ELECTRONIC CIGARETTES AND THE POTENTIAL RISKS OF DEVELOPING ORAL CANCER

CIGARROS ELETRÔNICOS E OS RISCOS POTENCIAIS PARA O DESENVOLVIMENTO DE CÂNCER BUCAL

LOS CIGARRILLOS ELECTRÓNICOS Y LOS POSIBLES RIESGOS DE DESARROLLAR CÁNCER BUCAL

https://doi.org/10.56238/sevened2025.014-007

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ABSTRACT

Electronic cigarettes emerged strongly in the global market and, despite limited research on their adverse effects, were initially considered a less harmful substitute for conventional smoking. After just over 20 years since their global introduction, there has been a significant

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increase in studies involving users of these devices, focusing on their potentially oncogenic effects, including clinical cases of oral neoplasms attributed to their use, indicating a new public health concern. This integrative review conducted searches on MEDLINE, PubMed Central, EMBASE, and Cochrane databases, investigating cellular changes associated with the development of oral cancer in human users of electronic cigarettes. The PIO acronym guided the research: Population – electronic cigarette users; Intervention – analysis of cells from the oral cavity exclusively of these users; Outcome – genetic mutations or cellular alterations indicative of oral neoplasms related to use. From 493 publications found, after deduplication in Rayyan and application of inclusion and exclusion criteria, 11 articles were selected. Data analysis revealed that electronic cigarettes are not a suitable alternative to conventional cigarettes, as they predispose users to neoplastic development and increasingly affect a more vulnerable population, especially young people.

Keywords: Oral Cancer. Head And Neck Cancer. Electronic Cigarettes. Nicotine.

RESUMO

Os cigarros eletrônicos surgiram com grande força no mercado mundial e, apesar de poucas pesquisas sobre seus efeitos adversos, foram inicialmente considerados um substituto menos nocivo ao tabagismo convencional. Após pouco mais de 20 anos desde sua introdução global, observa-se um aumento significativo de estudos com usuários desses dispositivos, focando em seus efeitos potencialmente oncogênicos, incluindo casos clínicos de neoplasias bucais atribuídas ao consumo, o que aponta para um novo problema de saúde pública. Nesta revisão integrativa, foram realizadas buscas nas plataformas MEDLINE, PubMed Central, EMBASE e Cochrane, buscando alterações celulares associadas ao desenvolvimento de câncer bucal em usuários humanos de cigarros eletrônicos. Utilizou-se o acrônimo PIO para guiar a pesquisa: População - usuários de cigarros eletrônicos; Intervenção - análise de células da cavidade bucal exclusivamente desses usuários; Desfecho - mutações genéticas ou alterações celulares indicativas de neoplasias bucais decorrentes do consumo. Das 493 publicações encontradas, após desduplicação no Rayyan e aplicação dos critérios de inclusão e exclusão, selecionaram-se 11 artigos. A análise dos dados revelou que os cigarros eletrônicos não constituem uma boa alternativa aos cigarros convencionais, pois predispõem ao desenvolvimento neoplásico e atingem de forma crescente e inesperada um público mais vulnerável, especialmente os jovens.

Palavras-chaves: Câncer Bucal. Câncer de Cabeça e Pescoço. Cigarros Eletrônicos. Nicotina.

RESUMEN

Los cigarrillos electrónicos han irrumpido con fuerza en el mercado global y, a pesar de la limitada investigación sobre sus efectos adversos, inicialmente se consideraron un sustituto menos dañino del tabaco convencional. Poco más de 20 años después de su introducción global, se ha observado un aumento significativo de estudios con usuarios de estos dispositivos, centrados en sus posibles efectos oncogénicos, incluyendo casos clínicos de cáncer oral atribuidos al consumo, lo que apunta a un nuevo problema de salud pública. En esta revisión integrativa, se realizaron búsquedas en MEDLINE, PubMed Central, EMBASE y Cochrane, buscando alteraciones celulares asociadas con el desarrollo de cáncer oral en usuarios humanos de cigarrillos electrónicos. El acrónimo PIO se utilizó para guiar la investigación: Población: usuarios de cigarrillos electrónicos; Intervención: análisis de células de la cavidad oral exclusivamente de estos usuarios; Resultado: mutaciones genéticas o alteraciones celulares indicativas de cáncer oral resultante del consumo. De las 493 publicaciones encontradas, tras la deduplicación en Rayyan y la aplicación de los criterios de inclusión y exclusión, se seleccionaron 11 artículos. El análisis de datos reveló que los cigarrillos electrónicos no son una buena alternativa a los cigarrillos convencionales, ya que

predisponen al desarrollo de neoplasias y afectan cada vez más e inesperadamente a una población más vulnerable, especialmente a los jóvenes.

Palabras clave: Cáncer Oral. Cáncer de Cabeza y Cuello. Cigarrillos Electrónicos. Nicotina.

