branski RC. Electronic cigarettes: a primer for clinicians. *Otolaryngol Head Neck Surg*. 2015;153(1):5-14.
46. Harrell PT, Simmons VN, Correa JB, Padhya TA, Brandon TH. Electronic nicotine delivery systems (“e-cigarettes”): review of safety and smoking cessation efficacy. *Otolaryngol Head Neck Surg*. 2014;151(3):381-393.
47. Bold KW, Kong G, Morean M, et al. Trends in various e-cigarette devices used by high school adolescents from 2017-2019. *Drug Alcohol Depend*. 2021;219:108497.
48. The Wall Street Journal. Puff Bar has overtaken Juul as the favorite e-cigarette for teens. 2021. Accessed February 27, 2022. <https://www.wsj.com/articles/puff-bar-has-overtaken-juul-as-the-favorite-e-cigarette-for-teens-11633021209>
49. Henningfield JE, Zaatari GS. Electronic nicotine delivery systems: emerging science foundation for policy. *Tob Control*. 2010;19(2):89-90.
50. Choi K, Forster JL. Beliefs and experimentation with electronic cigarettes. *Am J Prev Med*. 2014;46(2):175-178.
51. Sharma A, McCausland K, Jancey J. Adolescent's health perceptions of e-cigarettes: a systematic review. *Am J Prev Med*. 2021;60(5):716-725.
52. Russell C, Katsampouris E, Mckeganey N. Harm and addiction perceptions of the JUUL e-cigarette among adolescents. *Nicotine Tob Res*. 2020;22(5):713-721.
53. Farsalinos K, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*. 2014;11(4):4356-4373.
54. Strombotne K, Buckell J, Sindelar JL. Do JUUL and e-cigarette flavours change risk perceptions of adolescents? Evidence from a national survey. *Tob Control*. 2021;30(2): 199-205.
55. Tegin G, Mekala HM, Sarai SK, Lippmann S. E-cigarette toxicity. *South Med J*. 2018;111(1):35-38.
56. Eshraghian E, Al-Delaimy W. A review of constituents identified in e-cigarette liquids and aerosols. *Tob Prev Cessat*. 2021;7:10.

57. Qu Y, Kim KH, Szulejko JE. The effect of flavor content in e-liquids on e-cigarette emissions of carbonyl compounds. *Environ Res*. 2018;166:324-333.
58. Flieger J, Kawka J, Tatarczak-Michalewska M. Levels of the thiocyanate in the saliva of tobacco smokers in comparison to e-cigarette smokers and nonsmokers measured by HPLC on a phosphatidylcholine column. *Molecules*. 2019;24(20):3790.
59. Fels Elliott DR, Shah R, Hess CA, et al. Giant cell interstitial pneumonia secondary to cobalt exposure from e-cigarette use. *Eur Respir J*. 2019;54(6):1901922.
60. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One*. 2013;8(3):e57987.
61. White AV, Wambui DW, Pokhrel LR. Risk assessment of inhaled diacetyl from electronic cigarette use among teens and adults. *Sci Total Environ*. 2021;772:145486.
62. Salamanca JC, Meehan-Atrash J, Vreeke S, Escobedo JO, Peyton DH, Strongin RM. E-cigarettes can emit formaldehyde at high levels under conditions that have been reported to be non-averse to users. *Sci Rep*. 2018;8(1):7559.
63. Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. *N Engl J Med*. 2015;372(4):392-394.
64. Bustamante G, Ma B, Yakovlev G, et al. Presence of the carcinogen N'-nitrosonornicotine in saliva of e-cigarette users. *Chem Res Toxicol*. 2018;31(8):731-738.
65. Kosmider L, Sobczak A, Prokopowicz A, et al. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. *Thorax*. 2016;71(4):376-377.
66. Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicol In Vitro*. 2014;28(2):198-208.
67. Ureña JF, Ebersol LA, Silakov A, Elias RJ, Lambert JD. Impact of atomizer age and flavor on *in vitro* toxicity of aerosols from a third-generation electronic cigarette against human oral cells. *Chem Res Toxicol*. 2020;33(10):2527-2537.
68. Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical composition and evaluation of nicotine, tobacco alkaloids, pH, and selected flavors in e-cigarette cartridges and refill solutions. *Nicotine Tob Res*. 2015;17(10):1270-1278.
69. Varlet V, Farsalinos K, Augsburg M, Thomas A, Etter JF. Toxicity assessment of refill liquids for electronic cigarettes. *Int J Environ Res Public Health*. 2015;12(5):4796-4815.
70. Zhou Y, Irshad H, Dye WW, Wu G, Tellez CS, Belinsky SA. Voltage and e-liquid composition affect nicotine deposition within the oral cavity and carbonyl formation. *Tob Control*. 2021;30(5):485-491.
71. Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tob Control*. 2014;23:ii4-ii10.
72. Schober W, Szendrei K, Matzen W, et al. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health*. 2014;217(6):628-637.
73. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res*. 2014;16(6):655-662.
