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Review

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The carcinogenicity of e-cigarettes: a qualitative risk assessment

Bernard W. Stewart [1*], Henry Marshall [2], Billie Bonevski[3], Hayley J. Griffin[4], Ashley M. Hopkins [3], Malinda Itchins[5], Cassandra J. Mazza [6], Natansh D. Modi [7], Marissa Ryan [8], Megan Varlow [9], Freddy Sitas [10]

[1]Discipline of Paediatrics and Child Health, University of New South Wales, Sydney, NSW 2052, Australia
[2]Department of Thoracic Medicine, The Prince Charles Hospital and the University of Queensland Thoracic Research Centre, Brisbane, QLD 4032, Australia
[3]Flinders Health and Medical Research Institute, College of Medicine & Public Health, Flinders University, Adelaide, SA 5042, Australia
[4]Clinical Oncology Society of Australia, GPO Box 4708, Sydney, NSW 2001, Australia
[5]Royal North Shore Hospital and Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2065, Australia
[6]Cancer Care Services, Sunshine Coast Health, Birtinya, QLD 4575, Australia
[7]Clinical and Health Sciences, University of South Australia, Adelaide, SA 5000, Australia
[8]Pharmacy Department, Princess Alexandra Hospital, Metro South Health, Brisbane, QLD 4102, Australia
[9]Cancer Council Australia, Sydney NSW 2001 (present address, Cancer Institute NSW, Sydney 2065), Australia
[10]International Centre for Future Health Systems, and School of Population Health, University of New South Wales, Sydney, NSW 2052, Australia
*Corresponding author. Discipline of Paediatrics and Child Health, University of New South Wales, Sydney, NSW 2052, Australia. E-mail: b.stewart@unsw.edu.au.

Abstract

This review involves a qualitative carcinogenic risk assessment of nicotine-based e-cigarettes. Though direct epidemiological evidence of cancer causation takes time to accumulate, carcinogenicity of e-cigarettes is evident from different types of investigation including, with respect to studies in humans, some case reports but mainly involving monitoring of biomarkers of exposure and biomarkers of harm implicating tumorigenesis. Complementary laboratory investigations of e-cigarette aerosols and constituent chemicals include rodent bioassays and a range of approaches to elucidate mechanism(s). In respect of e-cigarettes, each of these types of investigation have been subject to successive reviews, sometimes more than once per year. Consequently, this over-arching review is restricted to publications since 2017 to avoid possible selection bias. Physiological evidence of exposure using biomarkers reveals DNA damage correlated with vape-derived metabolites attributable to carcinogens including nicotine-derived nitrosamines, volatile organic compounds, flavour-derived agents, and certain metals. Biomarkers also indicate vaping-attributable oxidative stress, epigenetic change and inflammation in oral and respiratory tissue often specified in comparison with smoking. Rodent bioassays include inhalation exposure of mice to e-cigarette aerosol described as causing lung adenocarcinomas. Mechanistic data are presented using the key characteristics of carcinogens and taken together implicate a complex mixture mediating carcinogenicity via genotoxic and other processes. From 2017 to 2025, the conclusions in e-cigarette reviews addressing different avenues of investigation moved from describing a need for more evidence to notifying concern about e-cigarette carcinogenicity. Nicotine-based e-cigarettes are likely to be carcinogenic to humans who use them causing an indeterminate burden of oral cancer and lung cancer.

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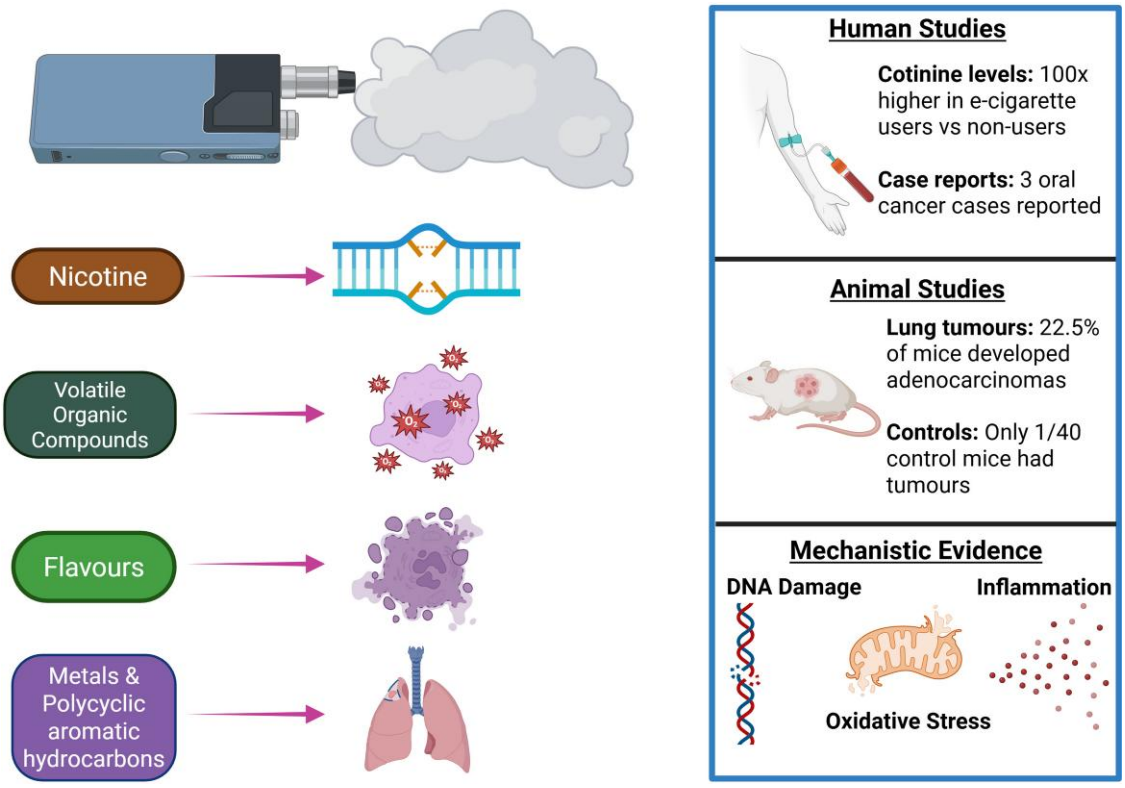
Graphical abstract



