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E-Cigarettes and Cancer Risk

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ABSTRACT

From the time of their introduction, the popularity of e-cigarettes (electronic nicotine-delivery systems) has been rising. This trend may reflect the general belief that e-cigarettes are a less hazardous alternative to combustible cigarettes. However, the potential cancer-related effects of increased activation of the sympathoadrenal system induced by the inhalation of nicotine, the primary component of the e-cigarettes, are completely overlooked. Therefore, the aim of this review is to describe mechanisms that may connect the use of e-cigarettes and an increased risk for cancer development, as well as their stimulatory effect on cancer progression. Available preclinical data indicate that activation of the sympathetic nervous system by nicotine inhaled from e-cigarettes may stimulate cancer development and growth by several mechanisms. This issue might be especially important for oncological patients as they may have the misconception that compared with combustible cigarettes, e-cigarettes represent a risk-free alternative.

Introduction

During the last 50 years, a robust body of evidence has accumulated documenting the negative health consequences of both active tobacco smoking and exposure to secondhand smoke. For example, evaluation of epidemiologic data has shown that at least 12 types of human cancers can be attributed to smoking (1). Therefore, it is not surprising that as information about the negative consequences of smoking is spreading within populations, more and more smokers are choosing e-cigarettes (electronic nicotine-delivery systems) as a "less harmful" source of nicotine.

The first commercially available e-cigarette, a device that is designed to deliver nicotine without tobacco smoke by heating a nicotine solution, was invented in 2003 by the Chinese pharmacist Lik Hon in Hong Kong. Since the introduction of e-cigarettes, they have been become increasingly popular among never-smokers and adolescents, as well as smokers who want to reduce the health risks of smoking or would like to quit smoking (2). This fact is documented by data from the 2011–2018 National Youth Tobacco Survey of U.S. middle and high school students. It was shown that the use of e-cigarettes increased in this group from 1.5% (220,000 students) in 2011 to 20.8% (3.05 million students) in 2018 (3). In the study investigating e-cigarettes use among adults in the United States, it was found that even if the weighted prevalence of current use of e-cigarettes decreased from 2014 to 2016 in some subgroups, the prevalence increased significantly among former smokers from 3.8% in 2014 to 4.8% in 2016 and never-smokers from 0.4% to 0.7% over the same time period (4). This increased popularity of e-cigarettes is also reflected in the variety of e-cigarette device models, numerous brands, and product designs that have been developed over the last few years. Today, the fourth generation of e-cigarettes is available with a heating temperature control mechanism (5, 6). However, even if the levels of carcinogens and toxins are substantially reduced in users of e-cigarettes in comparison with tobacco smokers (7), recent data have shown that the vapor from e-cigarettes also contains, in addition to nicotine, many toxic chemicals found in traditional cigarettes such as acetaldehyde, formaldehyde, acetone, acrolein, chromium, N-nitrosamines, and others (5, 6, 8). Moreover, the vapor derived from e-cigarettes accumulates in the airway epithelium in a similar fashion as smoke from combustible cigarettes (5). These facts indicate that the safety of e-cigarettes remains questionable, and it is still unknown as to whether their use can contribute to cancer development and progression (9). In addition, there are no data about the potential toxic effects of long-term exposure to the vapor produced by nicotine-containing cartridge fluid (10). Therefore, it is not surprising that increased attention is being paid to the effects of substances inhaled by e-cigarette users on their body. However, research into the potentially harmful effects of e-cigarettes in humans is faced with several issues. First, the relatively short period of time during which e-cigarettes have been on the market results in a lack of relevant data, especially those related to the chronic consequences of vapor inhalation (6). Moreover, many factors affecting the composition of inhaled vapor (e.g., device voltage, resistance, temperature, e-liquid flavors and ingredients, nicotine content, and puff topography of e-cigarettes users) and thus the degree of harm have been only recently identified, which makes comparison of previously published studies difficult (5, 6, 11). Nonetheless, there is an increasing number of both cell culture and animal model studies investigating the various biological, toxicological, and immunological effects of exposure to both the liquid used in

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e-cigarettes and the vapor generated by it on different organ systems, including respiratory, cardiovascular, immune, nervous, or uropoetic (10, 12–15). Importantly, prospective, randomized studies on e-cigarettes are starting to be performed (6).

Recently, the direct modulation of processes in cells or organs by the chemicals present in vapor of e-cigarettes has been studied. These investigations were focused on nicotine because a variety of its harmful effects, including stimulation of cancer growth, are well documented (15–19). In addition, the additives and substances generated by the heating process in e-cigarette cartridges have been widely studied due to their potentially toxic and mutagenic effects (5). However, the potential cancer-related effect of increased activation of the sympathoadrenal system induced by inhalation of nicotine, the primary component of e-cigarettes, has been overlooked in the available studies.

