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REVIEW ARTICLE

E-cigarette use and potential lung cancer risk: a systematic review

Uso de cigarrillos electrónicos y potencial riesgo de cáncer de pulmón: una revisión sistemática

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ABSTRACT

The use of electronic cigarettes has significantly increased in recent years, particularly among young populations, raising concerns about their potential impact on respiratory health. This systematic review aimed to synthesize the available evidence regarding the association between electronic cigarette use and the risk of developing lung cancer. Systematic reviews, meta-analyses, and review articles published in English between 2015 and 2024 were included, while studies with limited or outdated information were excluded. The findings indicate that the aerosols produced by these devices contain various toxic and potentially carcinogenic substances. However, current evidence remains insufficient to establish a definitive causal relationship between vaping and the onset of lung cancer. There is a clear need for long-term longitudinal studies to comprehensively assess the chronic effects of electronic cigarette use on pulmonary health.

Keywords: electronic cigarettes, vaping, lung cancer, oncological risk, respiratory health, toxic substances.

RESUMEN

El uso de cigarrillos electrónicos ha experimentado un notable incremento en los últimos años, especialmente entre la población joven, suscitando inquietudes sobre sus posibles repercusiones en la salud respiratoria. Esta revisión sistemática tuvo como objetivo sintetizar la evidencia disponible acerca de la relación entre el uso de cigarrillos electrónicos y el riesgo de desarrollar cáncer de pulmón. Se seleccionaron revisiones sistemáticas, metaanálisis y artículos de revisión publicados en inglés entre 2015 y 2024, excluyéndose aquellos con información limitada o desactualizada. Los hallazgos indican que los aerosoles generados por estos dispositivos contienen diversas sustancias tóxicas y potencialmente carcinógenas. Sin embargo, la evidencia actual sigue siendo insuficiente para establecer una asociación causal definitiva entre el vapeo y la aparición de cáncer pulmonar. Se destaca la necesidad de investigaciones longitudinales a largo plazo que permitan evaluar de manera integral los efectos crónicos del uso de cigarrillos electrónicos sobre la salud pulmonar.

Palabras clave: cigarrillos electrónicos, vapeo, cáncer de pulmón, riesgo oncológico, salud respiratoria, sustancias tóxicas.

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INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide in both sexes. In 2018, lung cancer was the cause of approximately 1,761,000 deaths, 18.4% of all cancer deaths worldwide. With approximately 1,185,000 deaths in 2018, lung cancer was the leading cause of death among men in 93 countries, including the United States, Russia, and China (Thandra et al., 2021). Smoking is declining due to multiple cultural factors, including bans on tobacco and flavored product advertising and increased taxes (McNeill et al., 2017). In contrast, vaping is less regulated and has increased in popularity in many countries, as these restrictions are not yet enforced (Herman & Tarran, 2020), especially among youth and individuals adopting lifestyles with limited attention to long-term metabolic health risks. Lifestyle patterns are known to play a critical role in chronic disease development, including diabetes mellitus and respiratory complications (Anchundia et al., 2024).

Modern e-cigarettes, commercially developed in 2003, were heralded as a novel smoking cessation therapy (O'Callaghan et al., 2022). These electronic devices are designed to vaporize chemical compounds, and the term "vaping" refers to the perception that the exhaled vapor resembles water vapor. In reality, it consists of fine particles of chemicals mixed in vegetable glycerin (VG) and/or propylene glycol (PG) (Oriakhi, 2020).

In recent years, there has been an increase in respiratory illnesses associated with the use of vaping devices, including airway irritation, mucus hypersecretion, and inflammatory reactions. It has been proposed that the mechanism of injury is related to the combination of high temperatures and different aerosol components, resulting in a pro-inflammatory effect characterized by airway hyperresponsiveness, increased airway resistance, impaired antimicrobial activity, and endothelial cell destruction (Groot et al., 2018). This potential impact on respiratory health is especially relevant in vulnerable populations such as older adults, where respiratory illness compromises quality of life, as highlighted by recent evidence linking nutritional status with overall well-being in aging populations (Angulo et al., 2024).