74. Hess I, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. *Public Health Res Pract*. 2016;26(2):2621617.
75. Goniewicz ML, Lee L. Electronic cigarettes are a source of thirdhand exposure to nicotine. *Nicotine Tob Res*. 2015;17(2):256-258.
76. McMillen R, Klein JD, Wilson K, Winickoff JP, Tanski S. E-cigarette use and future cigarette initiation among never smokers and relapse among former smokers in the PATH study. *Public Health Rep*. 2019;134(5):528-536.
77. Barufaldi L, Guerra R, de Albuquerque RC, et al. Risk of smoking relapse with the use of electronic cigarettes: a systematic review with meta-analysis of longitudinal studies. *Tob Prev Cessat*. 2021;29:29.
78. Löhler J, Wollenberg B. Are electronic cigarettes a healthier alternative to conventional tobacco smoking? *Eur Arch Otrhinolaryngol*. 2019;276(1):17-25.
79. Osibogun O, Bursac Z, Maziak W. E-cigarette use and regular cigarette smoking among youth: population assessment of tobacco and health study (2013-2016). *Am J Prev Med*. 2020;58(5):657-665.
80. Khouja JN, Suddell SF, Peters SE, Taylor AE, Munafò MR. Is e-cigarette use in non-smoking young adults associated with later smoking? A systematic review and meta-analysis. *Tob Control*. 2020;30(1):8-15.
81. US Department of Health and Human Services. Surgeon general releases advisory on e-cigarette epidemic among youth. 2018. Accessed August 4, 2021. <https://www.hhs.gov/about/news/2018/12/18/surgeon-general-releases-advisory-e-cigarette-epidemic-among-youth.html>
82. Food and Drug Administration (FDA), HHS. Statement from FDA Commissioner Scott Gottlieb, M.D., on new enforcement actions and a youth tobacco prevention plan to stop youth use of, and access to, JUUL and other e-cigarettes. 2018. Accessed September 7, 2021. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-enforcement-actions-and-youth-tobacco-prevention>
83. Seitz CMS, Kabir Z. Burn injuries caused by e-cigarette explosions: a systematic review of published cases. *Tob Prev Cessat*. 2018;4:32.
84. Morse J, Tittman S, Gelbard A. Oropharyngeal injury from spontaneous combustion of a lithium-ion battery: a case report. *Laryngoscope*. 2019;129(1):45-48.
85. Brownson EG, Thompson CM, Goldsberry S, et al. Explosion injuries from e-cigarettes. *N Engl J Med*. 2016;375(14):1400-1402.
86. Vaught B, Spellman J, Shah A, Stewart A, Mullin D. Facial trauma caused by electronic cigarette explosion. *Ear Nose Throat J*. 2017;96(3):139-142.
87. Dekhou A, Oska N, Partiali B, Johnson J, Chung MT, Folbe A. E-cigarette burns and explosions: what are the

- patterns of oromaxillofacial injury? *J Oral Maxillofac Surg.* 2021;79(8):1723-1730.
88. Harrison R, Hicklin D. Electronic cigarette explosions involving the oral cavity. *J Am Dent Assoc.* 2016;147(11):891-896.
 89. Rogér JM, Abayon M, Elad S, Kolokythas A. Oral trauma and Tooth avulsion following explosion of e-cigarette. *J Oral Maxillofac Surg.* 2016;74(6):1181-1185.
 90. Brooks JK, Kleinman JW, Brooks JB, Reynolds MA. Electronic cigarette explosion associated with extensive intraoral injuries. *Dent Traumatol.* 2017;33(2):149-152.
 91. Cason DE, Morgan DE, Pietryga JA. Injuries from an exploding e-cigarette: a case report. *Ann Intern Med.* 2016;165(9):678-679.
 92. Kumetz EA, Hurst ND, Cudnik RJ, Rudinsky SL. Electronic cigarette explosion injuries. *Am J Emerg Med.* 2016;34(11):2252.e1-2252.e3.
 93. Moore J, Mihalache G, Messahel A. “Exploding” electronic cigarette: a case report. *Br J Oral Maxillofac Surg.* 2016;54(9):1056-1057.
 94. Norii T, Plate A. Electronic cigarette explosion resulting in a C1 and C2 fracture: a case report. *J Emerg Med.* 2017;52(1):86-88.
 95. Creamer MR, Everett Jones S, Gentzke AS, Jamal A, King BA. Tobacco product use among high school students—youth risk behavior survey, United States, 2019. *MMWR Suppl.* 2020;69(1):56-63.
 96. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(45):1013-1019.
 97. Fracol M, Dorfman R, Janes L, et al. The surgical impact of e-cigarettes: a case report and review of the current literature. *Arch Plast Surg.* 2017;44(6):477-481.
 98. Hrywna M, Bover Manderski MT, Delnevo CD. Prevalence of electronic cigarette use among adolescents in New Jersey and association with social factors. *JAMA Netw Open.* 2020;3(2):e1920961.