1 INTRODUCTION

Cancer comprises a group of diseases, characterized by the disordered growth of cells that divide rapidly and uncontrollably, resulting from several etiological factors, including genetic, environmental, cultural, socioeconomic, habits, and even the aging process (Santos & Padilha, 2022). This condition is manifested by dysregulation of genes responsible for essential cellular functions, such as the control of cell growth, multiplication, and differentiation (Tommasi et al., 2021).

This chapter results from a study on the development of oral cancers associated with the use of electronic cigarettes (EC), considering that the habit of smoking is the main predisposing factor for oral tumors and, according to the WHO, preventable (Benedetto, 2016). Malignant oral neoplasms affect the lips, structures such as gums, tongue, bones, salivary glands, and oropharynx (Furtado et al., 2019), presenting signs ranging from white or red lesions to wounds that do not heal and can cause chronic pain in the bone regions and throat (Vinay et al., 2025).

It is important to remember that the mouth is an organ of the stomatognathic system of extreme relevance for quality of life, and pathologies in this region can compromise essential functions such as chewing, swallowing, speaking and breathing (Mehanna, Paleri, West & Nutting, 2010). Being the entrance to the upper aerodigestive tract, the mouth is the first site of contact for injuries with this system (Patel, Gargade & Mangrulkar, 2023).

Oral cancer is believed to be the sixth most common type of cancer in the world (Vinay et al., 2025). It is estimated that in 2025, 586,500 new cases of oral cancer will be diagnosed, resulting in 282,200 deaths caused by the disease (World Health Organization, 2024).

With the intention of producing something safer for users' health than combustible cigarettes, the American inventor Herbert A. Gilbert designed and patented the first type of electronic cigarette in 1963 (Jardim & Santos, 2025; Nogueira, Fernandes & Nedel, 2025). Despite the production of the prototypes, the "smokeless non-tobacco cigarettes", as they were called, were never commercialized. Unlike the model that has been increasingly disseminated and commercialized, developed by the Chinese Hon Lik in 2003, who founded Dragonite International Ltd. (Jardim & Santos, 2025).

The twenty-first century has brought us electronic cigarettes as an alternative to combustible cigarettes, accompanied by the feeling of reduced harm to health compared to their paper precursors (Cardenia et al., 2018; Wu & Chiang, 2024). In recent years, they have gained popularity among young people in primary and secondary schools, always advertised as a safer alternative to conventional cigarettes (Catala-Valentin, 2020; Tellez et al., 2021). Has a substitute finally been found that is not the main predisposing factor for oral cancer, or

is the mistake once again made, considering that conventional cigarettes were even distributed in hospitals before they were recognized as carcinogenic in 1960?

The impression that the consumption of electronic cigarettes is safer than that of combustible cigarettes is due to the lack of knowledge about the heating process of the e-liquid, which can generate new decomposition compounds, suggesting a great risk to the health of users (Palaia et al., 2025). Research has shown that these compounds are potent carcinogens, capable of even crossing the placental barrier and causing genotoxic damage to fetal tissue (Lima et al., 2023).

E-cigarettes are battery-powered devices that heat and release aerosols inhaled by the user, which are sourced from a liquid compound that can include propylene glycol, glycerin, nicotine, contaminants such as polycyclic aromatic hydrocarbons, nitrosamines, organic and inorganic chemicals such as toxic metals, as well as endotoxins and flavoring compounds (Layden et al., 2020). With about 16 thousand options available, including models, flavors, and flavors, electronic cigarettes have contributed to the increase in the popularity of the habit of smoking, especially among young people, who also believe that these devices are less harmful to health (Lima et al., 2025). However, numerous studies contradict this perception and point to the harm caused, especially in the oral cavity, the gateway to vaporization (Palaia et al., 2025).

Although 20 years have passed since the introduction of electronic cigarettes on the world market, the consequences of their use remain quite controversial. In 2023, the United Kingdom, hoping to significantly reduce smoking, distributed through its health system, the National Healthcare System (NHS), 1 million electronic cigarettes to chronic smokers, with the aim of reducing the consumption and harmful effects of conventional cigarettes. However, the campaign has generated concern among researchers who believe that the health risks outweigh the benefits (Lang et al., 2023).

The associations between vaping and the development of oral cancer are being extensively investigated, and the carcinogenic potential of the aerosol constituents of e-cigarettes has been increasingly questioned. These compounds can alter the oral microbiome, induce oral epithelial cell death, and cause DNA damage. In addition, the presence of nicotine in the devices has been shown to promote the development of oral leukoplakia, a potentially malignant disorder (Yeoh, 2024).