Some comparative trials show that e-cigarettes activate the same signaling pathways as regular cigarettes; this condition is called “e-cigarette use-associated lung injury,” but further evidence is still needed (Abelia et al., 2023). There is evidence to suggest that e-cigarette use may increase the risk of certain types of cancer. The presence of carcinogens in the body fluids of e-cigarette users inherently means that cells are at risk of oncogenic transformation (Sahu et al.,

2023a). For all of the above reasons, this review aimed to analyze the relationship between e-cigarette use and the potential risk of developing lung cancer in the general population.

METHODOLOGY

A systematic review was conducted by the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, analyzing all available studies that provided data on e-cigarette use and the potential risk of lung cancer, following consecutive stages of identification, screening, eligibility, and inclusion.

Additionally, a comprehensive literature search was conducted across the academic databases PubMed, ScienceDirect, and Google Scholar to identify original research articles, systematic reviews, and meta-analyses. The search strategy combined controlled vocabulary and free-text terms, using the following keywords and Boolean operators: ("lung cancer" OR "pulmonary neoplasms") AND ("e-cigarettes" OR "electronic cigarettes") AND ("vaping" OR "electronic nicotine delivery systems" OR "ENDS"). The search was limited to articles published in English between 2015 and 2024. No restrictions were applied regarding study design in the initial search phase. Searches were performed across all fields to maximize sensitivity and capture all potentially relevant records.

Systematic reviews, meta-analyses, and review articles in English and from open-access journals were included. The exclusion criteria used were: undergraduate theses, editorials, articles published in closed-access journals, those in a language other than English, those with outdated information, and/or those unrelated to the main topic. Additionally, Zotero version 6.0.36 was used to manage bibliographic references.

The research questions posed were: What are the toxic mechanisms that link e-cigarette use with the potential risk of lung cancer? Moreover, what specific components of e-cigarettes are associated with an increased risk of developing lung cancer, and what are their mechanisms of action?

Through a hierarchical search, 78 articles were retrieved from the databases; after removing duplicates, 77 remained for the review. A total of 19 articles were selected that met the inclusion criteria, and none were excluded based on the established exclusion criteria in the review methodology. Figure 1 shows the flowchart used for article selection, taking into account the levels of the PRISMA protocol.

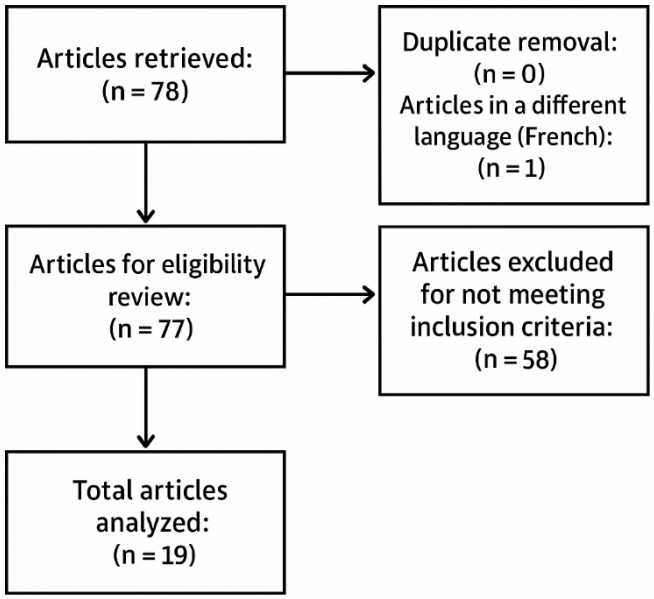

Figure 1. Flowchart of the final selection of articles, taking into account the PRISMA protocol levels used in this systematic review.

