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Contemporary Review

Do Electronic Cigarettes Impart a Lower Potential Disease Burden Than Conventional Tobacco Cigarettes?: Review on E-Cigarette Vapor Versus Tobacco Smoke

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Objectives/Hypothesis: Development and utilization of electronic cigarettes (ECs) resulted from the search for healthier alternatives to conventional tobacco cigarettes (TCs) and the search for alternative methods for quitting TCs. This review compares the potential disease burden presented by TC smoke to that of EC vapor.

Methods: Potential disease burden of EC vapor versus TC smoke was assessed by reviewing clinical studies that measured inhaled components. Chemicals and carcinogens produced by vapor versus smoke were compared.

Results: Studies show that EC vapors contain far less carcinogenic particles than TC smoke. Whereas ECs have the ability to reach peak serum cotinine/nicotine levels comparable to that of TCs, ECs do not cause an increase in total white blood cell count; thus, ECs have the potential to lower the risk of atherosclerosis and systemic inflammation. Use of ECs has been shown to improve indoor air quality in a home exposed to TC smoke. This reduces secondhand smoke exposure, thus having the potential to decrease respiratory illness/asthma, middle-ear disease, sudden infant death syndrome, and more. However, some studies claim that propylene glycol (PG) vapor can induce respiratory irritation and increase chances for asthma. To minimize risks, EC manufacturers are replacing PG with distilled water and glycerin for vapor production.

Conclusion: Based on the comparison of the chemical analysis of EC and TC carcinogenic profiles and association with health-indicating parameters, ECs impart a lower potential disease burden than conventional TCs.

Key Words: Electronic cigarette; vapor; vaping; tobacco cigarette; smoke; carcinogen; disease burden; second-hand smoke exposure.

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INTRODUCTION

Introduced to U.S. markets in 2007, electronic cigarettes (ECs) are a fairly new concept lacking set regulations for manufacturing and use.[1] Although this new nicotine-delivery device offers solutions to some of the health problems associated with the conventional tobacco cigarette (TC), there remains great caution and hesitation concerning its approval by the U.S. Food and Drug Administration (FDA) and the common public. EC use is novel and unfamiliar, making it difficult at this point and time to assess the long-term health effects on users (active vapers) and nonusers who are exposed to EC vapor (passive vapers). More uncertainty arises from the highly variable quality control and the lack of uniform manufacturing standards.[2,3] Finally, there is ongoing debate over the regulation of availability, purchase, and use in the United States, leaving the population conflicted about introducing a new drug delivery product that has the potential to attract young nonsmokers rather than to encourage current smokers to quit.

This review covers current research that focuses on the components and potential health risks associated with EC vapor and presents a thorough comparison of the components and known health problems of TC smoking. Acute (short-term) or chronic (long-term) and active or passive vaping on complete blood count, lung function, and myocardial function is investigated and reported to present potential disease burden.

Positive Aspects

Advocates of ECs encourage EC development and use as an alternative and supplemental method for quitting TC use. Whether ECs are used to replace nicotine therapy or to supplement it, ECs offer another form of nicotine delivery without the known adversaries of TC combustion and the resulting smoke. Some studies have shown that EC use provides a more natural way to decrease TC smoking because the act of "smoking" an EC mimics the habits surrounding TC smoking; that is, taking cigarette breaks, having an actual object to puff and produce "smoke" (vapor), and carrying (cartridge) packs around.[4]

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This is a welcome alternative to current nicotine replacement therapies such as nicotine patches and gum, which offer no solution to the physical hand–mouth motion associated with TC smoking. Furthermore, ECs have been found to reduce TC cravings for smokers and those implementing nicotine replacement therapy.[4] In addition, EC use helps quitters avoid relapse.[5,6] Above all positives, ECs do not require the combustion of chemicals to attain a TC-comparable dose of nicotine. The single most harmful aspect of TC use is the combustion of chemicals. Upon burning, TCs release thousands of carcinogens in the form of smoke into the air, where it is exposed to smokers and nonsmokers. EC has the potential to diminish secondhand smoke exposure to nonsmokers and children of smokers while satisfying nicotine cravings.[4,7,8]