 99. Food and Drug Administration (FDA), HHS. Products, ingredients, & components. 2020. Accessed September 2, 2021. <https://www.fda.gov/tobacco-products/products-guidance-regulations/products-ingredients-components>
 100. Centers for Disease Control and Prevention. Smoking & tobacco use: fast facts and fact sheets. 2022. Accessed September 2, 2021. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Ftobacco%2Fdata_statistics%2Ffact_sheets%2Findex.htm
 101. Jackler RK. What every otolaryngologist should know about electronic cigarettes, especially JUUL. American Academy of Otolaryngology—Head and Neck Surgery. 2019. Accessed September 2, 2021. <https://bulletin.entnet.org/home/article/21247521/what-every-otolaryngologist-should-know-about-electronic-cigarettes-especially-juul>
 102. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. *Lancet Oncol.* 2008;9(7):667-675.
 103. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2020;396(10258):1123-1249.
 104. Reuther WJ, Hale B, Matharu J, Blythe JN, Brennan PA. Do you mind if I vape? Immediate effects of electronic cigarettes on perfusion in buccal mucosal tissue—a pilot study. *Br J Oral Maxillofac Surg.* 2016;54(3):338-341.
 105. Page F, Hamnett N, Wearn C, Hardwicke J, Moiemmen N. The acute effects of electronic cigarette smoking on the cutaneous circulation. *J Plast Reconstr Aesthet Surg.* 2016;69(4):575-577.
 106. Lei W, Lerner C, Sundar IK, Rahman I. Myofibroblast differentiation and its functional properties are inhibited by nicotine and e-cigarette via mitochondrial OXPHOS complex III. *Sci Rep.* 2017;7:43213.
 107. Jaleel Z, Blasberg E, Troiano C, et al. Association of vaping with decreased vascular endothelial growth factor expression and decreased microvessel density in cutaneous wound healing tissue in rats. *Wound Repair Regen.* 2021;29(6):1024-1034.
 108. Rau AS, Reinikovaite V, Schmidt EP, Taraseviciene-Stewart L, Deleyiannis FWB. Electronic cigarettes are as toxic to skin flap survival as tobacco cigarettes. *Ann Plast Surg.* 2017;79(1):86-91.
 109. Krishnan NM, Han KD, Nahabedian MY. Can e-cigarettes cause free flap failure? A case of arterial vasospasm induced by electronic cigarettes following microsurgical breast reconstruction. *Plast Reconstr Surg Glob Open.* 2016;4(1):e596.
 110. Troiano C, Jaleel Z, Spiegel JH. Association of electronic cigarette vaping and cigarette smoking with decreased random flap viability in rats. *JAMA Facial Plast Surg.* 2019;21(1):5-10.
 111. Agochukwu N, Liao JY. Debunking the myth of e-cigarettes: a case of free flap compromise due to e-cigarette use within the first 24 hours. *J Plast Reconstr Aesthet Surg.* 2018;71(3):451-453.
 112. Sanford NN, Sher DJ, Xu X, Aizer AA, Mahal BA. Trends in smoking and e-cigarette use among US patients with cancer, 2014-2017. *JAMA Oncol.* 2019;5(3):426-428.
 113. Dautzenberg B, Garelik D. Patients with lung cancer: are electronic cigarettes harmful or useful? *Lung Cancer.* 2017;105:42-48.
 114. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine Tob Res.* 2015;17(6):704-709.
 115. Polosa R, Rodu B, Caponnetto P, Maglia M, Raciti C. A fresh look at tobacco harm reduction: the case for the electronic cigarette. *Harm Reduct J.* 2013;10:19.
 116. Beaglehole R, Bates C, Youdan B, Bonita R. Nicotine without smoke: fighting the tobacco epidemic with harm reduction. *Lancet.* 2019;394(10200):718-720.
 117. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med.* 2019;380(7):629-637.

118. Chan GCK, Stjepanović D, Lim C, et al. A systematic review of randomized controlled trials and network meta-analysis of e-cigarettes for smoking cessation. *Addict Behav.* 2021;119:106912.
119. Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2020;10:CD010216.
120. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet.* 2013;382(9905):1629-1637.
121. Wang RJ, Bhadriraju S, Glantz SA. E-cigarette use and adult cigarette smoking cessation: a meta-analysis. *Am J Public Health.* 2021;111(2):230-246.
122. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med.* 2016;4(2):116-128.
123. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2016;9:CD010216.
124. Ghosh S, Drummond MB. Electronic cigarettes as smoking cessation tool: are we there? *Curr Opin Pulm Med.* 2017;23(2):111-116.
125. Patil S, Arakeri G, Patil S, et al. Are electronic nicotine delivery systems (ENDs) helping cigarette smokers quit?—current evidence. *J Oral Pathol Med.* 2020;49(3):181-189.
126. Pound CM, Zhang JZ, Kodua AT, Sampson M. Smoking cessation in individuals who use vaping as compared with traditional nicotine replacement therapies: a systematic review and meta-analysis. *BMJ Open.* 2021;11(2):e044222.