Keywords E-cigarettes, carcinogenicity, review, risk assessment, public health

1. Introduction

Electronic cigarettes (e-cigarette) are known to increase risk of addiction, poisoning, toxicity from inhalation, trauma and burns, though cancer is not specified in this context [1]. A risk of cancer may be inferred because e-cigarettes users are more likely to become tobacco smokers than a nonsmokers [2]. A separate consideration, and the subject of this review, is the carcinogenicity of e-cigarettes independently.

Since they were first marketed, e-cigarette design has varied to include pod and disposable devices including JUUL, but all include certain components: a battery, a coil of varying electronic resistance, and a container for the e-liquid which typically contains nicotine and flavouring which is heated to generate an aerosol inhaled by the user [3]. This review is restricted to e-cigarettes delivering nicotine rather than other agents such as cannabis [4]. Hence the term is interchangeable with electronic nicotine delivery systems or ENDS.

This review is based on qualitative risk assessment; a level of determination beyond hazard identification and distinct from quantitative risk assessment [5, 6]. It takes account of the mode of exposure but does not address quantitative differences exemplified by varying amounts of aerosol chemicals inhaled due to e-cigarette design or any relevant parameter.

In the absence of epidemiological studies contrasting tumour incidence in e-cigarette users and nonusers, carcinogenicity is indicated by human data including case reports and studies of biomarkers of exposure and tumorigenesis. Complementing such studies are laboratory investigations including rodent bioassays and mechanistic data concerning individual or categories of chemicals in e-cigarette aerosols and the aerosols themselves. These mechanistic data have been ordered using the key characteristics of carcinogens [7].

Almost every data set mentioned above addressing e-cigarettes, including each of the key characteristics, has prompted multiple reviews so comprehensive citation is not practicable. To ensure objectivity and avoid reliance on a subset of publications selected by us, we have therefore restricted coverage to all available relevant reviews since 2017 together with contemporary studies. These caveats explain in part why such a comprehensive, but concise carcinogenicity assessment has rarely, if ever, been conducted. Indeed, an assessment of e-cigarette carcinogenicity which purports to be based on all the available publications, must involve citation selection and be vulnerable to criticism on those grounds. This assessment, however, is objective in addressing by citation all the available reviews (and single studies not otherwise covered) since 2017 and is therefore objectively definitive. Otherwise, a carcinogenicity assessment claiming to address all available literature must involve citation selection, thus compromising objectivity.

Irrespective of methodology, the predominant approach to adverse effects of e-cigarettes has involved a comparison with tobacco smoking. Unlike that approach, our focus is the carcinogenic impact of e-cigarettes in their own right. The evidence that e-cigarettes may cause cancer must exclude findings made concerning dual users who both smoke and vape, since

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any inference of carcinogenic risk in this context can be attributed, at least in part, to tobacco smoke.

Exclusion of dual use findings from an assessment of the carcinogenicity of e-cigarettes does not qualify or detract from these findings as describing one aspect of the cancer burden expected from e-cigarette usage. This will be particularly so if dual use results in higher cancer risks in dual users than smokers. The prospect of a carcinogenic risk in never-smokers who vape adds to, and cannot be construed as detracting from, all other scenarios identifying cancer development in those who vape.

The potential carcinogenicity assessment offered here is not predicated on the authors' determination. Rather we will indicate consistency across all relevant parameters of changing perspectives from before 2017 through to 2025 leading to an unavoidable determination. Thus, in specifying what may be concluded from the multiple studies assessed in any one review, the conclusion offered by the author(s) of that review, rather than our opinion, is provided.

2. Physiological evidence of carcinogen exposure

Analysis of e-liquids and e-cigarette aerosols, not described here, has identified multiple known and potential carcinogens [3]. This section deals with physiological evidence of exposure to such chemicals consequent upon vaping as these findings contribute to a qualitative risk assessment. Accordingly, investigations of foetal exposure and passive or second-hand exposure to e-cigarette aerosols are not addressed. These carcinogens are nicotine and its metabolites, N-nitroso derivatives of nicotine, volatile organic compounds, polycyclic aromatic hydrocarbons (PAHs), metals and flavouring agents.

2.1. Nicotine and its metabolites

E-cigarettes are a means of inhaling nicotine which in this context has been implicated as a tumour promoter or possible carcinogen in its own right [8, 9] as discussed later in this assessment. Nicotine in e-liquids can exist as a free-base or in protonated (salt) form [10]. There is no simple relationship between the concentration of nicotine in e-liquids and the intake of nicotine from e-cigarettes as measured by blood levels [11].

In humans, nicotine is predominantly metabolized to cotinine which has a much longer half-life in biofluids than nicotine [12]. A 2021 review by McDonough *et al.* [13] includes tabulation of six studies of cotinine levels in either serum or urine from e-cigarette users. The authors noted reliable differentiation between higher levels in e-cigarette users than nonusers, but questioned differentiation between vapers and smokers. One subsequent study of serum cotinine levels showed no difference between smokers and vapers after adjustment for age and gender [14].

Concerning urinary cotinine, as reviewed in 2023 [15], a more than 100-fold difference between e-cigarette users and nonusers involved geometric means of 124.3 ng/mg as against 0.42 ng/mg creatinine. As reported more recently in 2025 among 3353 exclusive e-cigarette users, nicotine e-cigarettes users exhibited higher mean concentrations of total nicotine equivalents and cotinine compared with non-nicotine e-cigarette users, differences in both cases being at least 100-fold [16].