Negative Aspects

ECs have received negative attention for several valid reasons. A major concern is that current TC smokers will use ECs to cope in nonsmoking environments and will continue smoking TC in smoking-designated areas; something known as dual use.[4] Another concern is that ECs could become an attractive starter product for young nonsmokers who were initially turned off by the consequences of TC.[4] The claims made by EC could be the tipping factor for those sitting on the fence to start nicotine use and could cause a gateway effect. Furthermore, many criticize the fruit-flavored and other appetizing flavors of EC cartridges, claiming that this is an attractant for young nonsmokers. There is also concern that ECs may become the reason that many smokers forego traditional cessation methods that have a history of effectiveness.[4]

Furthermore, several studies have presented data indicating the challenge of effective EC vaping. This means that many users have difficulty extracting the nicotine from the EC device. Studies show that the reasons for this are three-fold: 1) EC and TC require different puffing techniques[9]; 2) EC use requires practice, so there is a learning curve for effective vaping[10]; and 3) users have preferences for different types and generations of ECs, indicative of inconsistent manufacturing and production.[11]

Finally, ECs receive the greatest criticism for the unknown effects on health and potential disease burden. Without the ability to study the long-term effects of ECs, it is difficult to measure the health risks associated with using ECs over conventional TCs. Current research is concerned with the excessive propylene glycol content in the vapor, and also the potential of accidental poisoning from liquid cartridge contents.[4]

Combustion Versus Vaporization

Combustion. It is well known that a TC delivers nicotine and produces smoke by way of heat and combustion. Combustion is the burning of chemicals that changes the properties of ingredients in a cigarette. The burning of a cigarette produces 4,000 chemicals, of which 100 have been identified as known carcinogens—cancer-causing agents.[12–14] Carcinogens are also agents that promote or aggravate the onset of cancer. The World Health Organization and the International Agency for Research on Cancer have evaluated 900 chemicals often found in the conventional TC that have cancer-causing potential. Although the bulk of these chemicals have been categorized as group 2A (probably carcinogenic to humans) and group 2B (possibly carcinogenic to humans), 100 chemicals have been classified as group 1 (carcinogenic to humans). An extensive list of these chemicals has shown that TCs contain everything from arsenic (rat poison) to polonium (radioactive, cancer-causing element).[14]

Vaporization. ECs do not require combustion to deliver TC-comparable doses of nicotine,[5] nor do they include many of the potentially carcinogenic additives that are found in TC. They are essentially electronic inhalers that work by way of vaporization—activation of a battery heats a cartridge liquid (usually containing humectants, nicotine, and flavoring) to a maximum temperature of 55°C to release aerosolized nicotine and smokeless vapor. Humectants are often propylene glycol or vegetable glycerin.[2] The aerosolized nicotine is readily delivered into the respiratory tract.

Carcinogenic content: smoke versus vapor. In order to compare the disease burden of TC versus EC, carcinogen and particle content in TC smoke is compared to that of EC vapor. Exhaled vapor composition is expected to differ from liquid composition.

Indoor air quality. One study, done by McAuley, et al. comparing the particles and components found in EC vapor and TC smoke in indoor air samples showed that EC vapor posed a significantly lower risk than TC smoke under identical experimental conditions and methods.[15] The analysis covered volatile organic compounds (VOCs), carbonyls, polyaromatic hydrocarbons, tobacco-specific nitrosamines (N′-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT), N′-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)), nicotine, and glycols (propylene glycols/PG, diethylene glycols/DEG). The findings of this studying were found to be in agreement with the findings of several other studies, including Schripp et al.,[1] Lauterbach et al.,[37] Laugeson et al.,[38] and FDA.[39] See Table I for a summary of the analyses.