127. Ibrahim S, Habiballah M, Sayed IE. Efficacy of electronic cigarettes for smoking cessation: a systematic review and meta-analysis. *Am J Health Promot.* 2021;35(3):442-455.
128. Wang JB, Olgin JE, Nah G, et al. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. *PLoS One.* 2018;13(7):e0198681.
129. Kim CY, Paek YJ, Seo HG, et al. Dual use of electronic and conventional cigarettes is associated with higher cardiovascular risk factors in Korean men. *Sci Rep.* 2020;10(1):5612.
130. Martinez U, Simmons VN, Sutton SK, et al. Targeted smoking cessation for dual users of combustible and electronic cigarettes: a randomised controlled trial. *Lancet Public Health.* 2021;6(7):e500-e509.
131. Owusu D, Huang J, Weaver SR, et al. Patterns and trends of dual use of e-cigarettes and cigarettes among U.S. adults, 2015-2018. *Prev Med Rep.* 2019;16:101009.
132. King BA, Patel R, Nguyen KH, Dube SR. Trends in awareness and use of electronic cigarettes among US adults, 2010-2013. *Nicotine Tob Res.* 2015;17(2):219-227.
133. Martínez Ú, Martínez-Loredo V, Simmons VN, et al. How does smoking and nicotine dependence change after onset of vaping? A retrospective analysis of dual users. *Nicotine Tob Res.* 2020;22(5):764-770.
134. Glantz SA, Bareham DW. E-cigarettes: use, effects on smoking, risks, and policy implications. *Annu Rev Public Health.* 2018;39:215-235.
135. Camara-Medeiros A, Diemert L, O'Connor S, Schwartz R, Eissenberg T, Cohen JE. Perceived addiction to vaping among youth and young adult regular vapers. *Tob Control.* 2021;30(3):273-278.
136. American Academy of Otolaryngology–Head and Neck Surgery. Position statements on e-cigarettes. 2021. Accessed September 2, 2021. <https://www.entnet.org/resource/position-statements-on-e-cigarettes/>
137. Bahmed K, Lin CR, Simborio H, et al. The role of DJ-1 in human primary alveolar type II cell injury induced by e-cigarette aerosol. *Am J Physiol Lung Cell Mol Physiol.* 2019;317(4):L475-L485.
138. Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PLoS One.* 2015;10(2):e0116732.
139. Ganapathy V, Manyanga J, Brame L, et al. Electronic cigarette aerosols suppress cellular antioxidant defenses and induce significant oxidative DNA damage. *PLoS One.* 2017;12(5):e0177780.
140. Lerner CA, Rutagarama P, Ahmad T, Sundar IK, Elder A, Rahman I. Electronic cigarette aerosols and copper nanoparticles induce mitochondrial stress and promote DNA fragmentation in lung fibroblasts. *Biochem Biophys Res Commun.* 2016;477(4):620-625.
141. Lee HW, Park SH, Weng M, et al. E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc Natl Acad Sci USA.* 2018;115(7):E1560-E1569.
142. Thorne D, Crooks I, Hollings M, Seymour A, Meredith C, Gaca M. The mutagenic assessment of an electronic-cigarette and reference cigarette smoke using the Ames assay in strains TA98 and TA100. *Mutat Res Genet Toxicol Environ Mutagen.* 2016;812:29-38.
143. Tommasi S, Bates SE, Behar RZ, Talbot P, Besaratinia A. Limited mutagenicity of electronic cigarettes in mouse or human cells in vitro. *Lung Cancer.* 2017;112:41-46.
144. Schaal CM, Bora-Singhal N, Kumar DM, Chellappan SP. Regulation of Sox2 and stemness by nicotine and electronic-cigarettes in non-small cell lung cancer. *Mol Cancer.* 2018;17(1):149.
145. Zahedi A, Phanthong R, Chaili A, Remark G, Talbot P. Epithelial-to-mesenchymal transition of A549 lung cancer cells exposed to electronic cigarettes. *Lung Cancer.* 2018;122:224-233.
146. Muthumalage T, Lamb T, Friedman MR, Rahman I. E-cigarette flavored pods induce inflammation, epithelial barrier dysfunction, and DNA damage in lung epithelial cells and monocytes. *Sci Rep.* 2019;9(1):19035.
147. Aug A, Altraja S, Kilk K, Porosk R, Soomets U, Altraja A. E-cigarette affects the metabolome of primary normal human bronchial epithelial cells. *PLoS One.* 2015;10(11):e0142053.
148. Madison MC, Landers CT, Gu BH, et al. Electronic cigarettes disrupt lung lipid homeostasis and innate

- immunity independent of nicotine. *J Clin Invest.* 2019; 129(10):4290-4304.
149. Gellatly S, Pavelka N, Crue T, et al. Nicotine-free e-cigarette vapor exposure stimulates IL6 and mucin production in human primary small airway epithelial cells. *J Inflamm Res.* 2020;13:175-185.