2.2. N-nitroso derivatives of nicotine

In relation to e-cigarettes specifically, nicotine may mediate carcinogenic activity by its conversion to nitrosamine compounds. Studies of the tobacco-specific nitrosamines in biofluids predominantly involve *N*′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridul)-1-butanone (NNK) as indicated by its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) [17]. Eight studies reporting urinary levels of NNN or NNAL in samples from e-cigarette users are tabulated in a 2021 review. These studies are summarized as recording lower levels in vapers compared to smokers [13]. In respect of tobacco-specific nitrosamine measurements among other indicators, a national cohort study reported harm reduction associated with transitioning from cigarette use to e-cigarette use, noted as a lower ***relative risk*** (bold in the original) [18]. Higher levels of the genotoxic nitrosamine, 1-(methylnitrosoamino)-4- (3-pyridinyl)-1,4-butanediol in vapers than smokers were reported following urinary analyses involving about 35 individuals in each grouping [19].

2.3. Volatile organic compounds

Volatile organic compounds (VOCs) in e-cigarette aerosols typically arise as degradation products and their metabolites have been detected in the urine of e-cigarette users. They include acrolein, benzene, 1,3-butadiene, formaldehyde, ethylene oxide, *o*-toluidine, trichloroethylene, acrylamide, *N*,*N*-dimethylformamide, styrene, acetaldehyde, acrylonitrile, 1-bromopropane crotonaldehyde and propylene oxide. All of these chemicals occur in tobacco smoke which is the major source of exposure. Similar assessments have now been made for e-cigarette aerosols [20, 21].

A 2023 review of exposure biomarkers in e-cigarette users [22] documents 13 studies on acrolein, 10 on 1,3-butadiene, 9 on acrylonitrile, 8 on each of acrylamide and crotonaldehyde and 7 on benzene, among other compounds. The authors conclude that consistent, although limited, evidence shows that e-cigarette users have elevated levels of biomarkers of VOCs including acrylamide and acrylonitrile than nonusers. Reported in 2025, from levels of urinary biomarkers for six VOCs in youth who vape, smoke, 'dual-use' or neither, exclusive vaping was distinguished only by higher exposure to toluene and acrylamide in sensitivity analysis using a past 24-h measure [23].

2.4. Polycyclic aromatic hydrocarbons

A 2017 assessment noted few studies on exposure to PAHs from vaping [24]. A subsequent study quantified seven PAH urinary biomarkers in never-tobacco users ($n = 1700$) and exclusive non-combustible products users ($n = 860$) including smokeless products ($n = 509$) and e-cigarette users ($n = 280$) Among many comparative assessments made, levels of 3-hydroxyfluorene and 1-hydroxypyrene were significantly higher in e-cigarette and in smokeless product users than in never users [25].

2.5. Metals

E-cigarettes are a source of exposure to metals from the heating coils, soldered joints, and other metallic components [26, 27].

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Reviewing metal/metalloid exposure from e-cigarettes in 2020, Zhao *et al.* [28] identified 24 studies, four of which described levels in biofluids of users. Most levels were similar or higher than levels found in smokers. A subsequent review referred to the serious health effects associated with such metal exposure [13]. A 2025 study found elevated nickel concentrations were observed among e-cigarette users compared to nonsmokers [29].

2.6. Flavouring agents

Substances identified with flavours in e-liquids include furaneol, benzyl alcohol, ethyl maltol, ethyl vanillin, corylone, and vanillin were significantly correlated with cytotoxicity [30]. Aldehydes originating from flavouring agents affect cytochrome P450 2A6, which is involved in the oxidative metabolism of nicotine [3].

Vapers had higher levels than smokers of flavouring agents such as delta-decalactone in the context of what is described as a comprehensive profiling of urinary biochemicals that were dysregulated due to vaping [19].

3. Indicators of carcinogenicity in humans

Risk of cancer from e-cigarettes can be inferred from direct tissue injury associated with tumourigenesis and from cancer-related biomarkers and emerging case reports [31]. In summarizing the relevant literature, priority is given to findings contrasting e-cigarette users with nonusers, even when determinations about smokers are recorded. Few, if any, of these publications distinguish between different designs of e-cigarette.

3.1. Tissue injury predisposing to cancer development

As comprehensively assessed in relation to smoking, similar tissue injury in the respiratory tract caused by e-cigarettes has been assessed as consistent with a progression towards cellular transformation and the development of cancer [31].

Characteristic respiratory pathology identified by the US Center for Disease Control as ‘E-cigarette and vaping associated lung injury’ (EVALI) is now widely recognized and was initially attributed to nicotine, flavour products, and tetrahydrocannabinol (THC) oils [32]. However, as Gordon and Fine [4] explained, EVALI cases do not differentiate between the impact of nicotine inhalation with THC implicated and changes attributable to inhalation of illicit drugs with vitamin E acetate involved. In the context of identifying tissue injury specifically attributable to nicotine-based e-cigarettes, studies based on EVALI have not been considered.

In a study typical of many, bronchoscopies from e-cigarette users when compared to healthy nonsmokers indicated friable and erythematous morphology, with other data suggesting injury mediated by propylene glycol/vegetable glycerine [33]. Among many reviews of such injury, Miyashita and Foley [34] documented disruption to lung function and gas exchange, impaired respiratory immunity and host defence systems, and respiratory inflammation and injury. Thus, Ghosh *et al.* [35] concluded that vaping may not be safer than smoking.

A 2021 review tabulated seven investigations of vaping-induced inflammation as involving pro-oncogenic proteases, including neutrophil elastase and matrix metalloproteases, modulated cell signalling, tissue remodelling, and leukocyte recruitment [13]. Another review [36] noted increased reactive aldehyde species causing accumulation of 4-hydroxynonenal described as inducing apoptosis, mitochondria dysfunction, and protein inactivation.