Collected air quality data was presented to expert toxicologists, who determined the total cumulative hazard indices and excess lifetime cancer risks (ELCRs) values and translated the values to disease burden. The following summarizes the findings:

Child and adult exposure to noncancer and cancer analytes in vapor and smoke

- *Vapor*. Child and adult: no significant risk
- *Smoke*. Child: exceeded high-risk limit; adult: significant risk

Child and adult exposure to carcinogens in vapor and smoke

- *Vapor*. No cumulative ELCR exceeding cancer risk limit of 1×10^{-5}
- *Smoke*. Adult exposures approached ELCR risk limit of 1×10^{-5}

Overall, TC smoke contains significantly more carcinogens and carcinogenic analytes than EC vapor. This

TABLE I.
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Component	Detection in Vapor versus Smoke
VOC*	Vapor: Below LOD, except for ethylbenzene, benzene and toluene.
	Smoke: Orders of magnitude higher than found in vapor
Carbonyls*	Vapor: Low concentration, except for acetone, formaldehyde, acetaldehyde
	Smoke: Orders of magnitude higher than found in vapor
PAH†	Vapor: Below LOD, except for benzo(a)pyrene, which was found in same concentration as in smoke
	Smoke: Above LOD
TSNA*	Above LOD for both vapor and smoke, but significantly higher in smoke
Nicotine*	Above LOD for both vapor and smoke, but significantly higher in smoke
DEG*	Detected in some vapor and smoke samples, but below toxic levels
Glycols*	Significantly higher concentration in vapor than smoke
Particle count*	Vapor: Low particle count across all EC-liquids tested; significantly lower than smoke particle count

*Values found in McAuley et al.[15] in agreement with Schripp et al.,[1] Lauterbach et al.,[37] Laugesen et al.,[38] and FDA.[39]

†Lauterbach et al.[37] found benzo(a)pyrene below LOD for vapor and 40 times higher in smoke.

DEG = ; EC = electronic cigarettes; FDA = U.S. Food and Drug Administration; LOD = limit of detection; PAH = polyaromatic hydrocarbons; TSNA = tobacco-specific nitrosamines; VOC = volatile organic compounds.

study by McAuley et al. concludes that EC vapor poses significantly lower risk than TC smoke, and that there are no recognizable health impacts from the vapor produced by any of the four EC liquids tested in this study.[15]

Secondhand Exposure

EC vaping results in second hand vapor exposure. Upon exhalation, VOCs and ultrafine particulates are released into the indoor air resulting in potential passive vaping by non-vaping individuals inhaling the same air.[1] Some studies claim that heat alone causes formation of formaldehyde, acetaldehyde, and methylglyoxal.[16] However, continuous monitoring of the indoor air environment during EC vaping did not detect any significant increase in formaldehyde concentration.[1] Thorough comparison to emissions from conventional TC shows that EC vapor and consequent passive vaping is safer than TC smoke and subsequent SHSe. Although everything from 1,2-propanediol to benzene to formaldehyde was detected in EC vapor, the levels were close to the limit of detection (LOD). Some studies show that the presence of those particles is no different than what would be produced simply from the physiological metabolism and exhalation of an individual who does not use TC or EC products.[1,17]

The FDA has expressed concern about ECs due to the high propylene glycol (PG) content in EC vapor. However, PG has been safely used in numerous consumer and household products from food to cosmetics to pharmaceuticals. At worst, PG was found to be irritating to the throat upon constant inhalation. Some users reported upper airway irritation following short-term use of EC, claiming this was due to excessive exposure to propylene glycol.[18] Current FDA-approved Nicotrol Inhalers[1] also have this side effect on users. Furthermore, in response to PG concerns, most EC manufacturers have begun to eliminate this potential risk by replacing PG with glycerol and water vapors, thereby increasing EC safety.