RESULTS AND DISCUSSION

The systematic review included a total of 19 studies, focusing exclusively on the possible relationship between e-cigarette use and the development of lung cancer. During this selection process, duplicate documents and articles that did not meet the inclusion criteria were excluded, thus ensuring the quality and relevance of the information analyzed.

Regarding the study designs analyzed, it is important to note that most were reviews, whether narrative or systematic. This inclusion allowed us to expand the state of the art on the topic and focused the work in the right direction, as shown in Table 1. It is also important to highlight the selection of recent literature, which is exclusively in English, helping to ensure the relevance and currency of the findings and facilitating comparison with other international research.

As shown in Figure 2, the year with the highest number of articles included in the review was 2021, with seven studies (37%), followed by 2023 with four studies (21%). These findings highlight the emerging nature of the topic and the growing interest of the medical community in exploring the potential association between electronic cigarette use and lung cancer.

Table 1. Summary of reviewed studies on electronic cigarette use and lung cancer risk

Reference	Study Type	Country	Methodology	Main conclusions
Abelia et al. (2023)	Narrative review	Indonesia	Comparative risk analysis of cigarettes *vs.* e-cigarettes	Both products pose pulmonary oncologic risks; e-cigarettes deliver lower carcinogen loads but carry non-negligible risks.
Balata et al. (2019)	Narrative review	International	Analysis of clinical advances in NSCLC prevention	Early diagnosis and control of risk factors, including e-cigarette use, are critical in lung cancer management.
Banks et al. (2023)	Umbrella systematic review	Australia	Global evidence synthesis on e-cigarettes	Mixed evidence; potential harm reduction in smokers, but long-term adverse effects remain uncertain.
Bonner et al. (2021)	Narrative review	USA	Review of vaping toxicology and chemistry	Toxic compounds in e-liquids may induce pulmonary damage; greater regulatory oversight is needed.
Bozier et al. (2020)	Systematic review	Australia	Synthesis of recent studies	E-cigarettes expose users to toxic aerosols; the potential for chronic respiratory impairment remains under evaluation.
Bracken-Clarke et al. (2021)	Narrative review	Ireland	Review of current clinical data	Insufficient evidence of a direct association between vaping and lung cancer; uncertainties persist.
Cai & Wang (2017)	Narrative review	China	Focus on oxidative stress	E-cigarettes generate reactive oxygen species, which may contribute to carcinogenic processes.
Cao et al. (2021)	Narrative review	China	General toxicological review	Multiple toxic components in e-cigarettes may affect various systems; limited human data are available.
Díez-Izquierdo et al. (2018)	Systematic review	Spain	Evaluation of thirdhand smoke	Thirdhand smoke poses cumulative risks; regulatory policies should address this exposure.
Gotts et al. (2019)	Narrative review	USA	Review of respiratory effects	Evidence of inflammatory and functional pulmonary alterations associated with e-cigarette use.
Herman & Tarran (2020)	Symposium review	USA	Integration of experimental findings	E-cigarettes affect pulmonary, neurological, and cardiovascular systems; risks may be underestimated.
Ioakeimidis et al. (2016)	Narrative review	Greece	Critical evaluation of cessation use	E-cigarettes may aid smoking cessation but require long-term risk evaluation.
Masso-Silva et al. (2021)	Narrative review	USA	Physiological review	Acute and chronic respiratory function alterations and inflammation linked to vaping.

Reference	Study Type	Country	Methodology	Main conclusions
McDonough et al. (2021)	Narrative review	USA	Biomarker assessment of toxicity	Elevated systemic biomarkers of damage in e-cigarette users: implications for overall health.
Sahu et al. (2023b)	Narrative review	India	Update on carcinogenic risks	Possible association between e-cigarette use and oncologic risk; longitudinal studies are needed.
Sala & Gotti (2023)	Narrative review	Italy	ENDS assessment	The widespread use of ENDS presents regulatory challenges, as the risks associated with them remain poorly characterized.
Snoderly et al. (2021)	Narrative review	USA	Analysis of devices and the market	Device diversity complicates risk standardization; new biological effects are emerging.
Stefaniak et al. (2021)	Narrative review	USA	Review of flavoring agents and cannabis toxicology	Flavorings and additives in e-cigarettes may increase the toxicity of inhalation.
Tzortzi et al. (2020)	Systematic review	Greece	Review of associated injuries and diseases	Growing evidence of acute and chronic pulmonary injuries associated with e-cigarette use.