150. Zhang S, Zhang J, Chen H, et al. Combined cytotoxicity of co-exposure to aldehyde mixtures on human bronchial epithelial BEAS-2B cells. *Environ Pollut.* 2019;250:650-661.
151. Rowell TR, Reeber SL, Lee SL, et al. Flavored e-cigarette liquids reduce proliferation and viability in the CALU3 airway epithelial cell line. *Am J Physiol Lung Cell Mol Physiol.* 2017;313(1):L52-L66.
152. Wu Q, Jiang D, Minor M, Chu HW. Electronic cigarette liquid increases inflammation and virus infection in primary human airway epithelial cells. *PLoS One.* 2014; 9(9):e108342.
153. Hwang JH, Lyes M, Sladewski K, et al. Electronic cigarette inhalation alters innate immunity and airway cytokines while increasing the virulence of colonizing bacteria. *J Mol Med.* 2016;94(6):667-679.
154. Corriden R, Moshensky A, Bojanowski CM, et al. E-cigarette use increases susceptibility to bacterial infection by impairment of human neutrophil chemotaxis, phagocytosis, and NET formation. *Am J Physiol Cell Physiol.* 2020;318(1):C205-C214.
155. Chung S, Baumlin N, Dennis JS, et al. Electronic cigarette vapor with nicotine causes airway mucociliary dysfunction preferentially via TRPA1 receptors. *Am J Respir Crit Care Med.* 2019;200(9):1134-1145.
156. Glynos C, Bibli SI, Katsaounou P, et al. Comparison of the effects of e-cigarette vapor with cigarette smoke on lung function and inflammation in mice. *Am J Physiol Lung Cell Mol Physiol.* 2018;315(5):L662-L672.
157. Garcia-Arcos I, Geraghty P, Baumlin N, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax.* 2016;71(12):1119-1129.
158. Clapp PW, Lavrich KS, van Heusden CA, Lazarowski ER, Carson JL, Jaspers I. Cinnamaldehyde in flavored e-cigarette liquids temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. *Am J Physiol Lung Cell Mol Physiol.* 2019;316(3):L470-L486.
159. Sussan TE, Gajghate S, Thimmulappa RK, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PLoS One.* 2015;10(2):e0116861.
160. Crotty Alexander LE, Drummond CA, Hepokoski M, et al. Chronic inhalation of e-cigarette vapor containing nicotine disrupts airway barrier function and induces systemic inflammation and multiorgan fibrosis in mice. *Am J Physiol Regul Integr Comp Physiol.* 2018;314(6):R834-R847.
161. Tang M, Wu XR, Lee HW, et al. Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. *Proc Natl Acad Sci USA.* 2019;116(43):21727-21731.
162. McAlinden KD, Eapen MS, Lu W, Sharma P, Sohail SS. The rise of electronic nicotine delivery systems and the emergence of electronic-cigarette-driven disease. *Am J Physiol Lung Cell Mol Physiol.* 2020;319(4):L585-L595.
163. Reidel B, Radicioni G, Clapp PW, et al. E-cigarette use causes a unique innate immune response in the lung, involving increased neutrophilic activation and altered mucin secretion. *Am J Respir Crit Care Med.* 2018;197(4):492-501.
164. Staudt MR, Salit J, Kaner RJ, Hollmann C, Crystal RG. Altered lung biology of healthy never smokers following acute inhalation of E-cigarettes. *Respir Res.* 2018;19(1):78.
165. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *N Engl J Med.* 2020;382(8):697-705.
166. Isik Andrikopoulos G, Farsalinos K, Poulas K. Electronic nicotine delivery systems (ENDS) and their relevance in oral health. *Toxics.* 2019;7(4):61.
167. Figueredo CA, Abdelhay N, Figueredo CM, Catunda R, Gibson MP. The impact of vaping on periodontitis: a systematic review. *Clin Exp Dent Res.* 2021;7(3):376-384.
168. Briggs K, Bell C, Breik O. What should every dental health professional know about electronic cigarettes? *Aust Dent J.* 2021;66(3):224-233.
169. Couch ET, Chaffee BW, Gansky SA, Walsh MM. The changing tobacco landscape. *J Am Dent Assoc.* 2016; 147(7):561-569.
170. Iskandar AR, Zanetti F, Kondylis A, et al. A lower impact of an acute exposure to electronic cigarette aerosols than to cigarette smoke in human organotypic buccal and small airway cultures was demonstrated using systems toxicology assessment. *Intern Emerg Med.* 2019; 14(6):863-883.
171. Franco T, Trapasso S, Puzzo L, Allegra E. Electronic cigarette: role in the primary prevention of oral cavity cancer. *Clin Med Insights Ear Nose Throat.* 2016;9:7-12.
172. Grando SA. Connections of nicotine to cancer. *Nat Rev Cancer.* 2014;14(6):419-429.
173. Wisniewski DJ, Ma T, Schneider A. Nicotine induces oral dysplastic keratinocyte migration via fatty acid synthase-dependent epidermal growth factor receptor activation. *Exp Cell Res.* 2018;370(2):343-352.