Meanwhile, it has been well established that TC smoking and secondhand smoke exposure (SHSe) increases the risks of tuberculosis, cardiovascular risk, lung cancer mortality, emphysema, laryngitis, cancer of the throat and lung, and other fatal health implications.[19–21] The impact of smoke from conventional TCs on indoor air quality has been extensively studied and shows that hundreds of ingredients form carcinogenic and volatile combustion products, which are then released as fine particulate matter into the air.[14]

Effects on Complete Blood Count and Associated Potential Disease Burden

Acute and chronic active TC smoking increases the white blood cell (WBC) count, as does passive TC smoking through SHSe.[22,23] Specifically, nonsmokers who are exposed to passive TC smoking and active TC smokers showed a significant increase in WBC, lymphocyte, and granulocyte count.[24]

An increase in WBC count and analysis of total blood count is an objective way to gain an overview of an individual's systemic and cardiovascular health status. Elevated or deflated cell counts could indicate overall systemic problems ranging from infection and inflammatory disease to bone marrow and immune diseases.[25] Elevated levels of circulating WBCs are involved in low-grade inflammation, as seen associated with atherosclerosis. Chronic active TC smoking elevates proteins' acute inflammatory load such as interleukins 4, 5, and 6 and interferon gamma.[24]

Meanwhile, chronic passive TC smoking (SHSe) has shown elevated levels of C-reactive protein, in addition to elevated levels of IL-4/5/6 and interferon gamma, which can be indicative of cancers, cardiovascular disease, fibrosis, and obstructive sleep apnea.[23] The same study found that active and passive EC vaping showed no significant change in complete blood count indices and no increase in WBC count.[24]

Effects on Lung Function and Associated Potential Disease Burden

Lung function parameters are measured as indicators of the respiratory health of individuals following chronic and acute exposure to TC smoke and EC vapor. Lung function is measured by spirometry, which calculates volume and speed that air can be inhaled and exhaled; breath carbon monoxide (CO) monitor, which assesses exhaled CO; and breath nitric oxide (NO) analyzer, which measures the fraction of exhaled nitric oxide (FeNO). FeNO indices are used as noninvasive markers of bronchial inflammation.

Studies show that acute active and chronic passive EC vaping generated smaller changes in lung function compared to acute active and passive TC smoking for both current smokers and never-smokers.[26] Although it seems that the ECs have minimal deleterious effects, another study shows that EC use results in greater negative clinical changes. It has been reported that acute use of EC for 5 minutes results in an immediate decrease of FeNO, which consequently results in an increase of total respiratory impedance and peripheral flow resistance.[18] Because other studies have shown that changes in flow resistance precedes peak expiratory flow (PEF) and forced expiratory volume (FEV), spirometry alone is not an effective way to measure lung function.[27] Although negative clinical changes have been reported, changes may be too small to be of major clinical importance or to indicate dyspnea or breathing difficulties. It is important to note that Vardavas et al.'s study was limited to a comparison between sham ECs (control) and real ECs. There was no comparison to TC use.[18] This study is strictly used to demonstrate that EC use has potential for negative clinical changes.

Acute active and passive TC smoking repeatedly undermined lung function. TC smoking contributes to the development of chronic lung disease. Studies found an increased production rate of growth factors and type 1 procollagen in the small airways,[28] leucocyte bounding to endothelial cells,[29] increased lung inflammation,[30] and increased platelet activation[31]—all of which are linked chronic lung disease and eventual carcinoma.

Effects on Myocardial Function and Associated Potential Disease Burden

A study by Farsalinos et al. evaluated acute effects of EC use versus TC use on left ventricular myocardial function.[32] Assessment was done through complete echocardiographic exams and measurement of Doppler flow parameters. All participants—who were ex-smokers—showed similar characteristics of baseline echocardiogram and hemodynamic parameters. Participants were exposed to relative amounts of nicotine through either EC or TC use.

Those who smoked TCs presented data indicative of acute impairment of left ventricular function, such as a decrease in Em velocity and Em/Am ratio and an increase in isovolumic relaxation time and myocardial performance index.

Those who vaped ECs showed no signs of alterations from baseline levels, indicating that there were no acute adverse effects on cardiac function.