To date, most studies on e-cigarettes have been conducted in vitro. However, research involving human beings has already been published. This study explored human research on possible oral cell alterations that may indicate carcinogenesis associated with the use of these devices, as well as clinical cases of oral neoplasms attributed to their use, aiming to

broaden the reflection on the safety desired by public health systems that bet on vaporization as a method for conventional smoking cessation. From this perspective, recent studies focused on cells, biomarkers, and case reports exclusively in human users of e-cigarettes were selected, with the aim of presenting an up-to-date and evidence-based study.

Because it is a recent topic that requires special attention from the scientific community, mainly due to the erroneous perception of the absence of maleficence by the user population, more studies should be carried out, published and widely disseminated in a way that is understandable to the general public as well. Being a public health issue, this issue cannot be restricted to the academic-scientific sphere, and Dentistry needs to take a stand.

2 THEORETICAL FOUNDATION

For a better understanding, a theoretical framework was made about electronic cigarettes and their components, the presence of tumor biomarkers, the cytotoxic and genotoxic effects that can trigger oral neoplasms, in addition to data on public health and regulation of EC consumption. The importance of the theme suggests that more detailed studies on the consequences of the use of ECs should be carried out, because although they may appear to be less harmful and apparently milder than combustible cigarettes, the use of these devices can bring highly undesirable outcomes, difficult to resolve and, consequently, the need for highly complex treatments.

2.1 ELECTRONIC CIGARETTES

Smoking is a psychosocial habit widely recognized for its high addictive capacity and for the serious damage to the health of users and those around them. Systemically, cigarette consumption is associated with the development of diseases such as cancer, chronic respiratory problems, and interference with the efficacy of drugs, maintaining a strong industry that causes more than 7 million deaths annually worldwide (Sadhasivam et al., 2024).

With the intention of creating a product that would not compromise the health of users, that would resemble conventional cigarettes and provide the same pleasure of smoking, in 1963, in Beaver Falls, Pennsylvania, USA, the American Herbert A. Gilbert designed and patented the first electronic cigarette. A smoker, Gilbert idealized the device as a possible substitute for combustible cigarettes (Jardim & Santos, 2025; Nogueira, Fernandes & Nedel, 2025). Although it produced prototypes called smokeless non-tobacco cigarettes, these were never manufactured on a large scale or commercialized due to the technological limitations of the time (Santos et al., 2021).

A few decades later, in 2003, in Beijing, the Chinese pharmacist Hon Lik developed another model of electronic cigarette, a liquid vaporizer containing nicotine, also with the purpose of offering greater health safety. He founded Dragonite International Ltd. and achieved great success in the commercialization of the "e-cig". Later, he sold the patent to Imperial Tobacco Group (Jardim & Santos, 2025).

E-cigarettes are battery-powered devices that heat and release aerosols inhaled by the user, originating from a liquid compound that may contain propylene glycol, glycerin, nicotine, as well as contaminants such as polycyclic aromatic hydrocarbons, nitrosamines, organic and inorganic chemicals, including toxic metals, endotoxins, and flavoring compounds (Layden et al., 2019). It should be noted that some of these metals, such as nickel, chromium, cadmium, tin, aluminum, and lead, are potentially carcinogenic (Gaur & Agnihotri, 2019).

The first generations of e-cigarettes were disposable, similar to conventional cigarettes, developed to deliver nicotine to the user. Newer generations are refillable, have different formats than traditional cigarettes, and can provide various substances in addition to nicotine, including tetrahydrocannabinol (THC), the main psychoactive component of cannabis (King, Jones, Baldwin, & Briss, 2020).

Although they are considered a safer alternative to conventional cigarettes, e-cigarettes use more than 7,000 flavorings that, along with the nicotine liquid, can be added to the humectants propylene glycol and vegetable glycerin to make up the e-liquid, which is heated, vaporized, inhaled and absorbed by the oral and aerorespiratory mucous membranes. This process generates carcinogenic carbonyls, such as formaldehyde, acetaldehyde, and acrolein, which are responsible for highly addictive effects (Tellez et al., 2020). Cigarette dependence, as well as withdrawal symptoms, is related to the release of dopamine in response to frequent exposure to the product (Pemberton, 2018).

According to Klawinski et al. (2021), electronic cigarettes have 4 basic components:

1. Cartridge or capsule: compartment that stores the e-liquid.
2. Atomizer: heating element.
3. Battery.
4. Inhalation nozzle.

According to Kotewar et al. (2023), the FBs were divided into four generations:

- First-generation CEs, or "cig-a-likes," featured fixed, low-voltage electrodes and resembled conventional cigarettes in feel and appearance. Currently, they are no longer sold.

- Second-generation CE: Wider batteries with variable voltage, described as "pen-style batteries." Composed of translucent "clearomizers" (tanks), they also have larger and refillable fluid reservoirs.
- Third-generation CE: Called "Mods" because they involve modified batteries that allow users to adjust the voltage and power of the device. Some variants offer additional functions such as customization and mobile phone charging. They can be more robust than clearomizers.
- Fourth-generation CE: presented in the "pod" style, more compact, with fixed voltage and batteries in different formats, including USB or teardrop-shaped, with modifications appearing more and more quickly.