174. Salturk Z, Çakır Ç, Sünnetçi G, et al. Effects of electronic nicotine delivery system on larynx: experimental study. *J Voice.* 2015;29(5):560-563.
175. Ha TAN, Madison MC, Kheradmand F, Altman KW. Laryngeal inflammatory response to smoke and vape in a murine model. *Am J Otolaryngol.* 2019;40(1):89-92.
176. Sancilio S, Gallorini M, Cataldi A, di Giacomo V. Cytotoxicity and apoptosis induction by e-cigarette fluids in human gingival fibroblasts. *Clin Oral Investig.* 2016; 20(3):477-483.
177. Alanazi H, Park HJ, Chakir J, Semlali A, Rouabhia M. Comparative study of the effects of cigarette smoke and electronic cigarettes on human gingival fibroblast

- proliferation, migration and apoptosis. *Food Chem Toxicol.* 2018;118:390-398.
178. Sundar IK, Javed F, Romanos GE, Rahman I. E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget.* 2016;7(47):77196-77204.
179. Sancilio S, Gallorini M, Cataldi A, Sancilio L, Rana RA, di Giacomo V. Modifications in human oral fibroblast ultrastructure, collagen production, and lysosomal compartment in response to electronic cigarette fluids. *J Periodontol.* 2017;88(7):673-680.
180. Vermehren MF, Wiesmann N, Deschner J, Brieger J, Al-Nawas B, Kämmerer PW. Comparative analysis of the impact of e-cigarette vapor and cigarette smoke on human gingival fibroblasts. *Toxicol In Vitro.* 2020;69:105005.
181. Martinez JD, Easwaran M, Ramirez D, Erickson-DiRenzo E. Effects of electronic (e)-cigarette vapor and cigarette smoke in cultured vocal fold fibroblasts. *Laryngoscope.* 2022; 133:139-146.
182. Lungova V, Wendt K, Thibeault SL. Exposure to e-cigarette vapor extract induces vocal fold epithelial injury and triggers intense mucosal remodeling. *Dis Model Mech.* 2022; 15(8):dmm049476.
183. Yu V, Rahimy M, Korrapati A, et al. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. *Oral Oncol.* 2016;52:58-65.
184. Tsai KYF, Hirschi Budge KM, Lepre AP, et al. Cell invasion, RAGE expression, and inflammation in oral squamous cell carcinoma (OSCC) cells exposed to e-cigarette flavoring. *Clin Exp Dent Res.* 2020;6(6):618-625.
185. Pushalkar S, Paul B, Li Q, et al. Electronic Cigarette Aerosol Modulates the Oral Microbiome and Increases Risk of Infection. *iScience.* 2020;23(3):100884.
186. Tellez CS, Juri DE, Phillips LM, et al. Cytotoxicity and genotoxicity of e-cigarette generated aerosols containing diverse flavoring products and nicotine in oral epithelial cell lines. *Toxicol Sci.* 2021;179(2):220-228.
187. Duggar M, Swanson H, Hill-Odom M. Determining the effects of e-cigarette vapor on oral epithelial cells in a cultured cell model. *FASEB J.* 2018;32:692.3.
188. Ji EH, Sun B, Zhao T, et al. Characterization of electronic cigarette aerosol and its induction of oxidative stress response in oral keratinocytes. *PLoS One.* 2016;11(5): e0154447.
189. Ji EH, Elzakra N, Chen W, et al. E-cigarette aerosols induce unfolded protein response in normal human oral keratinocytes. *J Cancer.* 2019;10(27):6915-6924.
190. Rouabhia M, Park HJ, Semlali A, Zakrzewski A, Chmielewski W, Chakir J. E-cigarette vapor induces an apoptotic response in human gingival epithelial cells through the caspase-3 pathway. *J Cell Physiol.* 2017;232(6):1539-1547.
191. Sun YW, Kosinska W, Guttenplan JB. E-cigarette aerosol condensate enhances metabolism of benzo(a)pyrene to genotoxic products, and induces CYP1A1 and CYP1B1, likely by activation of the aryl hydrocarbon receptor. *Int J Environ Res Public Health.* 2019;16(14):2468.
192. Welz C, Canis M, Schwenk-Zieger S, et al. Cytotoxic and genotoxic effects of electronic cigarette liquids on human mucosal tissue cultures of the oropharynx. *J Environ Pathol Toxicol Oncol.* 2016;35(4):343-354.
193. Song JJ, Go YY, Mun JY, et al. Effect of electronic cigarettes on human middle ear. *Int J Pediatr Otorhinolaryngol.* 2018; 109:67-71.
194. Song JJ, Go YY, Lee JK, et al. Transcriptomic analysis of tobacco-flavored e-cigarette and menthol-flavored e-cigarette exposure in the human middle ear. *Sci Rep.* 2020;10(1):20799.