CONCLUSION

ECs are nicotine-delivery devices. As a result, EC users will always risk the potential disease burdens associated with nicotine use and related side effects such as increased blood pressure, heart rate, microvascular injury, and dependence. That said, ECs present decreased potential disease burden compared to TCs. It is generally understood that the toxicants from burning tobacco and TC components are responsible for most adverse health effects, whereas nicotine is responsible for the addictive quality in TCs.

Studies show that EC use has the potential to effectively allow TC smokers to quit or decrease TC use, thereby eliminating combustion of carcinogenic TC components and subsequent active and passive exposure to carcinogens exposed directly to smokers, secondhand smokers, and the environment.

Major concerns remain that persist, as well as considerations that should be taken into account. At present, the manufacturing and distribution of the EC device and cartridge manufacturing and production is unregulated and highly variable, which has resulted in ECs of differing design, materials, utilization, combustion voltage, and liquid cartridge concentration. This is confusing for the common consumer and also is a barrier to effectively studying the potential adverse and beneficial effects of ECs. Further concerns involve the novelty of EC use. Whereas ECs offer exciting potential in decreasing the disease burden imparted by use of TCs, the short-term existence of ECs in the public market should be taken into account. Presently, there are no long-term studies investigating the reduction of disease development in those who have switched from TC use to EC use, or in those who have been using ECs for an extensive period of time. Without this data, ECs can only claim potential for decreasing disease burden, as speculated by the lower carcinogenic profile found in ECs versus TCs. Chemical analyses show decreased carcinogenic content in ECs, but there is yet to be a study demonstrating that the decreased carcinogenic content is directly correlated to reduced disease development, such as cancer, in former TC smokers.

Last, we must take into account the role of health care providers as advocates or antagonists of EC use as therapy for smoking cessation—especially with regard to adolescents, the age group showing the most significant increase in EC use.[33] Whether providers support or oppose the use of ECs as a transitional nicotine delivery device, it is the responsibility of providers to be knowledgeable and up-to-date about emerging health care issues.[34] Important EC-related topics are the following: 1) consumer surveys and subjective views on vaping; 2) chemical analysis of e-cigarette liquid cartridges, vapor, and third-hand deposition of vapor; 3) nicotine content, delivery, and pharmacokinetics; and 4) clinical and physiological studies investigating the effects of acute EC use.[35] Furthermore, due to the controversy and unknowns surrounding ECs, perhaps the use of ECs should be strictly regulated and limited until studies show evidence of disease reduction. It is in the best interest of providers and users to incorporate screening, counseling, and education prior to EC use.[36]

As the debate on TC versus EC continues, there are a few key things to keep in mind: 1) TC combustion is a continuous process, meaning that carcinogens are actively and passively released during the entire smoking session. Meanwhile, ECs only release vapors during exhalation. 2) As ECs become increasingly sophisticated, they will be able to more effectively deliver accurate doses of nicotine, eliminating current issues regarding noncompliance or ease of use. 3) The EC components discussed in this review strictly apply to EC liquid cartridge components that are heated and vaporized. Heating the metal and silicate components of the actual device itself (to extreme temperatures) may present a whole new set of potential disease burdens associated with ECs. 4) Finally, the potential disease burden of long-term EC is unknown because ECs are a novel commodity, but analysis of parameters related to health after acute EC vaping could be indicative of long-term toxicity.

Future Research

Future research on ECs should cover: 1) long-term active and passive EC vapor inhalation and comparisons of various nicotine dosing; 2) modified, indoor air-quality study using other flavors of EC liquid cartridges—or flavored versus nonflavored liquid cartridges to determine additional pollutant in flavored liquids; 3) various voltages of EC to see whether increasing the heat of the EC will change the decomposition of components and lead to increased toxicity; and 4) repeated studies once EC production is more regulated and standardized. Current studies use different brands or types of EC with different doses of liquid cartridges, resulting in differing nicotine dosages.

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