Cameron *et al.* [37] reviewed deleterious effects of vaping on oral health as implicating oral cancer, noting that vaping is not risk-free because of dysbiosis, inflammation, periodontal diseases and changes to the oral microbiome. Alterations in the oral microbiome of e-cigarette users include significantly altered beta diversity in species and the most abundant species of *Porphyromonas* and *Veillonella*. Such dysbiosis in microbiome is related to elevated proinflammatory cytokines release and increased inflammation.

3.2. Biomarkers of malignant transformation

Some biomarkers indicating the prospect of malignant transformation coincide with certain key characteristics of carcinogens [7], namely indicators of DNA damage, oxidative stress, and epigenetic change. Findings outlined below primarily concern differentiating the effects of e-cigarettes from controls often identified as nonsmokers.

Typically, when assessing multiple studies of associations between usage of e-cigarettes and diseases including cardiovascular disease, stroke, asthma, and chronic obstructive pulmonary disease, meta-analysis is employed [1]. Cancer, and relevant meta-analyses, are not so included because comparable data are not available due to the relatively short time since e-cigarettes have been used by comparison with the latent period for, say, lung cancer. Moreover, the parameters used in the various studies of particular biomarker discussed in this section have proved to be so diverse as to preclude meta-analysis in respect of any group of such findings. This scenario is not known to the authors as being subject to any comprehensive elucidation, but is evident from the absence of ‘meta-analysis’ from the titles of the hundred-plus reviews listed in the References section.

3.2.1. Oxidative stress

Most relevant biomarker-monitoring studies of oxidative stress utilize the prostaglandin 8-isoprostane which is a by-product of lipid peroxidation and/or 8-hydroxy-2’-deoxyguanosine, a marker of oxidative DNA damage [38]. Referring to six tabulated studies in humans, McDonough *et al.* [13], concluded in 2021 that the results clearly show increased oxidative stress in e-cigarette users in comparison with nonsmokers. A 2025 summation tabulates 12 studies assessing oxidative stress markers most of which involved 4-hydroxynonenal which the review authors summarized as showing higher levels in e-cigarette users compared to nonsmokers [39].

A study published later in 2025 described oxidative injury from vaping based on e-cigarette users ($n = 38$) and nonusers ($n = 18$). A significant correlation between heavy metals, cytokines, and oxidative stress markers was recorded. The authors suggest effects observed may be attributable to exposure to metals [40].

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3.2.2. DNA damage

In 2022, reviewing DNA damage in human oral cells, Guo and Hecht [41] tabulated nine clinical studies providing determinations of various parameters in e-cigarette users and nonsmokers. E-cigarette users had significantly higher levels of *N*′-nitrosonornicotine and acrolein DNA adducts, metanuclear anomalies and lactate dehydrogenase enzyme expression and significantly lower levels of apurinic/apyrimidinic sites than nonusers. The authors concluded that e-cigarettes are implicated in DNA damage to oral cells, but there was limited evidence, noting that future studies with larger sample sizes are required.

In a later study including e-cigarette users ($n = 28$) and nonsmokers ($n = 39$), quantification of adducts showed that vapers had higher oxidative DNA damage than the controls. Alkylated DNA-adducts were identified in the urine of e-cigarette users. The authors concluded that vapers may be at higher risk of genotoxicity than those who do not and flavouring additives contributed to additional genotoxic damage [42].

3.2.3. Epigenetic change

As no reviews specifically on clinical studies of epigenetics as affected by e-cigarette usage were identified, some individual studies are described here. Using peripheral blood, patterns of methylation of long interspersed nuclear element 1 (*LINE-1)* showed a significant 18% decrease in vapers compared to nonsmokers [43]. Another study differentiated vapers based on RNA expression, as attributable to changes in DNA methylation [44].

Associations between e-cigarette use and epigenome-wide methylation from saliva were quantified in equal numbers ($n = 117$) of nonsmokers, vapers and smokers. DNA methylation at CpG sites was associated with e-cigarette use and these sites were distinct from those in smokers [45]. Herzog *et al.* [46] evaluated effects of tobacco or e-cigarette use on genome-wide DNA hypermethylation using over 3500 buccal/saliva, cervical, or blood samples. In smokers, the data predicted lung cancer. Alarmingly, as specified by the authors, these CpGs were also hypermethylated in e-cigarette users with a limited smoking history.

A 2025 study of the oral cell methylome described substantial overlap in differentially methylated region-associated genes between vapers and smokers relative to nonusers [47]. In the same year, comparison of exosomal miRNA profiles between exclusive e-cigarette users ($n = 15$) and nonusers ($n = 15$) identified five plasma exosomal miRNAs upregulated in e-cigarette users. Gene enrichment analysis of predicted target genes regulated by these five significant miRNAs uncovered numerous target genes associated with cancer-related signalling pathways [48].

Altered transcription has also often served as an epigenetic marker [49]. Following analyses of bronchial epithelial cells from groups of about 10 vapers, smokers, and former smokers, e-cigarette usage induced both distinct and shared patterns of gene expression relative to smoking [50]. The tumour suppressor TP53 was significantly upregulated in buccal samples from vapers [51]. Song *et al.* [52] report that e-cigarette usage alters gene expression in a pattern similar to smoking.

3.2.4. Inflammation

In addition to histological studies already described, inflammation in e-cigarette users has been monitored using biomarkers including cytokines such as interleukins, interferon, tumour necrosis factors (TNF), chemokines, and proteases [13]. In common with oxidative stress, variation in biomarkers of inflammation is indicative of diseases apart from cancer. Thus, established biomarkers of inflammation commonly used to implicate cancer have been monitored in vapers with reference to respiratory or cardiovascular disease. Accordingly, with a focus on cardiovascular disease, 37 studies involving e-cigarette usage have been tabulated with respect to increased, no change or decreased, no significant changes in general inflammatory biomarker levels; some trends were evident for particular biomarkers [53].