Differences between Combustible and e-Cigarettes

E-cigarettes are considered a less hazardous alternative to combustible cigarettes (20). In support of this, significantly lower levels of toxic substances have been observed in e-cigarette vapor compared with cigarette smoke (21). Consistent with these findings, significantly lower concentrations of biomarkers of exposure to tobacco-specific nitrosamines (TSNA), polycyclic aromatic hydrocarbons, most volatile organic compounds were observed in e-cigarette users when compared with concentrations found in tobacco smokers (22). However, it should be noted that levels of TSNAs, namely, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, are significantly lower in non-smokers than in e-cigarette smokers (8, 22).

Whereas concentrations of non-nicotine toxic substances in the blood of e-cigarette smokers are significantly lower than in users of combustible cigarettes, the concentration of nicotine is increasing as new generations of e-cigarettes emerge. Even if the first generation of e-cigarettes had inefficient nicotine delivery, users of newer, third-generation models achieve nicotine plasma levels comparable with levels found in smokers of combustible cigarettes (23).

Direct Carcinogenic Effects of e-Cigarettes

In 2014, two studies demonstrated the possible carcinogenic effects of e-cigarettes in immortalized, human bronchial epithelial cells. They found that exposure of these cells in culture medium to the vapor of e-cigarettes induced a similar pattern of gene expression as found in cells exposed to tobacco smoke (24, 25). Later, the findings of Park and colleagues (26) showed that exposure to clinically relevant concentrations of e-cigarette vapor-conditioned media enhanced cancer-associated processes of "at-risk" airways, including a demonstrated capacity for malignant transformation. The authors observed enhanced colony growth in anchorage-independent assays and increased cell invasion–associated morphologic changes in three-dimensional air–liquid interface models. In addition, they found that exposure of mutant epithelial cells to e-cigarette vapor-conditioned media induced airway gene-expression changes similar to those seen with combustible cigarette smoke exposure (26). It was also demonstrated that e-cigarette aerosol increased the proinflammatory cytokines IL6 and IL8 and diminished lung glutathione levels in human and mice lung epithelial cells (27). Importantly, data have shown that increased IL6 levels might, through the STAT3 signaling cascade, promote lung cancer cell growth (28).

In 2017, Canistro and colleagues demonstrated that e-cigarette vapor has powerful comutagenic and cancer-initiating effects in a rat lung cancer model. They showed that e-cigarettes have a booster effect on phase-I carcinogen-bioactivating enzymes, including activators of polycyclic aromatic hydrocarbons (PAH), increased oxygen-free radical production, and DNA oxidation to 8-hydroxy2′-deoxyguanosine (9). Later, Lee and colleagues published data showing an enhanced susceptibility of lung epithelium to oncogenic transformation and tumorigenesis via the action of nicotine metabolites, as well as the subsequent generation of mutagenic nucleotide products in the lung and urinary bladder of mice exposed to e-cigarette vapor, with similar results found in human bronchial epithelial and urothelial cell cultures. In addition, both the DNA-repair activity and expression of the repair proteins XPC and OGG1/2 were significantly reduced in the lungs of mice as well as in human bronchial epithelial cell cultures after exposure to e-cigarette vapor (29, 30). Interestingly, e-cigarettes induce DNA-strand breaks in the human epithelial cell line HaCaT independent of nicotine, while there is evidence that e-cigarette vapor exaggerates the extent of nicotine induced DNA damage (31).

In 2018, Staudt and colleagues demonstrated that even short-term use of e-cigarettes induces tumor- and metastasis-promoting factors related to lung cancer in small airway epithelium (32). It has also been shown that e-cigarettes enhance both the migration and stemness of non–small cell lung cancer cells through expression of the embryonic stem cell factor Sox2 (33, 34). Recently, Tommasi and colleagues reported significant epigenetic changes in the oral cells of users of e-cigarettes. Further analysis revealed that these deregulated genes are associated with signaling pathways implicated in cancer (35).

E-cigarette–related activation of nicotinic receptors in the cancer microenvironment

Nicotinic receptors are expressed on the surface of tumor and immune cells (36, 37), enabling nicotine to directly affect the tumor microenvironment. As a result, this alkaloid has a pronounced tumor-promoting effect on several types of cancers (36, 38).