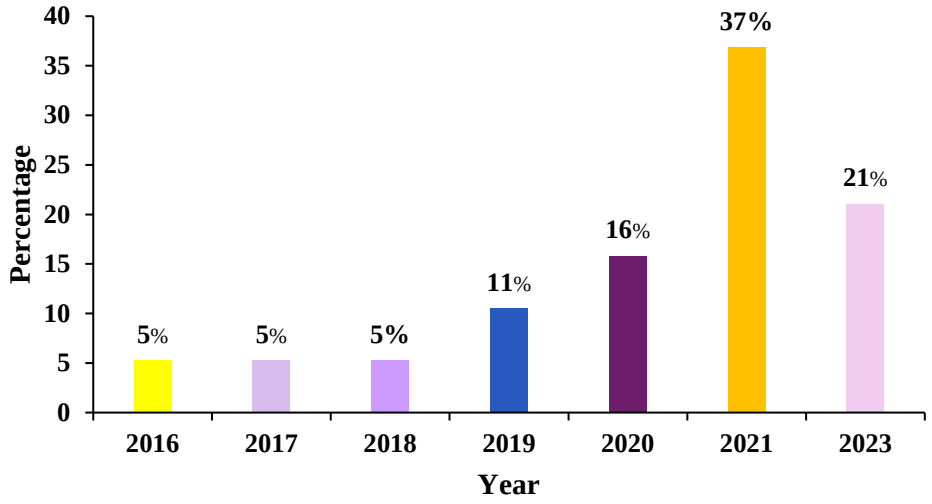

Figure 1. Annual distribution of publications on electronic cigarette use and its association with lung cancer.

Fourteen narrative reviews were found, representing the highest percentage (74%) of the types of scientific articles included in this systematic review, as shown in Figure 3.

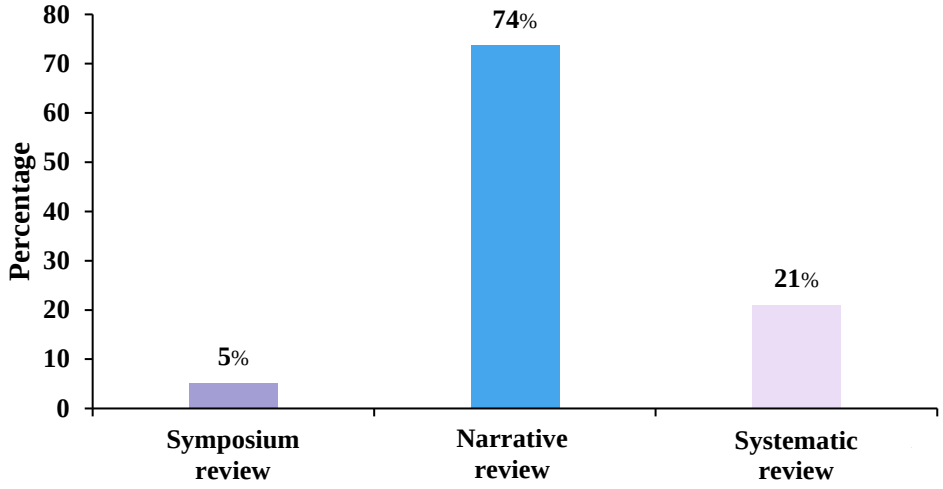

Figure 2. Distribution of publication types on electronic cigarette use and its association with lung cancer.