195. Go YY, Mun JY, Chae SW, Chang J, Song JJ. Comparison between in vitro toxicities of tobacco- and menthol-flavored electronic cigarette liquids on human middle ear epithelial cells. *Sci Rep.* 2020;10(1):2544.
196. Rouabhia M, Piché M, Corriveau MN, Chakir J. Effect of e-cigarettes on nasal epithelial cell growth, Ki67 expression, and pro-inflammatory cytokine secretion. *Am J Otolaryngol.* 2020;41(6):102686.
197. Carson JL, Zhou L, Brighton L, et al. Temporal structure/function variation in cultured differentiated human nasal epithelium associated with acute single exposure to tobacco smoke or E-cigarette vapor. *Inhal Toxicol.* 2017;29(3): 137-144.
198. Manyanga J, Ganapathy V, Bouharati C, et al. Electronic cigarette aerosols alter the expression of cisplatin transporters and increase drug resistance in oral cancer cells. *Sci Rep.* 2021;11(1):1821.
199. Tommasi S, Caliri A, Caceres A, et al. Dereglulation of biologically significant genes and associated molecular pathways in the oral epithelium of electronic cigarette users. *Int J Mol Sci.* 2019;20(3):738.
200. Alqahtani S, Cooper B, Spears CA, Wright C, Shannahan J. Electronic nicotine delivery system-induced alterations in oral health via saliva assessment. *Exp Biol Med.* 2020;245 (15):1319-1325.
201. Hamad SH, Brinkman MC, Tsai YH, et al. Pilot study to detect genes involved in DNA damage and cancer in humans: potential biomarkers of exposure to e-cigarette aerosols. *Genes.* 2021;12(3):448.
202. Martin EM, Clapp PW, Rebuli ME, et al. E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke. *Am J Physiol Lung Cell Mol Physiol.* 2016;311(1): L135-L144.
203. Rebuli ME, Glista-Baker E, Hoffman JR, et al. Electronic-cigarette use alters nasal mucosal immune response to live-attenuated influenza virus. A clinical trial. *Am J Respir Cell Mol Biol.* 2021;64(1):126-137.
204. Schwarzmeier LÂT, da Cruz BS, Ferreira CCP, et al. E-cig might cause cell damage of oral mucosa. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2021;131(4): 435-443.
205. Cichońska D, Kusiak A, Kochańska B, Ochocińska J, Świetlik D. Influence of electronic cigarettes on selected antibacterial properties of saliva. *Int J Environ Res Public Health.* 2019;16(22):4433.

206. Stewart CJ, Auchtung TA, Ajami NJ, et al. Effects of tobacco smoke and electronic cigarette vapor exposure on the oral and gut microbiota in humans: a pilot study. *PeerJ*. 2018;6:e4693.
207. Hua M, Alfi M, Talbot P. Health-related effects reported by electronic cigarette users in online forums. *J Med Internet Res*. 2013;15(4):e59.
208. Hua M, Sadah S, Hristidis V, Talbot P. Health effects associated with electronic cigarette use: automated mining of online forums. *J Med Internet Res*. 2020;22(1):e15684.
209. Cho JH. The association between electronic-cigarette use and self-reported oral symptoms including cracked or broken teeth and tongue and/or inside-cheek pain among adolescents: a cross-sectional study. *PLoS One*. 2017;12(7):e0180506.
210. King JL, Reboussin BA, Wiseman KD, et al. Adverse symptoms users attribute to e-cigarettes: results from a national survey of US adults. *Drug Alcohol Depend*. 2019;196:9-13.
211. Kumral TL, Saltürk Z, Yildirim G, et al. How does electronic cigarette smoking affect sinonasal symptoms and nasal mucociliary clearance? *B-ENT*. 2016;12(1):17-21.
212. Soule EK, Bode KM, Desrosiers AC, Guy M, Breland A, Fagan P. User-perceived negative respiratory symptoms associated with electronic cigarette use. *Nicotine Tob Res*. 2020;22(suppl 1):S45-S53.
213. Li Q, Zhan Y, Wang L, Leischow SJ, Zeng DD. Analysis of symptoms and their potential associations with e-liquids' components: a social media study. *BMC Public Health*. 2016;16:674.
214. Luo J, Chen L, Lu X, Yuan J, Xie Z, Li D. Analysis of potential associations of JUUL flavours with health symptoms based on user-generated data from Reddit. *Tob Control*. 2021;30(5):534-541.
215. Chen L, Lu X, Yuan J, et al. A social media study on the associations of flavored electronic cigarettes with health symptoms: observational study. *J Med Internet Res*. 2020;22(6):e17496.
216. Jankowski M, Brożek G, Zejda J, Kurowski T, Knura M, Idzik A. The impact of cigarette and e-cigarette smoking on human health. *Eur Respir J*. 2017;50(suppl 61):PA4491.
217. Walele T, Bush J, Koch A, Savioz R, Martin C, O'Connell G. Evaluation of the safety profile of an electronic vapour product used for two years by smokers in a real-life setting. *Regul Toxicol Pharmacol*. 2018;92:226-238.