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Through binding to nicotinic receptors, nicotine may potentiate cancer cell survival (39, 40), tumor cell proliferation (41, 42), metastasis, invasion, epithelial–mesenchymal transition (43, 44), and angiogenesis (45, 46). It can also reduce cancer cell apoptosis induced by chemotherapy, radiotherapy, or receptor tyrosine kinase inhibitors (47–49). In addition, nicotine may stimulate proliferation and angiogenesis through the induction of norepinephrine and epinephrine synthesis in colorectal and pancreatic tumor cells, and this effect was blocked by the β-adrenergic receptor antagonists propranolol and ICI-118,551 (46, 50–52).

Indirect "Hidden" Tumor-Promoting Effects of e-Cigarettes

As mentioned above, many studies have been focused on determining the direct effects of e-cigarettes on normal and cancerous cells. However, nicotine inhaled from e-cigarettes may also indirectly exert tumor-promoting effects via stimulation of the sympathoadrenal system (**Fig. 1**).

The sympathoadrenal system stimulates cancer initiation and progression

Over the past two decades, a combination of neuroscientific and oncological research has gradually uncovered the role of the nervous system in cancer. It has been found that the sympathoadrenal system stimulates both carcinogenesis and processes related to tumor progression and metastasis (53–55). Such important effects are induced by norepinephrine released from nerve terminals in tissues innervated by the sympathetic nervous system, as well as by epinephrine and norepinephrine released from the adrenal medulla into the systemic circulation (56). Preclinical and clinical studies have shown that norepinephrine and epinephrine, via binding to β-adrenergic receptors, potentiate the induction of DNA mutations via induction of oxidative stress that reduces the efficiency of DNA-repair mechanisms (57, 58), activate oncogenes (59, 60), induce tumor-promoting inflammation (61), inhibit antitumor immunity by suppression of NK cell activity (62, 63), directly stimulate the proliferation of tumor cells by binding to β-adrenergic receptors expressed by these cells (64–66), protect cancer cells from apoptosis (67, 68), potentiate both neoangiogenesis (69, 70) and lymphatic vessel rearrangement (71) in tumor tissue, enhance matrix metalloproteinase activity (72, 73), and stimulate the mobility (55) and deformability (74) of tumor cells, leading to the development of metastases (75). In addition, published data indicate that catecholamine-induced increase of systemic vascular resistance might redirect blood flow to cancer tissue (76). Moreover, metabolic changes induced by an activated sympathoadrenal nervous system (77) might also affect cancer nourishment. Therefore, it is not surprising that approaches attenuating the effect of norepinephrine and epinephrine (e.g., sympathectomy or administration of β-blockers) can also help to impede the course of cancer progression, as documented by many preclinical and clinical studies (51, 78–86).

Nicotine activates the sympathoadrenal system

Importantly, it is well known that nicotine increases the release of norepinephrine and epinephrine due to its stimulatory effect at several levels of the sympathoadrenal system (87). This effect is mediated by mechanisms including (i) direct stimulation of nerve endings of sympathetic nerves, (ii) activation of nicotinic receptors on cell bodies of sympathetic postganglionic neurons, and (iii) activation of structures of the central nervous system that regulate sympathetic outflow (88). The net stimulatory effect of nicotine on the sympathoadrenal system is documented by the significantly increased plasma norepinephrine and epinephrine levels found in smokers (89). Importantly, the acute sympathomimetic effect of e-cigarettes is attributable to the inhaled nicotine but not the non-nicotine compounds found in the vapor of e-cigarettes (90).

E-Cigarettes and Patients with Cancer

Especially important is the issue of e-cigarettes usage by oncological patients. As noted by Sanford and colleagues, the popularity of e-cigarettes is rising not only in the general population but also among patients with cancer (91). This rise in the use of e-cigarettes in patients with cancer may result from the fact that e-cigarettes are being perceived as a less hazardous alternative to combustible cigarettes (20) due to reports that e-cigarettes produce a smaller quantity of pollutants compared with combustible cigarettes (8). Therefore, patients with cancer may assume that e-cigarettes are almost harmless from the point of view of their disease. However, as mentioned above, the stimulatory effect of nicotine inhaled from e-cigarettes on the sympathoadrenal system may represent an important factor that stimulates progression of their disease. In addition, their use might also be hazardous in individuals with a predisposition for oncological disease. Moreover, as data have shown that epinephrine and norepinephrine act as an angiogenic switch (92) that activates dormant tumors, e-cigarettes might participate in the clinical manifestation of previously dormant cancer. Importantly, the stimulatory effect of nicotine on cancer induction and progression might also be related to other nicotine-delivery systems (e.g., patch, nasal or mouth spray, inhalator, mouth strip, gum, lozenge, and microtabs).