As reflected in Figure 4, the studies compiled were conducted in various geographical areas, with the seven studies carried out in the United States (37%) being the most notable. This percentage is not surprising, given that the United States is one of the world's leading producers of

scientific knowledge.

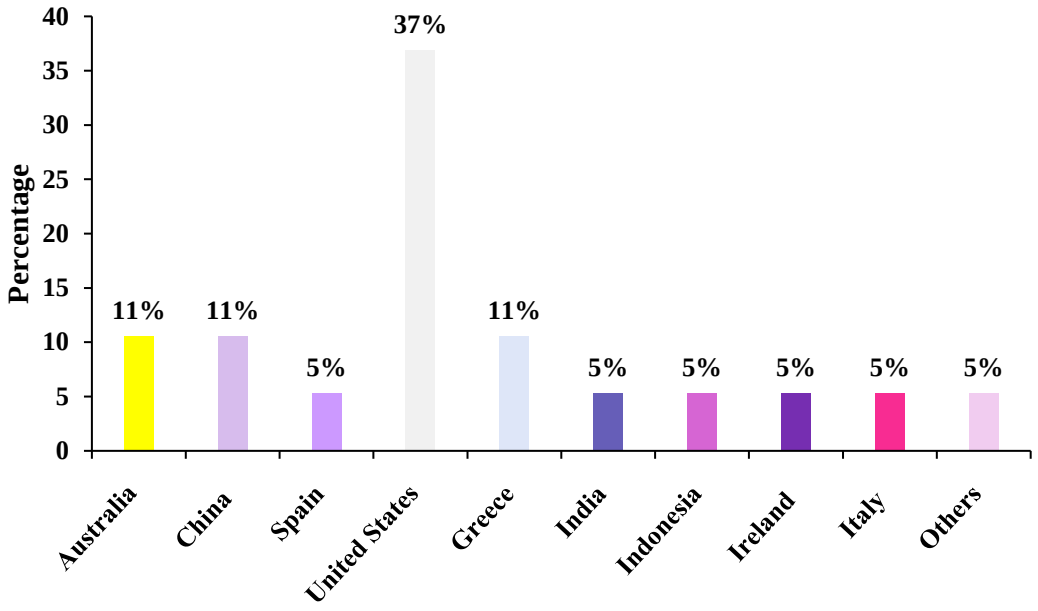

Figure 3. Country distribution of publications on electronic cigarette use and its association with lung cancer.

Toxic mechanisms that link e-cigarette use to the potential risk of lung cancer

Although the toxicity of e-cigarettes has been explored, the actual mechanisms underlying e-cigarette toxicity remain obscure. However, previous studies have shown that the toxic effects of e-cigarettes are related to oxidative stress, inflammatory response, and DNA damage (Cao et al., 2021).

E-cigarette aerosols contain reactive oxygen species (ROS). Oxidative stress is defined as "an imbalance between oxidants and antioxidants in favor of oxidants, which alters redox signaling and controls and/or causes molecular damage" (Síes, 2015). Reactive oxygen species (ROS) can cause membrane lipid breakdown, protein denaturation, DNA damage, mitochondrial dysfunction, and other forms of cellular macromolecular damage, thereby disrupting signal transduction and cellular metabolism (Ou et al., 2016).

According to existing reports, exposure of human pulmonary epithelium (Lerner et al., 2015), bronchial epithelial cells (Scheffler et al., 2015), human pulmonary vascular endothelial cells (Putzhammer et al., 2016), and human umbilical vein endothelial cells (Schweitzer et al.,

2015) to e-cigarettes can generate oxidative stress, increase endothelial cell permeability, and cause inflammation and cytotoxicity.

All flavored e-liquids generate reactive oxygen species (ROS), although the amounts vary by product; sweet or fruity-flavored e-liquids are more potent oxidants than tobacco-flavored e-liquids (Stefaniak et al., 2021). On the other hand, a study by Schweitzer et al. demonstrated that acrolein can cause oxidative stress and inflammation, leading to the loss of integrity in the lung endothelial cell barrier (Schweitzer et al., 2015).