In 2025, Śniadach *et al.* [39] tabulated tens of studies determining levels of inflammatory markers shown in multiple tables with reference to six pro-inflammatory cytokines exemplified by TNF-α and various interleukins. They conclude that e-cigarettes affect concentrations of anti-inflammatory cytokines, although to a lesser extent than do conventional cigarettes. Another contemporary review of salivary biomarker determination primarily involving inflammation recorded no distinction between the impact of smoking and vaping, with both scenarios differentiated from nonusers and ‘fresh air’ in particular studies [54].

3.2.5. Immunosuppression

Multiple clinical studies have shown that vaping adversely affects the immune system. These investigations, however, are not oriented to carcinogenesis, but address susceptibility in infection [55] or asthma [56]. Accordingly, while evidence of immunosuppressive activity has been described in this context, the investigators offer no speculation concerning carcinogenic risk.

3.3. Case reports

As distinct from other outcomes [57], this summation is restricted to cancer. One report involved two cases of oral carcinoma associated with chronic use of e-cigarettes. First, a 66-year-old male who used e-cigarettes 20 times per day for 13 years. Second, a 59-year-old male who reported using 30 e-cigarettes per day for 13 years. The authors concluded that the use of e-cigarettes may be associated with an increased risk of oral cancer [58].

Another report describes the case of a 19-year-old male with an extensive history of vaping who developed an aggressive, poorly responsive HPV-negative squamous cell carcinoma of the oral cavity [59]. The authors observe that, given the rarity of this disease in young patients and the absence of HPV infection, e-cigarette use may lead to oral cavity cancer.

No comparable notifications for lung cancer were discovered. However, a 51-year-old man with type 2 diabetes, hypertension, a 10-pack-year smoking history, and 11 years of e-cigarette use was reported to be diagnosed with an aggressive squamous cell lung carcinoma. The authors acknowledge that causality cannot be established but consider that the case highlights a potential association between e-cigarette use and malignancy [60].

To move beyond isolated case reports, longitudinal epidemiological studies linking e-cigarette use to cancer incidence through population-based registries are urgently needed to characterise carcinogenic risk amid rising global use.

4. Animal bioassays

Animal bioassay findings on e-cigarettes have been tabulated with reference to pulmonary, cardiovascular, CNS, reproductive,

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and other injury [61]. However, no review of carcinogenicity testing in animals is evident.

4.1. E-cigarette aerosols: carcinogenicity and related bioassays

Tang *et al.* [8] tested the carcinogenicity of e-cigarette aerosol in mice. One group ($n = 45$) was exposed to e-cigarette aerosol generated from e-liquid (nicotine [36 mg/ml] dissolved in polypropylene glycol and vegetable glycerine at a 1:1 ratio). The second group ($n = 20$) was exposed to polypropylene glycol and vegetable glycerine only. Mice were exposed for 4 h/day and 5 days/week for 54 weeks. A third group ($n = 20$) was exposed to ambient filtered air. Nine of 40 (22.5%) aerosol-exposed mice developed lung tumours identified as adenocarcinomas. Although no urinary bladder tumours occurred, hyperplastic changes to the bladder urothelium were evident in 23 of 40 (57.5%) mice exposed to e-cigarette aerosol. Concerning both lesions, one mouse among 40 controls had a lung tumour. When considered with other data, the aerosol is implicated as a lung and potential bladder carcinogen in the authors' view.

Pham *et al.* [62] concluded that e-cigarettes promotes breast carcinoma progression with a tropism to lung metastasis in mice genetically modified to model human familial adenomatous polyposis. In another study, the effect of e-cigarettes on polyp formation and colorectal cancer development was less than that of cigarettes, but both were considered to drive cancer development via the same mechanism [63].

4.2. Carcinogenicity of relevant chemicals

Propylene glycol and vegetable glycerine promoted and contributed to more aggressive, metastatic, and immunosuppressive tumours *in vivo*, aggravated by the presence of nicotine [64].

The prevailing thinking is that nicotine is noncarcinogenic, primarily because rats exposed to stream-air-vapourized nicotine via inhalation for 2 years showed no sign of tumour formation [65]. Otherwise the reviewing authors note different types of tumours including leiomyosarcoma have been observed in animals treated with nicotine via drinking water and subcutaneous injection in studies falling short of 'best practice' bioassay standards.

With specific reference to e-cigarette use, Lee *et al.* [66] directly measured DNA damage induced by tobacco-specific nitrosamines in different organs of e-cigarette aerosol-exposed mice prompting them to strongly suggest that *in vivo* nicotine inhaled from e-cigarettes can be nitrosated with carcinogenic effects [67].

Many other compounds in e-cigarette aerosols are carcinogenic in experimental animals. These chemicals include acrolein, benzene, 1,3-butadiene, formaldehyde, ethylene oxide, *o*-toluidine, trichloroethylene, acrylamide, *N*,*N*-dimethylformamide, styrene, acetaldehyde, acrylonitrile, 1-bromopropane, propylene oxide, nickel metal and its salts, and chromium (VI) compounds. Details of all such bioassays are recorded in the respective IARC *Monographs* (https://monographs.iarc.who.int).

5. Mechanistic data

The key characteristics of carcinogens are comprehensive to the extent that at least one is evident in respect of all known human carcinogens [7]. In contrast to that scenario, laboratory studies of e-cigarette aerosols have implicated all 10 key characteristics. Moreover, the scope of such studies has prompted specific reviews on each of the key characteristics in respect of e-cigarette aerosols. Such reviews published since 2017, together with individual studies not so included, are described in this section.

1. *Electrophilic or can be metabolically activated.* Multiple carcinogenic VOCs in e-cigarette aerosols are metabolized to generate relevant adducts, as has been recognized in this context [68].