Currently, an extensive variety of models and flavors available, estimated at around 16 thousand options available, has contributed to the increase in the popularity of ECs, especially among young people who believe that the devices are less harmful to health (Lima et al, 2025).

However, numerous studies disagree with this perception, and point to the harm caused, above all, in the oral cavity, the gateway to vaporization (Guo & Hecht, 2023).

So-called e-liquids contain a variety of chemical constituents that can confer adverse health effects, including, in addition to nicotine, propylene glycol and glycerin, contaminants such as polycyclic aromatic hydrocarbons, nitrosamines, volatile organic chemicals, inorganic chemicals such as toxic metals, endotoxins and flavoring compounds such as diacetyl and 2,3-pentanedione, constituents that can undergo thermal decomposition (pyrolysis) by the metal heating coils, processing novel aerosolized compounds with different toxicological profiles (Layden et al., 2019). E-cigarette users have elevated levels of biomarkers of volatile organic compounds such as acrylamide, acrolein and acrylonitrile, metals such as cadmium and selenium, and propylene glycol, compared to non-users, and may also be exposed to other carcinogenic chemicals such as benzene and chromium (Guo & Hecht, 2023).

Such products have never before been vaporized by human beings, and here is a question: If drugs should be thoroughly tested in guinea pigs, later in humans,

And it takes many years to get your patent approved, how can a device with so many chemical elements, some proven carcinogenic, simply be created and marketed almost indiscriminately?

2.2 CYTOTOXICITY AND GENOTOXICITY OF ECS IN ORAL CELLS

Numerous in vitro studies have investigated and reported the risk associated with the use of e-cigarettes by exposure of oral cells to liquids or vapors, demonstrating the tendency of

oral cells to develop DNA damage, oxidative stress, metabolic changes, changes in inflammatory biomarkers, cytotoxicity, and genotoxicity, either by toxicity related to nicotine, or to flavor additives (Palaia, 2025). It should be considered that EC users do not vape once a day, but there are countless times when the oral mucosa is subjected to the harmful effects of the product.

The first contact of the various inhaled chemicals with the aerosol of e-cigarettes occurs in the mouth, and the first research carried out on this interaction was studies in guinea pigs or in vitro, and demonstrated that exposure to e-cigarettes can produce various deleterious effects on oral health, such as dysbiosis, inflammation, dental and gum problems, periodontal diseases, and changes in the oral microbiome, also implying adverse effects on the head and neck and oral cells in the order of morphological aberrations, oxidative stress, cytotoxicity, genotoxicity, reduced viability of healthy cells, and delayed fibroblast migration (Guo & Hecht, 2022).

Despite the strong endorsement from Public Health England, which argued that e-cigarettes would be 95% less harmful than conventional cigarettes, recent studies point to potential risks, including the induction of endothelial dysfunction and DNA damage, highlighting the importance of more research on the long-term health impacts of e-cigarettes (Herzog et al., 2024). According to Lima et al. (2023), since the introduction of ECs on the market, research approaches on the risks of their long-term use have been very limited and, even though it is known that the levels of chemicals and metals present in ECs are lower, compared to combustible cigarettes, these compounds give rise to DNA-reactive carcinogens, genotoxins, which can result in mediators of cell mutation under oxidative stress, making the oral cavity the primary target of cancer development risk (Lima et al., 2023).

Genotoxic effects of nuclear abnormalities, such as micronuclei, karyolysis, binucleates have been associated with smoking, and micronucleus frequencies reinforce the idea that these are products of early events in the development of the human oncogenic pathway, especially in the oral cavity, which is the front of exposure to cigarettes (Abdul et al., 2022). Such effects were also corroborated in a study by Schwarzmeier et al. (2021), by the use of EC.

DNA damage is usually rectified by DNA polymerase review, recognizing damaged sites, but it can fail when a cell accumulates a large amount of DNA damage in a short time, saturating repair systems, and not preventing replication from occurring in cells with unrepaired lesions, leading to the development of mutations that can result in cancer (Hamad et al., 2021). Regarding genetic mutations, according to Du, Zheng, Lu & Zhang (2025), the

most commonly found type in tongue squamous cell carcinoma is the TP53 mutation, a tumor suppressor gene, with rates ranging from 27.7% to 60%, and result in oncogenic properties, where mutations produce non-functional P53 proteins (responsible for repairing DNA damage and promoting apoptosis). associated with unfavorable outcomes, since the uncontrolled proliferation of cells with damaged DNA can collaborate with tumorigenesis.