While existing studies suggest a clear relationship between e-cigarette use and various toxic effects, such as oxidative stress and DNA damage, further research is critical to fully understand the underlying mechanisms and long-term risks associated with these devices, as current data suggests that e-cigarettes are not harmless and can cause damage at the cellular level.

The information provided indicates that more regulations are needed for e-cigarettes, as they are harmful to human health. The presence of ROS in aerosols and the consequences they bring create an alarming health picture. These toxic exposures interact with social determinants such as access to health education, nutrition, and chronic disease prevalence, which collectively influence the onset of diseases such as hypertension and pulmonary impairment (Ávila & García, 2024). The lack of regulation has led to aggressive marketing, especially to young people. This demographic is simultaneously experiencing an increasing incidence of lifestyle-related diseases such as type II diabetes, often associated with poor dietary and physical activity habits, highlighting the converging risks of modern health behaviors (Cedeño et al., 2024).

This research-based information reveals some of the many adverse effects of e-cigarettes on lung tissue and cells. It also mentions acrolein as a specific causative agent of oxidative stress. This knowledge sparks interest in conducting further research to extend this information to the entire consumer population.

The variety of flavors entails a variety of risks. With a wide range of flavors available in vaping liquids, the health risks associated with vaping can vary from product to product. Consumers should be aware that sweet and fruity flavors can be particularly harmful due to their increased capacity to generate ROS.

Iskandar et al. (2016) demonstrated through experiments that e-cigarettes induce an inflammatory response, while Lerner et al. (2016) found that e-cigarettes are capable of generating large amounts of the inflammatory cytokine IL-8. Another evaluation by Sussan et al. (2015) found

that the number of macrophages in bronchoalveolar lavage fluid increased by 58%, while IL-6 production increased 24 h after exposure, twice a day for two consecutive weeks.

On the other hand, García et al. noted that e-cigarettes containing nicotine activate the PKCα signaling pathway and the ERK signaling pathway through α7nAchR, and secrete inflammatory factors such as IL-6. They also reported that normal human bronchial epithelial cells (NHBE) cultured at the air-liquid interface of e-cigarettes containing nicotine were able to increase the secretion of IL-6 and IL-8 after 5 days of nicotine exposure (García-Arcos et al., 2016).

The information provided suggests that e-cigarettes can create and promote a microenvironment that fosters lung inflammation, facilitated by macrophages and IL-6, which contribute to the inflammatory process. The aforementioned data underscore the importance of ongoing studies to elucidate the relationship between chemical mediators and the long-term effects of exposure to these aerosols in e-cigarettes. E-cigarettes can also cause DNA damage, which can be caused by the aforementioned endogenous reactive oxygen species or metabolic byproducts, potentially causing cancer (Ou & Schumacher, 2018).

For example, a study by Lerner et al. demonstrated that copper nanoparticles and e-cigarette aerosols induced the production of mitochondrial reactive oxygen species (ROS) and caused DNA fragmentation in lung fibroblasts (Lerner et al., 2016). Similarly, a study by Anderson et al. (2016) revealed that e-cigarette aerosol caused DNA damage and reduced cell viability in a concentration-dependent manner.

Since DNA damage is a key risk factor for cancer and aging, it is critical to take preventative measures to protect our DNA. This includes avoiding exposure to harmful chemicals, such as those found in vaping liquids, and maintaining a healthy lifestyle. Further research is necessary to fully comprehend the mechanisms by which various types of DNA damage contribute to cancer development and the aging process.

Specific components of e-cigarettes are associated with an increased risk of developing lung cancer, and their action mechanism

Several chemicals and ultrafine particles known to be toxic, carcinogenic, and/or responsible for causing respiratory problems have been identified in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions (Sala & Gotti, 2023).