   Consistent with this general knowledge, after inhalation by rats of aerosol for 4 weeks, lung tissue exhibited increased phase-I carcinogen-bioactivating enzymes [69]. A condensate of e-cigarette aerosol enhanced metabolism of benzo[a]pyrene in a human oral keratinocyte cell line by inducing CYP1A1/1B1 mRNA and protein [70]. As recently reported, in a DNA damage-based bacterial bioassay system, e-liquids tested positive when assayed in the presence of S9 microsomal mix [71].
2. *Genotoxic.* The genotoxic and carcinogenic potential of compounds associated with e-cigarettes was reviewed in 2019 [72]. The authors concluded that compounds found in e-cigarettes are still a matter of research and their effects on health are yet unknown. Two years later, a review included 'Genotoxicity of e-cigarettes' which specified that such genotoxicity had been variously demonstrated, and may be attributable in part to nicotine [73].

   In their 2022 review, Tang *et al.* [74] distinguish the causative agents and DNA damage mediated by tobacco smoke from that attributable to nicotine, propylene glycol, and vegetable glycerol as inhaled by vapers. They proposed that e-cigarette nicotine can be nitrosated in mouse and human cells becoming nitrosamines, thereby causing two carcinogenic effects, induction of DNA damage and inhibition of DNA repair. As assessed by Guo and Hecht [41], *in vitro* studies demonstrate that e-cigarette liquid or aerosol can induce DNA damage, oxidative stress, DNA double-stranded breaks, and hence genotoxicity in different types of oral cells.
3. *Alters DNA repair or causes genomic instability.* Cigarette aerosols contain nicotine, propylene glycol, and vegetable glycerine which result in particular modified bases, namely O^6-methyl-deoxyguanosines and cyclic γ-hydroxy-1,*N2*–propano-deoxyguanosine in DNA. Accordingly, DNA repair processes induced by smoking may be distinguished from those attributable to vaping [74].

   Chronic exposure of lung epithelial cells to nicotine upregulates Ras signalling, disrupts redox state and mitigates tumour suppressor functions such as p53, leading to perturbed cell growth restriction and further weakening of the genomic stability [75].
4. *Induces epigenetic alterations.* In 2021, Yan *et al.* [76] reviewed epi-mutational effects of e-cigarette with particular reference to DNA methylation, histone modifications and

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ncRNA expression tabulating four experimental studies involving aerosols and tens of similar studies involving its constituents. They conclude that such epi-mutational changes would likely lead to diseases such as lung cancer. A later review of e-cigarette-induced epigenetic change noted that short-term use induced lung cancer-related tumour-promoting factors and metastasis and that nicotine inhalation from e-cigarettes can promote tumour growth [77].

5. *Induces oxidative stress.* Oxidative stress induced by e-cigarette aerosols in the oral cavity and along the respiratory tract is relevant to COPD, cardiovascular disease, atherosclerosis, neural injury, and cancer. Concerning cancer specifically, a 2022 review contrasting evidence of oxidative stress caused by smoking with that attributable to vaping products noted effects of e-cigarettes on oxidative stress-related endothelial dysfunction and oxidative stress-related carcinogenesis [38].

   Another 2022 review on toxicity mediated by e-cigarettes on the respiratory system, when addressing oxidative stress tabulated 11 relevant laboratory studies. The authors noted that two common e-cigarette solvent carriers can induce oxidative stress and also described the impact of flavouring agents in this context. They concluded that both e-cigarettes and their main ingredients affect oxidative stress [78].
6. *Induces chronic inflammation*. Reviewing multiple studies using animal models and *in vitro* studies, in 2022 Park *et al.* [36] concluded that exposure to e-cigarettes induces secretion of proinflammatory cytokines TNFα, IL6, and IL1B in epithelial cells and immune cells of the upper airway and lung. As assessed in 2023, e-cigarette aerosols have been shown to increase levels of cytokines IL-8 and COX2. In respiratory tissue, e-cigarettes increase the pulmonary signalling for neutrophils and alveolar macrophages independent of whether the e-liquid contained nicotine [79].

   As reported in 2025, rats exposed for 6 weeks to e-cigarette aerosol or similarly exposed to tobacco smoke evidenced a significant increase in serum proinflammatory cytokines, particularly in the aerosol-exposed group [80]. Another 2025 study recorded qualitative similarity of inflammation and oxidative stress molecular indicators in rat lungs attributable to e-cigarette, cigarette, and waterpipe emissions accompanied in all cases by histopathological changes [81].
7. *Immunosuppression.* A 2025 review of immunological effects tabulates six *in vitro* studies of e-cigarettes indicating, amongst other evidence, that the aerosol disrupts epithelial barriers, increasing susceptibility to bacterial and viral infections. Additionally, e-cigarette exposure modulates adaptive immunity, affecting T and B cell function and increasing systemic inflammatory markers [82]. Propylene glycol and vegetable glycerine are reported to promote tumour cell migration in migration assays and can be a promoter of tumour cell proliferation and invasiveness *in vitro*, with the authors noting that nicotine also has immunomodulatory effects [64].
8. *Modulates receptor-mediated effects*. Specification of receptor-based processes as one of the key characteristics of carcinogens recognizes that most nongenotoxic carcinogens act via such processes. However, almost all studies addressing e-cigarette carcinogenicity are oriented towards genotoxicity. While the few that describe the toxicity of e-cigarette aerosol with reference to receptor-based activity, most have not concerned malignant transformation. An example of such a study is the observation that inhalation of e-cigarette aerosol causes airway mucociliary dysfunction *in vitro* and *in vivo* through nicotine as mediated by TRPA1 and not nicotinic acetylcholine receptors [83].
9. *Cellular immortalization.* Immortalization may be identified with inhibition of senescence and transformation of mammalian cell lines often recognized as a short-term test for carcinogenesis. Tellez *et al.* [84] found that a flavoured e-liquid aerosol transformed each of two lines, while an unflavoured one was less effective by this criterion. In 2023, these investigators observed that there have been a relative lack of such studies.
10. *Alters cell proliferation, cell death or nutrient supply.* There are few, if any, studies addressing e-cigarette-mediated cell proliferation in relation to carcinogenesis. Having identified 18 relevant publications, Wilson *et al.* [85] undertook a systematic review of the adverse effects of e-cigarettes on head and neck, including oral cells. The authors suggest that future research must investigate chronic e-cigarette use and if it leads to periodontal disease and/or cancer.