Another factor in the development of tumors may be from a pathology resulting from an uncontrolled inflammation, and the role of "inflammatomes" in carcinogenesis should be considered, which are currently being studied because they are a complex platform that, when activated, promotes the release of pro-inflammatory cytokines, such as interleukin IL-1β and, as this cytokine seems to play a primary role in the progression of cancer, it can even be used as a potential biomarker in tumor progression (Idris, Ghazali & Koh, 2015). Kamal & Shams (2022), report that IL-1β causes inflammation by acting directly on numerous cell species, in response to cell damage or infections, and that tumor development can be promoted by an altered signaling pathway of transforming growth factor-β, or TGF-β, a polypeptide cytokine that regulates cell changes that increase in malignant tumors.

Lactate dehydrogenase (LDH), an enzyme involved in aerobic glycolysis, catalyzes the pyruvate to lactate reaction, and when oxidative stress is present, it is released out of the cell, raising extracellular LDH levels, including in saliva, and which may suggest tissue damage and cell necrosis, as seen in patients with potentially malignant oral diseases, it can serve as a biomarker for the predictability of these diseases (López-Pintor et al., 2025). LDH concentrations in saliva, expressing cell death, can be considered an inherent indicator of the effect of damage that causes the loss of oral mucosal integrity (Pandarathodiyil et al., 2021).

Many mucosal base lesions are pro-mutagenic if left unrepaired, and the removal of damage to these DNA bases generates the so-called apurin/pyrimidine site (Jacobs & Schär, 2012). Toxicants and carcinogens resulting from tobacco and e-cigarettes can damage DNA, resulting in the formation of these sites and the initiation of the carcinogenic process (Guo, Ikuemonisan, Hatsukami & Hecht, 2021). Elevated levels of apurine (PA) sites have been associated with tumor progression and resistance to oncotherapy, making them important indicators for cancer diagnosis and monitoring and treatment (Wang, Yi, Li, & Li, 2025).

N'-nitrosonornicotine (NNN) is an important carcinogenic N-nitrosamine formed by the nitrosation of tobacco alkaloids, nicotine and nornicotine. Although it seems specific to tobacco, the carcinogen NNN, in addition to being present in traces of the EC fluid, can result from two sources: from the direct consumption of tobacco-containing products, or it can be formed endogenously from nornicotine, which, in addition to being a constituent of tobacco,

is also a metabolite of nicotine (Bustamante et al., 2018). The International Agency for Research on Cancer has classified NNN as a human carcinogen (Nikam, et al., 2024).

Other genetic dysregulations that may contribute to cancer development are aberrant RNA transcriptions, by overexpression or underexpression, observed by RNA sequencing (Tommazi et al., 2019; Casotti et al., 2024). This recent technology has been adopted by clinical research and has been helping high-precision medicine, as it consists of a high-throughput sequencing method, measuring complementary DNA transcripts, where they are mapped to a gene, and their profusion must be related to gene expression (Casotti et al., 2024).

Metalloproteinases are key enzymes involved in the remodeling of the extracellular matrix, regulating numerous cellular and immunological processes under homeostatic and pathological conditions (Ioannou, Katsoulieris & Nikolaos, 2025). Myeloproteinase expression levels are significantly associated with the infiltration of a good number of immune cells, including monocytes and dendritic cells (Wang et al., 2025).

Mechanisms of epigenetic alterations, such as DNA methylation at key sites in the genome, are linked to the emergence of cancer, where the sequential accumulation of genetic and epigenetic changes in proto-oncogenes and tumor suppressor genes originate neoplastic cells (Santos, & Padilha, 2022). DNA methylation is understood as an epigenetic modification that regulates gene expression that does not alter the DNA sequence, and plays an important role in the maintenance of cell identity and in the modulation of biological functions that, due to hypomethylation or hypermethylation, can lead to anomalous expression of essential genes, collaborating with the progression of diseases (Zutin et al., 2025).

Despite being highly efficient, human cells have a certain fragility under the effect of aggressive products. Our immune system is overloaded, directing the defenses towards the aggressor agent and reducing the defense capacity, which makes us more susceptible to inflammation, infections and viral agents. Chronic use of e-cigarettes can compromise the immune response, providing users with a greater susceptibility to respiratory infections, including colds, flu, bacterial pneumonia, tuberculosis, and the infection caused by COVID-19, for example (Rocha et al., 2022).

2.3 PUBLIC HEALTH POLICIES AND REGULATION

In 2010, France and England held an online forum dedicated to conventional smoking cessation and the use of vapes, bringing together 3,587 participants who call themselves "vapers". Most reported that e-cigarettes helped them quit smoking or reduce consumption (96%), and of these, 87% perceived the device as less toxic than conventional cigarettes

(Benedetto, 2016). However, clinical cases indicate that vaporization can cause serious consequences, including the development of oral neoplasms and cancer in exclusive users of these devices (Nguyen et al., 2017; Klawinski et al., 2021).