Contrary to popular belief, electronic nicotine delivery systems do not typically combust tobacco, which prevents the release of hazardous compounds. In contrast, the high temperatures

(>200 °C) reached with e-cigarette solutions are specific to tobacco. E-cigarettes contain acetaldehyde, a possible carcinogen, as well as metals, nitrosamines, and carbonyl compounds, including acrolein and formaldehyde, which are considered human carcinogens by the International Agency for Research on Cancer (Sahu et al., 2023).

Regarding carbonyl compounds, formaldehyde-containing hemiacetals were detectable by nuclear magnetic resonance spectroscopy during the evaporation process. Propylene glycol and glycerol are known formaldehyde releasers, which may accumulate in the respiratory system more rapidly than gaseous formaldehyde, potentially increasing the likelihood of developing cancer. This risk is five times greater than the risk from chronic smoking (Sahu et al., 2023).

E-cigarettes, despite their harmless appearance, release a complex mix of chemicals and ultrafine particles that pose a serious health risk. A wide range of toxic, carcinogenic, and highly respiratory-irritating compounds have been identified in the aerosols, cartridges, and refill liquids of these devices. This chemical cocktail, when inhaled, can cause a range of health problems, from chronic lung diseases to the development of cancer. On the other hand, acetaldehyde is also found in e-cigarette (EC) aerosols. The cancer risk from acetaldehyde exposure may be particularly significant for long-term EC users, as repeated exposure to the chemical can interfere with DNA replication, induce DNA damage, and form DNA adducts, which increase cancer risk. Studies have shown that acetaldehyde levels in EC aerosols can vary widely depending on the type of EC device, power settings, and other factors (Sahu et al., 2023). Acetaldehyde exposure will impair mucus clearance from the mucosa or submucosa, resulting in decreased host defense capabilities (Kosmider et al., 2016).

Acetaldehyde and other compounds in e-cigarettes are described as carcinogens and are highly toxic. This scientific information demonstrates that even though tobacco is not burned, there is a high risk for those who use it. This dispels the myths surrounding their use and alerts the public to the real risks to which they are exposed.

An important fact is mentioned, stating that these compounds can accumulate more quickly than gaseous formaldehyde, and thus this accumulation could have serious complications, even greater than the risk of chronic smoking. This finding warrants further investigation into this issue, which is alarming and has significant implications for the regulation and public perception of E-cigarettes.

Likewise, acrolein is a toxic chemical present in both tobacco smoke and e-cigarette

aerosol. It forms when glycerin, a common ingredient in e-liquids, is heated during the vaping process. Acrolein is a known respiratory irritant and can damage DNA, potentially leading to cancer.

Acrolein was also found to form DNA adducts at TP53 mutational hotspots similar to those found in smoking-related lung cancers, suggesting that acrolein may be a relevant etiological agent involved in the rise in e-cigarette use (Sahu et al., 2023). Similarly, a study by Schweitzer et al. demonstrated that acrolein can induce oxidative stress and inflammation, leading to a loss of integrity in the lung endothelial cell barrier.

Studies such as that of Sahu et al. (2023) have revealed that acrolein forms DNA adducts at the same critical sites found in smoking-associated lung tumors, suggesting a causal role in the development of lung cancer. Furthermore, acrolein induces oxidative stress and DNA damage, processes that contribute to the transformation of normal cells into cancer cells. Repeated exposure to this compound, present in e-cigarette aerosols, significantly increases the risk of developing lung cancer, even in individuals who have never smoked traditional tobacco.

Another component of ECs, menthol, uses its primary mechanisms of modulating nicotine metabolism and direct carcinogenic/proinflammatory effects, thus exerting its potentially carcinogenic effects. When exposed to various aromatic environmental chemicals (ECs), including those containing menthol, the ability of lung cancer cells to invade and metastasize was found to increase (Sahu et al., 2023).

The presence of flavorings in ECs is not simply a decoration or harmless flavor; they contribute to risk factors for serious diseases, increasing the risk of developing cancer. Menthol, in particular, is a key factor in nicotine addiction. This must be adequately communicated to the population that uses these e-cigarettes.

