Journal of Dental Sciences 19 (2024) 1919–1923

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Review article

Adverse effects of electronic cigarettes on human health

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Received 22 July 2024
Available online 3 August 2024

KEYWORDS
Adverse effects;
Electronic cigarettes;
Oral cancer;
Oral health;
Human health

Abstract Many people have associated e-cigarettes with adjectives such as trendy and cool, and regarded vaping as "a safer alternative to cigarette smoking". Compared with the conventional cigarettes, the public is less familiar with the dangers of e-cigarettes. E-cigarettes produce an aerosol by heating the e-liquid (usually comprising nicotine, flavorings, propylene glycol, vegetable glycerin, and other additives). Harmful substances are generated during the vaporization, such as formaldehyde. Cellular damages and DNA hypermethylation are also found to be associated with vaping. We reviewed the clinical neoplastic cases of patients with vaping history (three oral squamous cell carcinomas, one conjunctival squamous intraepithelial neoplasia, and one thoracic NUT-midline carcinoma). These patients tend to be younger than the average cancer patients. Although the exact relations between the cellular damages or DNA hypermethylation and vaping still need further investigations, we should be very careful about the dangers of using e-cigarettes as aids for cigarette smoking cessation.

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https://doi.org/10.1016/j.jds.2024.07.030
1991-7902/

Introduction

Electronic nicotine delivery systems (ENDS) are the devices that can heat the e-cigarette liquid comprising nicotine, flavorings, propylene glycol, vegetable glycerin, and other ingredients to generate an aerosol. The widely recognized term is "electronic cigarettes (e-cigarettes)" or "vapes". These products mainly consist of a cartridge and tank system for storage of liquid, a mouthpiece, a heating element, and a power source.[1]

The first commercialized e-cigarette product was launched in the US marketplace in 2007.[2] They were designed to produce an aerosol containing nicotine and other components so that the user can inhale the smoke. Thereafter, they have quickly become a popular source of nicotine for many people, especially for young adults (aged 18 to 24, 11.0%). It was reported that in 2021, 4.5% of adults aged 18 and over were current e-cigarette users.[3]

As an increase of their use, there are growing researches focusing on the impacts of e-cigarette to the oral health. Therefore, a well-organized review of associated researches on the impacts of e-cigarette to the oral health is important and of great value. In addition, we further explored the carcinogenic effects and comprehensively reviewed 5 clinical cases of neoplasm in patients with vaping history that have been reported so far, to the best of our knowledge.

Chemical compositions and their toxicity of e-cigarettes

Formaldehyde

Formaldehyde is one of the agents listed in the International Agency for Research on Cancer (IARC) group 1 carcinogen. During vaporization of vaping, formaldehyde-containing hemiacetals can be formed, and the concentration is even higher than that of nicotine. A conservative estimate of daily intake of formaldehyde of those who consume 3 mL of e-cigarette fluid per day at high voltage is 14.4 ± 3.3 mg, far more than that of those who smoke conventional cigarettes (1 pack per day).[4]

Flavorings

One of the selling points of e-cigarettes is the variety of flavors, which especially attract the young users. However, flavoring compounds in e-cigarette liquids are demonstrated to affect the chemical composition during vaporization of vaping and even generate toxicity. As mentioned above, although the e-liquids contain no formaldehyde or acetaldehyde, the generated aerosols contain considerable amounts of these toxic aldehydes. Thermal decomposition of these flavoring compounds is found to be the main source of aldehydes in the generated aerosols in a concentration-dependent manner.[5]

DNA methylation

DNA methylation or hypermethylation has been generally regarded as playing an important role in carcinogenesis. E-cigarette use is found to alter the epigenome of oral epithelial cells as the conventional cigarette smoking. E-cigarette users have altered levels of epithelial hypermethylation no matter it is a direct e-cigarette exposed site or not. When assessing their cytosine-phosphate-guanine (CpG) sites, there is a partial but not complete overlap of the CpG sites between conventional cigarette smokers and e-cigarette users. An overlapping of the epithelial hypermethylation sites that are directly exposed are mainly associated with growth factors and damage on genes such as *HDAC7* and *MTOR*.[6,7]