The authors state that the use of electronic cigarettes is a growing global trend and that the probability of starting the consumption of conventional cigarettes quadrupled among adolescents who used these devices, in addition to not collaborating with smoking cessation. Longitudinal studies suggest an association between e-cigarette consumption and conventional cigarette smoking initiation among young people who have never smoked (Barufaldi et al., 2021). The young population is the largest consumer of electronic cigarettes; in the US, use among adolescents increased from 11.7% to 27.5% between 2017 and 2019. In Great Britain, a study of students aged 15 to 16 showed a prevalence of 37.3%, while in Malaysia it reached 86.5%, being more common among students aged 19 and over (Alsanea et al., 2022). The irreversible effects of nicotine on the developing brain predispose to dependence, which worries doctors, health professionals, and the scientific community in the face of increased use among young people (Kotewar, Pakhale, Tiwari, Reche & Singi, 2023).

Advertising and ease of access, including through the internet, where sales occur without strict criteria, contribute to the increase in consumption among young people. Studies indicate that consumption is higher among adolescents due to the difficulty in controlling the minimum age for purchase (Carlos, Bomfim & Pavanello, 2025). According to Abrão, Diniz and Migliorini (2025), adolescence is marked by behavioral changes, new experiments, biological maturation of puberty and the search for identity. Substance use and abuse are associated with impairments in social, cognitive, and biological development. Teenagers seek to be accepted, "cool" and popular, which can lead them to attitudes that compromise the future of millions of them.

According to Sales et al. (2025), in view of the evidence on the use of electronic cigarettes and their influence on behavioral changes, such as increased impulsivity and a greater propensity to use other products, including combustible cigarettes and illicit drugs, stricter regulatory measures, educational campaigns, and prevention programs are essential to restrict this practice among young people. In addition, it is necessary to expand restrictions on the commercialization, control advertising and intensify the inspection of the sale of these devices. These strategies are essential to reduce the harm to public health, avoiding the trivialization of the use of electronic cigarettes among adolescents and adults (Sales et al., 2025).

It is curious to observe that some health professionals, even aware of the harm of smoking, maintain the habit. These professionals play a fundamental role in raising

awareness about the risks of tobacco. However, researchers point to an increase in the use of electronic cigarettes among health students, in addition to highlighting insufficient knowledge and misconceptions about these devices. Alsanea et al. (2022) associate this scenario with a negative influence on the use of electronic cigarettes, which can lead to adverse consequences for public health. The authors also report that much of the population is unaware that these devices contain other chemicals and metals, and can provide higher levels of nicotine than conventional cigarettes. This results in increased dependence and predisposition to health problems, especially in adolescence, when nicotine exerts long-lasting behavioral and neurological effects (Alsanea et al., 2022).

When they were introduced to the market, electronic cigarettes had no regulations or restrictions for their commercialization. Currently, in the United States, there are regulations that prohibit the use of these devices in indoor environments intended for the public, such as restaurants, theaters, hospitals, schools and workplaces, as well as laws that prevent the sale to minors in all 50 states. These regulations vary significantly between countries. Some maintain strict bans on the marketing of nicotine-containing e-cigarettes, such as Japan and the European Union, which regulates the sale, nicotine content and advertising. The United Kingdom has adopted a more favorable stance, promoting e-cigarettes as a harm reduction tool for smokers (Albadrani et al., 2024). In Brazil, despite the prohibition by the National Health Surveillance Agency (ANVISA), through the Resolution of the Collegiate Board

- RDC No. 855/2024, e-cigarettes continue to be widely used, with an estimated 600% increase in consumption between 2018 and 2023. This reality has generated intense legal and health debates, going beyond the scope of health law and becoming a public health problem (Baiano & Mendes, 2025).

Most vapers, as users call themselves, claim to vape nicotine to help quit smoking. However, some have never smoked conventional cigarettes, indicating that there is already a population that wants to quit using e-cigarettes, but faces difficulties due to the addictive properties of nicotine (Butler et al., 2025). Even knowing the harm of smoking, many smokers are unable to quit the habit, as nicotine dependence causes strong withdrawal symptoms in the absence of the drug. Therefore, the "weaning" process requires professional follow-up through pharmacological and non-pharmacological therapeutic approaches (Silva et al., 2025).

Governments, in an attempt to reduce cigarette consumption, usually adopt tax increases, a measure long considered by traditional tobacco control groups as one of the most effective ways to combat use. In addition to promoting the reduction of consumption by increasing prices, these measures generate revenue for the State. However, they also hinder

the transition from conventional cigarettes to e-cigarettes and encourage illicit practices, with the UK being a notable exception (Mzhavanadze, 2025).