It is also worth noting that ethyl maltol (EM) has been detected in the aerosols of numerous commercial e-cigarette vaping liquids. It has been discovered that the additional generation of radicals comes from its interaction with iron and copper, which are often present in the heating element or as impurities. Furthermore, it has been verified that it promotes additional pro-inflammatory effects and enhances systemic exposure to inhaled chemicals, triggering an inflammatory response, modifying local immune function, and damaging the function and integrity of the epithelial barrier. This powerfully demonstrates that ethyl maltol is carcinogenic, given the proven oncogenicity of free radicals both individually and collectively (Sahu et al., 2023).

In turn, according to Sahu et al. (2023), vitamin E, especially the acetate form, is an oily substance at room temperature and is sometimes added to e-liquids as a thickening agent. This has been implicated in several recently reported cases of e-cigarette-related lung injuries. The thermal decomposition of vitamin E produces highly toxic and irritating ketene gas (resulting from the removal of the aryl acetate group) and numerous other toxic and reactive chemicals with detectable carcinogenic activity, including benzene and several alkenes (Sahu et al., 2023).

The presence of toxic chemicals in e-cigarettes raises serious concerns about their health impact. Ethanol, a known carcinogen, is present in some e-liquids and can alter epigenetics, affecting gene expression even after fetal exposure. Although a direct link between ethanol in e-liquids and cancer has not been established, its ability to alter gene expression suggests a potential oncogenic risk. Furthermore, other components, such as vitamin E acetate, used as a thickener in some liquids, have been linked to serious lung injury and can break down into highly toxic and carcinogenic substances, such as benzene. These findings underscore the complexity of the chemical mix present in e-cigarette aerosols and the need for further research to assess the long-term health risks associated with their use entirely.

It should also be noted that nicotine is transformed into nitrosamines, which are carcinogenic compounds that can lead to DNA methylation intermediates (Sala & Gotti, 2023). Tobacco-specific nitrosamines, known as carcinogens, have been detected in the vapor of traditional cigarettes (Goniewicz et al., 2014) and e-cigarette liquid (Kim & Shin, 2013), even at lower levels than in traditional cigarettes.

Some toxic heavy metals, such as lead, chromium, nickel, and manganese, are present at higher concentrations in e-cigarette aerosols and liquids than in cigarettes, according to a new study by the California Department of Public Health. Respiratory conditions such as lung cancer have been linked to chromium and nickel in some e-cigarette brands (Sahu et al., 2023). Cadmium exposure is linked to lung cancer and can damage the kidneys.

It should be emphasized that there is a significant number of heavy metals in e-cigarettes, which raises the spectrum of toxicological concerns. These metals have been proven to cause lung cancer, and these toxicants are even present in higher concentrations than in conventional cigarettes. Therefore, it is essential to conduct further research to understand the long-term associated risks fully and to perform detailed toxicological assessments of different e-cigarette brands and models. The data obtained would be essential to inform the consumer population

adequately.

After analyzing the existing evidence on e-cigarette use and its association with lung cancer, it became clear that, despite the presence of many toxic and carcinogenic compounds in the aerosols from these devices, not enough is known about their long-term effects. Current results suggest that the risk of cancer may be increased, but further studies are needed to establish a clearer and stronger link between e-cigarette use and the development of lung cancer.

CONCLUSIONS

The growing concern about the use of e-cigarettes and their potential relationship with the risk of lung cancer is highlighted. Although current evidence suggests the presence of toxic and potentially carcinogenic compounds in the aerosols from these devices, a direct and conclusive causal relationship has not yet been established. The systematic review emphasizes the need for additional research to investigate the underlying biological mechanisms and long-term effects of vaping on lung health, as well as its potential role in the development of oncogenesis. These future findings will inform public health recommendations and ensure sound, evidence-based decision-making.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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