Impacts of e-cigarettes on oral health

As the increased use of e-cigarettes by the people, there are more and more studies on the adverse effects of e-cigarettes. The oral cavity and nearby are the sites that directly exposed to the aerosol, and accordingly, the adverse effects of e-cigarettes on oral health have been investigated. It has been demonstrated that there is an association between the use of e-cigarettes and caries risk level of patients, indicating that the e-cigarette users are prone to have a higher risk of developing dental caries.[8] Under the impact of e-cigarette, the oral microbiome may be altered, enriching the abundance of oral pathobionts, which cause epithelial cells more susceptible to infection.[9] The periodontal status (including peri-implant condition) of e-cigarette users is also proved to be worse than that of nonsmokers.[10] Besides, several oral mucosal lesions, such as nicotinic stomatitis, contact stomatitis, and candidiasis, are found to be associated with e-cigarette smoking.[11–13] Not only pathological changes have been related to the use of e-cigarettes, but also traumatic injuries that result from e-cigarette explosion, can be harmful to the users.[14]

In-vitro and in-vivo studies of adverse effects of e-cigarettes

On the other hand, some people might regard e-cigarettes as a safer alternative to conventional cigarettes or even for promoting smoking cessation. However, many experts have still debated this issue and conducted researches on them so far.[15–17] We have already mentioned the carcinogenicity of e-cigarettes in the previous section. At the cellular level, Wilson et al.[18] conducted a systemic review of adverse effects of e-cigarettes (including both e-cigarette liquid and vapor) on head, neck, and oral cells (including human gingival fibroblasts, oral epithelial cells, oral pharyngeal cells, head and neck squamous epithelial cells, premalignant keratinocytes, oral squamous carcinoma cells, and cultured cell lines). When these head, neck, and oral cells are exposed to e-cigarettes, several cellular adverse effects are found. These include aberrant cell morphology (such as larger, rounder, and less dense cells; atrophic oral cells; cells with large vacuoles, undistinguished mitochondria, and enlarged endoplasmic reticulum in the cytoplasm), detection of cytotoxicity (including round translucent and detached cells; apoptotic and necrotic cells), increased oxidative stress, reduced cell viability and proliferation, decreased cell metabolic activity, delayed fibroblast migration, and genotoxicity (such as breakage of DNA strands, DNA double-strand breaks, and specific DNA double-strand breaks in the Tp53 gene). However, most reviewed articles in this systematic review confirmed that conventional cigarette smoke is significantly more toxic to head, neck, and oral cells than e-cigarettes.[18] In oral squamous cell carcinoma (OSCC) cell lines, it is shown that e-cigarettes promote cell proliferation and induce morphological changes associated with an enhanced motility. Moreover, gene expression of some epithelial markers is decreased, whereas the expression of some mesenchymal proteins is enhanced.[19] Even though there are limited related studies, the use of mouse model to investigate the adverse effects of exposure to e-cigarettes is proved to be applicable for in vivo studies.[20] The short-term adverse effects are minimal in mice exposed to commercially available e-cigarettes, except the increased acidic mucus incretion in the larynx.[21] In addition to the head and neck region, other organs or systems may also be affected by vaping. The mice exposed to aerosol of e-cigarettes in a short term show extensive DNA damages in the lungs, heart, and bladder mucosae and diminished DNA repair in the lungs. After a prolonged exposure, the experimental mice developed the lung adenocarcinomas and bladder urothelial hyperplasia.[22,23]

Review of clinical cases of oral neoplasm in patients with vaping history

Here, we also reviewed three clinical cases of oral squamous cell carcinoma (OSCC) in the patients with history of vaping (Table 1). One is an OSCC occurring in a male patient who is 19 years old, an unusually young age to get the OSCC.[24] It has been reported that the young patients ($\leq$20 years old) associated with systemic diseases that predispose to cancer development such as xeroderma pigmentosum, Fanconi's anemia, and a history of bone marrow transplant may suffer from an OSCC.[25] However, this 19-year-old male patient is recorded as a relatively healthy subject using the e-cigarettes.[24] Therefore, the use of e-cigarettes may somehow play a role in the development of this OSCC. The other 2 patients have OSCCs occurring at the ages of 66 years and 59 years, respectively.[26] Both oral cancers are histopathologically confirmed as the basaloid squamous cell carcinoma (BSCC), which is a rare distinct variant of SCC. Tobacco and alcohol have been recognized as the risk factors for oral BSCC, but these two patients with possible vaping history also make us aware of the possible carcinogenic effect of e-cigarettes on the occurrence of oral BSCC.[27]

Table 1 Clinically reported cases of neoplasms in patients with vaping history.