Cytotoxicity and altered apoptosis have been addressed as reported by Khalil *et al.* [86]. Flavouring agents may increase bronchial epithelial cell apoptosis while altering airway cytokines [87]. Jabba *et al.* [68] provide evidence that adducts of favour aldehydes formed in e-liquids are cytotoxic and inhibit mitochondrial function in respiratory epithelial cells. Flavouring agents were also strongly implicated in a 2025 study of autophagy mediated by e-cigarette aerosol condensate [88].

6. Previous perspectives on carcinogenicity

This summation of carcinogenic risk assessments for e-cigarettes is limited to publications since 2017. Nonetheless, such passage of time since e-cigarettes were first marketed is almost trivial by comparison with the decades required to definitively establish cancer causation by tobacco smoking, a scenario which explains why all the following assessments primarily depend on some degree of extrapolation.

6.1. Oral cancer

A 2019 review focused on head and neck cancers included laboratory studies, case reports, and clinical studies, which taken together, were assessed as low-level evidence [89]. A contemporary review found e-cigarettes were less harmful than conventional cigarettes [90].

A 2020 assessment referred to DNA strand breaks following *in vitro* exposure to e-cigarette aerosols though the carcinogenic potential remained unclear [91]. Another assessment at this time indicated a potential carcinogenic risk head and neck

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cancers [92]. A year later, Sultan *et al.* [93] concluded that there is no strong evidence suggesting a direct role for e-cigarettes in oral cancer.

However, in 2024 two reviews on oral cancer [37, 94] referred to carcinogenic compounds in saliva of vapers in describing a carcinogenic risk, noting that definitive evidence that vaping causes of oral cancer is lacking. A 2025 review based on 12 studies highlighted cases of mucosal lesions and genetic instability associated with e-cigarette use which was considered a risk factor for oral cancer [95].

6.2. Lung cancer

A 2021 review of vaping and lung cancer specified concern regarding the potential oncogenicity of e-cigarettes/e-liquids [96]. Also in 2021, Petrella [97] concluded that the impact of e-cigarettes on lung cancer risk is unknown in the absence of relevant epidemiology.

Two years later, Petrella *et al.* [98] stated that although vaping was initially believed to have less harmful health consequences than smoking, there is now no robust evidence that e-cigarettes are a less dangerous alternative. Also in 2023, a review of lung cancer risk concluded that the toxic effects of vaping are essentially identical to that caused by smoking [99]. Similarly, growing concern about lung cancer risk, assessed as not well established, described possible synergism with toxic environmental exposures [100].

6.3. Bladder cancer

In 2017 components of e-cigarette aerosols were linked to urologic health risks [101]. Four years later, when assessing urinary carcinogenic biomarkers in e-cigarette 40 such compounds and four metals were identified [102]. When assessing tumour development from vaping in 2023, Sahu *et al.* [103] included bladder cancer, noting that e-cigarette users, compared to nonusers, have higher urinary levels of agents that are metabolized to bladder carcinogens.

6.4. Overall assessments of carcinogenicity

Shortly before 2020, evidence for the carcinogenicity of e-cigarettes was assessed as sparse [104, 105]. Then Mravec *et al.* [106] referred to 'direct carcinogenic effects' noting DNA damage and repair attributable to e-cigarettes aerosols, while indicating how nicotine may stimulate initiation and progression. A 2022 review addressed 'Cancer risk and main oncogenic molecular mechanisms triggered by e-cigarettes' referring to a wide spectrum of mechanistic evidence [3].

The reviews cited in this section [89–106] do not systematically describe studies addressing whether e-cigarette aerosol hastens the growth of pre-existing neoplasms or neoplasms associated with other risk factors. Accordingly, such tumour promotion is not assessed here, but warrants recognition as relevant to the potential carcinogenicity of e-cigarettes.

American Association for Cancer Research and the American Society of Clinical Oncology policy on e-cigarettes notes that DNA damage and inflammation, key steps in cancer development, are caused by vaping [107]. Evaluation of electronic nicotine delivery systems in *IARC Monographs* during 2025–2029 is 'high priority' based on animal and mechanistic evidence [108].

6.5. Carcinogenicity of aerosol components

The potential carcinogenicity of nicotine [109, 110] as relevant to vaping specifically has not apparently been reviewed. However, in relation to e-cigarettes specifically, a carcinogenic role for tobacco-specific N-nitroso derivatives has been described [17, 111].

Most assessments of carcinogens in e-cigarette aerosols involve comparisons with tobacco smoke. El-Hellani *et al.* [112] offer a different perspective based on mechanistic evidence in relation to what vapers inhale. E-cigarettes expose users to volatile organic carcinogens [113, 114]. Chromium and nickel, used in heating elements, contribute to the cancer risk from vaping as do cadmium, lead, and arsenic [115].

7. Assessment of qualitative carcinogenic risk

This qualitative carcinogenic risk assessment for e-cigarettes is predicated on multiple categories of evidence as evaluated by reviewers and authorities.

7.1. Physiological evidence of carcinogen exposure

Carcinogens inhaled by vapers are largely those inhaled by smokers, though some respective amounts vary markedly (Table 1). Detection of aerosol-related metabolites in urine proves absorption and excretion of these compounds including nicotine and many VOCs which generate recognized DNA adducts [3, 74, 106].