In 2023, with the hope of significantly reducing smoking, the British health system, NHS, distributed 1 million e-cigarettes to chronic smokers in a campaign entitled "Swap to Stop". This initiative has caught the attention of researchers who point to more health risks than benefits, due to concerns about long-term systemic damage caused by e-cigarettes and the potential for relapse with continued vaping (Lang et al., 2023). Nearly 25% of participants randomized to e-cigarette user groups in the study by Lang et al. (2023) became dual users, increasing the risk of respiratory diseases and developing oral cancer compared to smoking alone. Thus, it is perceived that, in an attempt to eliminate one problem, one can acquire another that enhances the deleterious effects of conventional cigarettes, and vice versa. Because there is no combustion, electronic cigarettes do not produce all the toxins present in conventional cigarette smoke, such as carbon monoxide. However, chemicals that were once characteristic only of tobacco, such as volatile organic compounds, nitrosamines, heavy metals, and silicate particles from the device's heating elements, may be present in e-cigarette aerosols at low levels but with strong biological potential (Pandarathodyiyl, 2021).

Seeking answers, numerous studies investigate the association of e-cigarettes with oral cancer, which can develop on the lips, tongue, mucosa, floor of the mouth, gum line, periodontium, bones, salivary glands, and oropharynx (Furtado et al., 2019). The following table (Chart 1) presents the estimate of new cases and deaths caused by oral tumors in the world in the years 2022 and 2025, according to the International Agency for Research on Cancer (World Health Organization, 2024).

Chart 1 - Numbers of new cases and deaths from oral cancer in the world.

Estimation of the Number of New Cases and the Number of Deaths from Oral Cancer				
	2022		2025	
Location	**New Cases**	**Number of deaths**	**New Cases**	**Number of Deaths**
Lips and oral cavity	390k	188k	415k	201k
Salivary glands	55.1k	23.9k	58.5k	25.5k
Oropharynx	106k	52.3k	113k	55.7k
Total	**551.1k**	**264.2k**	**586.5k**	**282.2k**

Source: Prepared by the author based on the International Agency for Research on Cancer - World Health Organization (2024).

Every year, the number of cases of oral cancer in the world increases, which is due to the immense number of smokers who overload health systems. However, very few information campaigns are seen in health institutions, schools, TV stations and social networks, tasks that health systems and their actors avoid performing efficiently.

3 HUMAN STUDIES

A synthesis of the results of human studies, such as clinical cases of carcinomas attributed to the use of e-cigarettes, clinical trials, and cross-sectional studies on gene or cellular alterations and mutations with carcinogenic potential, as well as tumor oral biomarkers that may indicate the presence of or predisposition to the development of malignancies related to the use of electronic smoking devices, resulted in the following table (Chart 2).

Chart 2 - Results of human studies on the cytotoxic and genotoxic effects promoted by the use of ECs.

Author	Type of study	Sample	Time of use/exposure to CE	Cell site of involvement or collection	Outcomes
Nguyen (2017)	Clinical cases	Case 1 Male/ 66 years old Case 2 Male/ 59 years old	20 times a day/13 years 30 times day/13 years	Tongue Vermilion of the lower lip	Basaloid squamous cell carcinoma
Tommasi (2019)	Cross-sectional study	Vapers (F/M)/ 22-55 years n=42	Minimum 6 months of exclusive use	Oral Cell RNA Sequencing	Aberrant transcripts represented by overexpression (74.4%) and RNA underexpression (25.6%)

Schwarzmeier (2021)	Cross-sectional study	Vapers (F/M)/ 17-60 years n=20	Minimum 5 months	Exfoliative cytology of the tongue and oral floor	Increase in micronuclei; induced cellular abnormalities: karyolysis, binucleation, broken eggs, nuclear buds

Hamad (2021)	Cohort study (3 visits/ NI intervals)	Vapers (F/M)/ 18.5+ n=3	Minimum 2 months	Buccal cell collection before and immediately after 20 puffs	Increased expression of the TP53 gene
Klawinski (2021)	Case report	Male/ 19 years old	Variable Quantity/ 4 Years	Tongue with extension for the buccal floor	Invasive squamous cell carcinoma
Pandarathodiyil (2021)	Cross-sectional study	Vapers (F/M)/ 26 ± 7.35 years n=29	Minimum 6 months	Saliva	LDH= 35.15 ± 24.34 mU/ml
Guo (2021)	Cohort study (1x month/6 months)	Vapers (F/M)/ 18+ n=30	Minimum 3 months of exclusive use	Oral cells	In 28 out of 30, 3.3 AP locations per 10^7 nts
Bustamante (2021)	Cross-sectional study	Vapers (F/M)/ 31.3 ± 12.2 years n=20	Minimum 3 months of exclusive use	Saliva and oral cell analysis	Endogenous formation of NNN
Kamal (2022)	Cross-sectional study	College student vapers n=50	Minimum 12 months	Unstimulated saliva sample	Elevated levels of inflammatory and cancer risk biomarkers IL-1β and TGF-β
Ye et al. (2022)	Cross-sectional study	Vapers (F2/M10) 22-53 years old	Not Informed	Saliva and Crevicular Gingival Fluid	Significant reduction in myeloperoxidase and metalloproteinase (MMP-9)
Herzog (2024)	Cross-sectional study	Vapers (F) 18 - 86 years n=152	Minimum 1 year of exclusive use	Oral cells	Change in DNA levels of hyperM and hypoM