218. Mokeem SA, Abduljabbar T, Al-Kheraif AA, et al. Oral candida carriage among cigarette- and waterpipe-smokers, and electronic cigarette users. *Oral Dis*. 2019;25(1):319-326.
219. Frossard S, Volansky P, Endara-Bravo AS. Acute uvulitis secondary to electronic cigarette use. *Am J Respir Crit Care Med*. 2015;191:A1556.
220. Bozzella MJ, Magyar M, DeBiasi RL, Ferrer K. Epiglottitis associated with intermittent e-cigarette use: the vagaries of vaping toxicity. *Pediatrics*. 2020;145(3):e20192399.
221. Miler JA, Hajek P. Resolution of recurrent tonsillitis in a non-smoker who became a vaper. A case study and new hypothesis. *Med Hypotheses*. 2017;109:17-18.
222. Huilgol P, Bhatt SP, Biligowda N, Wright NC, Wells JM. Association of e-cigarette use with oral health: a population-based cross-sectional questionnaire study. *J Public Health (Bangkok)*. 2019;41(2):354-361.
223. Akinkugbe AA. Cigarettes, e-cigarettes, and adolescents' oral health: findings from the population assessment of tobacco and health (PATH) study. *JDR Clin Transl Res*. 2019;4(3):276-283.
224. Ralho A, Coelho A, Ribeiro M, et al. Effects of electronic cigarettes on oral cavity: a systematic review. *J Evid Based Dent Pract*. 2019;19(4):101318.
225. Bardellini E, Amadori F, Conti G, Majorana A. Oral mucosal lesions in electronic cigarettes consumers versus former smokers. *Acta Odontol Scand*. 2018;76(3):226-228.
226. Bartram A, Jones N, Endersby S. Lichenoid eruption associated with use of an e-cigarette. *Br J Oral Maxillofac Surg*. 2016;54(4):475.
227. Farinha H, Martins V. Lingua villosa nigra associated with the use of electronic cigarette. *Acta Med Port*. 2015;28(3):393.
228. Tsiouma O, Andreou A, Sklavounou-Andrikopoulou A. E-cigarette and palatal ulcer: a possible relationship? *Oral Surg*. 2021;14(1):59-64.
229. Cant A, Collard B, Cunliffe D. Electronic cigarettes: necrotic ulcer. *Br Dent J*. 2017;222(4):226.
230. Nguyen H, Kitzmiller JP, Nguyen KT, Nguyen CD, Chi Bui T. Oral carcinoma associated with chronic use of electronic cigarettes. *Otolaryngology*. 2017;7(2):304.
231. Klawinski D, Hanna I, Breslin NK, Katzenstein HM, Indelicato DJ. Vaping the venom: oral cavity cancer in a young adult with extensive electronic cigarette use. *Pediatrics*. 2021;147(5):e2020022301.
232. Jones CD, Ho W, Gunn E, Widdowson D, Bahia H. E-cigarette burn injuries: comprehensive review and management guidelines proposal. *Burns*. 2019;45(4):763-771.
233. Andresen NS, Lee DJ, Kowalski CE, Bayon R. Fall with e-cigarette in mouth resulting in pharyngeal and esophageal burns. *JAMA Otolaryngol Head Neck Surg*. 2018;144(4):385-386.
234. Seo AD, Kim DC, Yu HJ, Kang MJ. Accidental ingestion of e-cigarette liquid nicotine in a 15-month-old child: an infant mortality case of nicotine intoxication. *Korean J Pediatr*. 2016;59(12):490-493.
235. Gill N, Sangha G, Poonai N, Lim R. E-cigarette liquid nicotine ingestion in a child: case report and discussion. *CJEM*. 2015;17(6):699-703.
236. Hughes A, Hendrickson RG. An epidemiologic and clinical description of e-cigarette toxicity. *Clin Toxicol*. 2019;57(4):287-293.
237. Richmond SA, Pike I, Maguire JL, Macpherson A. E-cigarettes: a new hazard for children and adolescents. *Paediatr Child Health*. 2018;23(4):255-259.

238. Tuhanoğlu B, Erkan SO, Özdaş T, Dericci Ç, Tüzün K, Şenkal ÖA. The effect of electronic cigarettes on voice quality. *J Voice*. 2019;33(5):811.e13-811.e17.
239. Sample HG. *The effect of electronic nicotine delivery systems on the vocal folds*. Master's thesis. Cleveland State University; 2019. Accessed September 2, 2021. <https://engagedscholarship.csuohio.edu/cgi/viewcontent.cgi?article=2148&context=etdarchive>
240. Patel S, Wooles N, Martin T. A systematic review of the impact of cigarettes and electronic cigarettes in otology. *J Laryngol Otol*. 2020;134:951-956.
241. Demir E, Topal S. Sudden sensorineural hearing loss associated with electronic cigarette liquid: the first case in the literature. *Int J Pediatr Otorhinolaryngol*. 2018;114:26-28.