7.2. Carcinogenicity in humans and experimental animals

A small number of case reports involving vapers have prompted cancer attribution [58, 59]. There are no epidemiological data involving exclusive usage of e-cigarettes and associated cancer(s) primarily because of the relevant timeframe.

In mice, following inhalation, e-cigarette aerosols are carcinogenic causing adenocarcinoma of the lung [8]. Of the chemicals absorbed by vapers, the major nicotine-derived N-nitroso compounds, together with benzene, 1,3-butadiene, formaldehyde, ethylene oxide, *o*-toluidine and trichloroethylene, are *carcinogenic to humans (Group 1)* in IARC Monographs (https://monographs.iarc.who.int).

7.3. Mechanistic evidence of carcinogenicity

In this review, investigations of carcinogenic mechanism(s) are documented according to type. One, the most persuasive,

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Table 1 Carcinogen exposure due to vaping.

Carcinogen type	Carcinogen	Metabolite analysed	Vapers[a] (%)	Smokers[a] (%)
Tobacco-specific nitrosamines	NNK	NNAL	431	21 996
	NNN	N/A	80	514
	NNN (saliva)	N/A	5740	37 770
Metals	Cadmium	N/A	30	86
	Lead	N/A	23	36
Volatile organic compounds	Acrylonitrile	N-Acetyl-S-(2-cyanoethyl)-L-cysteine	201	9322
		N-Acetyl-S-(1-cyano-2- hydroxyethyl)-L-cysteine	30	1055
	N,N-dimethyl-formamide	N-Acetyl-S-(N-methylcarb-amoyl)-L-cysteine	46	359
	Acrylamide	N-Acetyl-S-(2-carbamoyl-ethyl)-L-cysteine	95	N/A
	Propylene oxide	2-Hydroxy-propyl methacrylate	89	N/A
	Crotonaldehyde	N-Acetyl-S-(3-hydroxy-propyl-1-methyl)-L-cysteine	48	N/A
	Acrolein	3-Hydroxypropyl mercapturic acid	32	N/A
	Ortho-Toluidine	N/A	133	

Determinations involve urinary analysis except where otherwise stated. Table adapted from that shown in [107].
[a]Increase compared to nonusers.

Table 2 Evidence for manifestation of the 'key characteristics' of carcinogens by e-cigarette aerosols.

Key characteristic	Clinical evidence	Animal & *In vitro*	Overall result	Remarks
Is electrophilic	+++	+++	+++	Metabolites detected and cytochrome-P450 role
Is genotoxic	+++	+++	+++	Comprehensive data available and specifically reviewed
Alters DNA repair	+	+	+	Positive findings from a limited number of studies
Induces epigenetic change	+++	++	+++	DNA methylation and altered transcription
Induces oxidative stress	+++	++	+++	Multiplicity of clinical and *in vitro* studies
Induces chronic inflammation	+++	+++	+++	Predominantly clinical evidence
Is immunosuppressive	++	++	++	Multiple indicators described
Modulates receptor-mediated effects	+	–	+	Clinical evidence re nicotine receptors
Causes immortalization	+	+++	+++	Tumorigenicity in mice shows implicit immortalization
Alters cell behaviours or nutrient supply	++	++	++	Includes histopathological evidence from vapers

In the table, confidence in positive findings is indicated with reference to a range extending from a reasonable inference (+) to confirmatory evidence (+++); inadequate evidence is indicated by (–). The 'overall result' takes account of human (clinical) evidence, laboratory-based evidence (animal & *in vitro*) together with findings (any type of data) made concerning individual chemical components of e-cigarette aerosols.

involves comparison of e-cigarette users with nonusers with reference to tissue injury and/or biomarkers. The other concerns laboratory studies of e-cigarette aerosols and their chemical components.

Strength of evidence for carcinogenicity from these two types, and the overall outcome has been assessed with reference to the key characteristics of carcinogens [7] (Table 2). The highest rating is indicative of clear evidence. The wide spectrum of characteristics manifest by aerosols is indicative of a complex mixture rather than a single chemical. The data presented in Table 2 indicate that the mechanistic evidence for the carcinogenicity of e-cigarette aerosols is unequivocal.

7.4. Overall assessment

Determinations made with reference to the three evidence streams identified above, together with earlier assessments of carcinogenicity are wholly consistent in delivering a clear and authoritative assessment. E-cigarettes delivering nicotine are likely to be carcinogenic to humans who use them causing oral cancer and lung cancer. The burden of disease cannot be quantified from data presently available.

This assessment is primarily based on carcinogenicity of e-cigarette aerosol in mice and a broad spectrum of mechanistic findings, as determined from both studies in humans and from laboratory investigation as well as the known carcinogenicity for particular components of e-cigarette aerosols.

More research is required to characterize other target organs, highest risk sub-populations and those chemicals unequivocally contributing to the carcinogenic risk now evident. However, the prospect of increased understanding does not offset the need for regulating availability and increasing community awareness concerning the cancer risk that vaping presents.

Qualitative assessment of e-cigarette carcinogenicity is indicative of only one aspect of the potential burden of cancer reasonably anticipated from vaping. This also includes cancer attributable to vapers who transition to smoking and the impact of dual use. Moreover, cancer aside, a range of disease are attributable to vaping which can no longer be caricatured as safer than smoking [116].

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Author contributions

B.W.S. proposed the overall design and offered an initial draft. All authors then proposed various structural changes, modified text, and additional references resulting in a revised manuscript that was again assessed by all authors leading to minor corrections. Confirmatory assessments were received from Camile S. Farah (Hollywood Medical Centre, WA Australia) and Laura Kirsten (Nepean Cancer Services. NSW Australia). N.D.M. contributed the graphic abstract. All authors read and approved the final manuscript.

Conflicts of interest

None declared.

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Data availability

No new data are included in this review.

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