Type of study	Year	Author	Patient age (year)	Patient sex	Clinical presentation	Pathological diagnosis	Risk factors (arranged in chronological order)
Neoplasms in the oral cavity							
Case report	2017	Nguyen et al.[26]	66	Male	Several exophytic masses with surrounding hyperkeratotic areas at the tongue	Basaloid squamous cell carcinoma	E-cigarettes: 20 times per day for 13 years
Case report	2017	Nguyen et al.[26]	59	Male	A non-healing ulceration at the lower lip	Basaloid squamous cell carcinoma	E-cigarettes: daily for 13 years (uncertain quantity of daily use)
Case report	2021	Klawinski et al.[24]	19	Male	A non-healing ulceration at the left lateral border of the tongue	Poorly differentiated invasive squamous cell carcinoma	Conventional cigarettes: 0.5 pack per day for 1 year E-cigarettes: daily for 4 years (uncertain quantity of daily use)
Neoplasms in other human organs rather than the oral cavity							
Case report	2020	Shields et al.[29]	22	Male	Painless unilateral blurred vision (right eye)	Conjunctival intraepithelial neoplasia (CIN) with high-grade features	E-cigarettes: 5 vapes or more per day for 5 years
Case report	2022	Ballenberger et al.[32]	33	Male	A consolidative right lung opacity with multiple hypodense hepatic lesions with chest pain and fever	Thoracic NUT-midline carcinoma (poorly differentiated carcinoma with squamous and neuroendocrine features)	Conventional cigarettes: 20 packs per year for unknown duration E-cigarettes: for 1 year (uncertain quantity of daily use and frequency)

Review of clinical cases of neoplasm of other organs in patients with vaping history

Current evidence reveals that vaping may have deleterious health implications on almost all organs in the human body.[28] Like those cases related to OSCC, there is an extremely low number of the clinical premalignant and malignant lesions occurring in human organs in patients with vaping history, which are presented in Table 1. One is a vaping-related conjunctival squamous intraepithelial neoplasia in a young male patient.[29] Typically, conjunctival squamous intraepithelial neoplasia may be related to the sunlight, but other risk factors such as the immunosuppression, human papilloma virus infection, and smoking have also been proposed.[30,31] The authors of this study mentioned that the squamous intraepithelial neoplasia with high-grade features in this young male patient may be related to the 5-year chronic vapor exposure from e-cigarettes, but they also emphasized the need of further researches to get deep insight.[31] The other is a case of thoracic NUT-midline carcinoma, which is a rare, aggressive subtype of SCC defined by rearrangement of the NUTM1 (aka NUT) gene, although its risk factors have been still poorly understood so far.[32,33] However, its histopathological findings are generally consistent with a poorly differentiated carcinoma with focal squamous differentiation, sharing similar features to other cases and providing a possible clue to the association of this poorly differentiated carcinoma with the history of vaping.

Conclusion

There are growing number of studies demonstrating the adverse effects of vaping. Based on these findings, the safety of using e-cigarettes is questioned. During the process of vaporization, harmful substances, such as formaldehyde, are generated. The formaldehyde is one of the agents listed in the IARC group 1 carcinogen. E-cigarette users have also been detected to have altered levels of oral epithelial DNA hypermethylation, suggestive of the possible carcinogenic effects of e-cigarette vaporization products. We reviewed the clinical neoplastic cases of patients with vaping history, including three OSCCs, one conjunctival squamous intraepithelial neoplasia, and one thoracic NUT-midline carcinoma. Obviously, the harm of e-cigarettes is not only limited to the directly-exposed oral mucosal sites. Three of them aged under 40, and one of them is even a 19-year-old male. Nearly all these e-cigarette-induced lesions or carcinomas are reported to show the dangerous histopathological features of poor differentiation of neoplastic cells. Although further researches are need to explore the exact relations between the cellular damages or DNA hypermethylation and vaping, young patient group and worrisome histopathological features warn us about the dangers of e-cigarettes. Thus, it should be very cautious when broadly recommending e-cigarettes as aids for cigarette smoking cessation.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

This work was partially supported by the grant [NSTC 111-2314-B-006-037-MY2] of National Science and Technology Council, Taiwan to Yu-Hsueh Wu.

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