Recommendations for Clinicians

As there are an increasing number of new smokers that start with e-cigarettes instead of combustible cigarettes, these individuals should be informed of the potential interconnection between e-cigarettes and cancer (for recommendations on how to inform patients about the potential harmful effects of e-cigarettes see ref. 93). This information about the stimulatory effects of nicotine and other chemicals inhaled from

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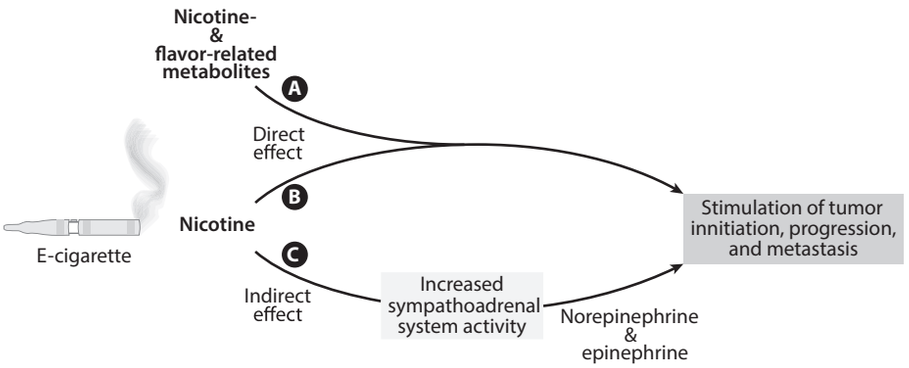

Figure 1.
Schematic depiction of the direct (**A** and **B**) and indirect (**C**) cancer-related effects of compounds inhaled from e-cigarettes.

e-cigarettes on cancer initiation, progression, and development of metastases must be especially provided to oncological patients and individuals with a predisposition to cancer. However, in patients with cancer that are not able to quit smoking and would like to switch from combustible to e-cigarettes, it is necessary to take into consideration the fact that available data indicate that the harmful effects of e-cigarettes are significantly lower than those of combustible cigarettes (7). Therefore, based on available data, e-cigarettes might be recommended to smokers with cancer as a less hazardous alternative (94). In addition, e-cigarettes might also be used in patients with cancer as an effective tool for smoking cessation (95). However, if patients with cancer are informed that even if e-cigarettes are a less hazardous alternative to combustible cigarettes, the risk of potentiating the progression of their disease by e-cigarettes still exists, this might motivate some patients with cancer to quit smoking.

Future Directions

Because e-cigarettes have only been on the market for 16 years (2), it is obvious that our understanding of their effects, especially long term, is still fragmentary. Even if data from recent studies indicate that compounds inhaled from e-cigarettes might participate in carcinogenesis, the indirect effects of nicotine on cancer initiation and progression in smokers of e-cigarettes, mediated by the sympathoadrenal system, have not yet been investigated. Therefore, there is an urgent need for preclinical studies using cancer models in which we can test the effect of long-term inhalation of nicotine from e-cigarettes on the activity of the sympathoadrenal system as determined by plasma epinephrine and norepinephrine levels, as well as their effect on cancer incidence and progression. In these preclinical studies, the fact that e-cigarettes differ in nicotine content (23) needs to be taken in consideration and therefore the effect of different concentrations of this compound on sympathoadrenal system activity and cancer needs to be determined. Similarly, it is necessary to elucidate the effect of e-cigarettes on the incidence and progression of cancer, development of metastases, recurrence of disease, and efficiency of oncological therapy in both retrospective and prospective clinical trials. In studies investigating the effect of e-cigarettes on the progression of disease in patients with cancer, it is necessary to take several factors into consideration:

(i) Whether patients with cancer started smoking before or after cancer diagnosis and the duration and frequency of smoking, as the stimulatory effect of nicotine on cancer initiation and progression might be dose and time dependent;
(ii) Type of cancer, as some cancers seem to be more sensitive to the stimulatory effect of the sympathoadrenal system (96);
(iii) Eventual therapy by β-blockers (e.g., as treatment of hypertension) as these compounds attenuate the effects of epinephrine and norepinephrine released by the sympathoadrenal system on cancer initiation and progression;
(iv) The typology of the individual, their age, and extent of social interactions, as these factors affect the activity of the sympathoadrenal system and are known to affect the clinical course of cancer (97).

Conclusion

Although e-cigarettes seem to be less harmful to users and therefore may appear to be a less hazardous alternative to combustible cigarettes, the above-mentioned facts indicating an interconnection between e-cigarettes containing nicotine and cancer support that much effort should be made to strictly regulate the e-cigarette market. This assumption is also supported by the fact that clinical trials investigating the long-term effects of e-cigarettes on cancer incidence and progression are still absent. Therefore, further preclinical and clinical studies focusing on elucidating the potential mechanisms and pathways interconnecting e-cigarettes and cancer are necessary.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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