4 DISCUSSION

The three clinical cases attributed to the use of e-cigarettes consisted of squamous cell carcinoma. In the two cases reported by Nguyen et al. (2017), the patients were 66 and 59

years old, vaped about 20 to 30 times a day for approximately 13 years, and had the tongue and vermilion of the lower lip as affected sites, respectively. The patient described by Klawinski et al. (2021) was significantly younger, at 19 years old, used the device variably throughout the day for 4 years, and had an invasive tumor on the tongue and oral floor, evidencing the possibility of oncogenic occurrence in different age groups and times of consumption.

Tomasi et al. (2019) observed that aberrant RNA transcripts associated with cancer were present in dysregulated genes in 62% of e-cigarette users and in 79% of smokers. TP53 gene expression, identified by Hamad et al. (2021), is another gene dysregulation associated with the development of neoplasms. In addition, DNA methylation, whether by hypermethylation or hypomethylation in key regions of the genome, is related to the emergence of cancer, as pointed out by Herzog et al. (2024).

Nuclear abnormalities, such as micronuclei, karyolysis, binucleated cells, and broken-eggs, have been observed in e-cigarette users and, due to their genotoxic effect, may represent early events in the development of the oncogenic pathway, especially in the oral cavity (Schwarzmeier et al., 2021). Guo, Ikuemonisan, Hatsukami, and Hecht (2021) reported increased DNA repair after the use of these devices, resulting in a greater number of apurinic/apyrimidine sites, which can initiate the carcinogenic process.

Kamal and Shams (2022) point out that interleukin-1β (IL-1β) causes inflammation by acting on several cell species, alone or in conjunction with other cytokines. Although macrophages are the main source of IL-1β, its production can also occur in epithelial cells and salivary glands in response to cell damage or infections. The authors also point out that tumor development can be promoted by alterations in the signaling pathway of transforming growth factor-β (TGF-β), a cytokine that regulates cell proliferation, differentiation, and apoptosis, whose increase is associated with tumor grade and malignant changes.

Pandarathodiyil et al. (2021) observed an increase in extracellular lactate dehydrogenase (LDH), signaling oxidative stress from the use of e-cigarettes. In the study by Ye et al. (2020), biomarkers indicated an association with systemic inflammation, tissue injury and repair, as well as angiogenesis, contributing to the pathogenesis of oral, respiratory, and cardiovascular diseases, suggesting that the chronic use of these devices may be linked to the development of chronic systemic and oral diseases, although to a lesser extent than traditional smoking. Bustamante (2021) demonstrated that, even with the presence of only traces of N-nitrosonornicotine (NNN) in the liquid of e-cigarettes, significantly lower amounts than in conventional cigarettes, there was endogenous production of NNN during use, which can greatly stimulate tumorigenesis.

6 CONCLUSION

It was observed that oral cancer is a disease that can be the result of numerous factors and be triggered in countless ways, even if by a single habit, at the cellular or genetic level, without age group of preference and with relatively short time of use or exposure to predisposing agents. However, it is a disease that can be avoided in most cases. But even though they are aware of the danger, more and more people, young or old, are exposed to the risk of potentially cancer-causing products. Many alterations or dysregulations can lead to the development of malignant neoplasms that, if they occur, should be diagnosed as early as possible, favoring the quality of life and survival of individuals. Unfortunately, these harmful psychosocial habits, such as smoking, can disrupt all, or part, of a system designed to function perfectly. Despite the need for further studies on the relationship between FBs and the development of oral tumors, the literature already provides good evidence on the carcinogenic potential of FBs and their association with smoking initiation, which provides us with a prognostic view of what is to come.

Greater attention should be paid to prevent the onset of e-cigarette use, especially by young people, who are highly influenced and challenging. More information campaigns about the harms of ECs are urgent, after all, many seek ECs as substitutes for conventional cigarettes, consuming them indiscriminately, and totally oblivious to the consequences.

Electronic cigarettes are already a public health problem, even in countries where they are banned or regulated. Therefore, a global approach is necessary, aiming at the development of strategies to prevent the onset of the habit, for the treatment of the addict and for his emotional support, corroborating the importance of public policies aimed at this population. It is extremely important that health professionals and support networks promote information and awareness for prevention, research and differentiated treatment for smokers or "vapers", enabling more positive perspectives for their lives and their future. Replacing one vice with another does not seem to be an acceptable option, since the substitute can be as harmful as the one replaced.

ACKNOWLEDGMENTS

A work like this would never be completed with a single author. The mutual collaboration between the authors was fundamental, very rich and worthy of immense gratitude, to this group that dedicates its life to science.

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