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REVIEW PAPER

Health consequences of smoking – focusing on alternative smoking methods

Skutki zdrowotne palenia w odniesieniu do alternatywnych wyrobów tytoniowych

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ABSTRACT

When e-cigarettes and, later on, heat-not-burn products were introduced to the market, it was hypothesized that they could have some positive effect on smoking cessation and reduction of smokers' exposure to dangerous substances. Despite some of their benefits, toxicological studies show the presence of some hazardous substances in their vapors, which may affect smokers' health in a similar way as tobacco cigarette compounds. There is a small amount of research studying the effects of these alternative cigarettes on health consequences in humans. In addition, the great majority of them compare only health effects of switching to e-cigarettes or heat-not-burn (HnB) products, without specifying their impact on non-smokers. Long-term exposure effects of e-cigarettes and heat-not-burn cigarettes and their effect on maternal health or fetus development are still unknown.

KEY WORDS

smoking, health consequence, tobacco cigarette, e-cigarette, heat-not-burn product.

STRESZCZENIE

Wprowadzenie na rynek produktów alternatywnych do wyrobów tytoniowych, takich jak e-papierosy czy papierosy typu IQOS, z założenia powinno pozytywnie wpływać na zmniejszenie narażenia palaczy na niebezpieczne związki chemiczne zawarte w dymie tytoniowym lub wspierać rzucenie palenia. Pomimo sugerowanych korzyści przeprowadzone badania toksykologiczne wykazały obecność w wytwarzanych w nich oparach niebezpiecznych związków chemicznych. Wyniki te sugerują, że palenie e-papierosów lub papierosów typu IQOS w podobny sposób do konwencjonalnych wyrobów tytoniowych może niekorzystnie wpływać na zdrowie ich użytkowników. Niewiele jest jednak badań z udziałem ludzi dotyczących konsekwencji zdrowotnych stosowania tych wyrobów. Większość z nich porównuje skutki zdrowotne ich używania zamiast konwencjonalnych papierosów bez określenia wpływu na osoby wcześniej niepalące. Ponadto nie zostały dotychczas ustalone skutki zdrowotne długotrwałego palenia e-papierosów lub papierosów typu IQOS oraz ich wpływ na rozwój płodu lub zdrowie kobiet w ciąży.

SŁOWA KLUCZOWE

palenie, konsekwencje zdrowotne, wyroby tytoniowe, e-papierosy, papierosy typu IQOS.

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INTRODUCTION

The first mention about tobacco smoking dates back to 5000 BC. Beginning with using tobacco during rituals or religious events, its cultivation and consumption increased significantly with the colonization of today's America by Europeans in the 16th century. The popularity of tobacco products grew at a rapid pace, which contributed to the development of the tobacco industry in the 18th century [1]. Currently, around 21% of the global population (35% of men and 6% of women) smoke some tobacco products. However, it is forecasted that the percentage of smokers worldwide in 2030 will decrease to 17%. In relation to World Health Organization (WHO) statistics, smoking contributes to 10% of deaths worldwide. Currently about 7 million of people die because of smoking each year, and this number may exceed 8 million in 2030 [2].

Increased popularity of tobacco products is followed by a great number of scientific reports indicating their harmfulness. Tobacco cigarette (TC) smoke contains a mixture of around 5000 chemical substances [3]. The main components of their aerosol are: nicotine, tar, carbon monoxide (CO), polyaromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), volatile organic compounds (VOCs), free radicals and heavy metals [4–6]. Many of these substances are classified as harmful or potentially harmful constituents (HPHCs) for humans [7]. The U.S. Food and Drug Administration published a list of 93 HPHCs present in tobacco products and cigarette smoke [8]. Furthermore, many of these chemicals are classified according to the International Agency for Research on Cancer (IARC) as carcinogenic for humans (group 1, i.e. nickel, benzene or 4-aminobiphenyl), probably cancerogenic for humans (group 2A, i.e. benzo[a] pyrene, 1,3-butadiene, formaldehyde or N-nitrosodimethylamine) or possibly carcinogenic for humans (2B, i.e. acetaldehyde, hydrazine, lead or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)) [9–11]. Exposure to such a huge number of toxic substances contributes to the development of tobacco-related diseases, such as cancer, cardiovascular disease, respiratory diseases such as chronic obstuctive pulmonary disease (COPD) and impairment of reproductive function and fetus development [12].

Quitting smoking or at least reducing the number of cigarettes smoked per day seem to be the best options for smoking addicts [13]. However, in order to limit smokers' exposure to hazardous substances accumulated in tobacco smoke, the tobacco industry has also introduced some novel products, such as electronic cigarettes and heat-not-burn products, to the market [14, 15]. These cigarettes are characterized by limited components and also significantly reduced numbers of some toxic constituents emitted with their aerosol. Therefore they may be less harmful than conventional tobacco cigarettes and they may potentially be used by smokers who do not want to quit smoking tobacco products completely. However, the safety of these products is still under debate. On the one hand, toxicological studies indicate the presence of dangerous substances in their vapors. However, their values are lower when compared to conventional cigarettes. Furthermore, presence of the aforementioned substances in these novel cigarettes' smoke may affect smokers' health in a negative way. Nevertheless, long-term exposure effects are still unknown, especially for never-smokers [16–21].

The following work attempts to summarize current knowledge about health consequences of two most popular novel cigarettes: e-cigarettes and heat-not-burn products. Due to the rapidly growing market of alternative smoking devices, it is necessary to clearly determine benefits and any potential risks of using such products instead of conventional tobacco cigarettes, especially for non-smokers who want to try these products. Therefore, this review compares only the currently known health consequences of smoking tobacco, electronic and HnB cigarettes, based on findings from studies with humans.

HEALTH CONSEQUENCES OF SMOKING CONVENTIONAL TOBACCO CIGARETTES

Tobacco constituents and substances derived from their pyrolysis, as well as some additional ingredients of tobacco cigarettes, have an adverse effect on the smokers' body. By inhaling these hazardous substances, various biological processes are activated in smokers' bodies [22]. The spectrum of health consequences of tobacco smoking depends on many factors, such as: type of tobacco products, number of years of smoking, number of cigarettes

smoked per day, age of smoking initiation, the likelihood of cessation and nicotine dependence [23].

The first adverse health effects of smoking may be observed immediately or shortly after using cigarettes. Huge amounts of toxic substances absorbed by smokers with tobacco aerosol increase the amount of free radicals and reduce activity of antioxidants, which leads to an oxidative-antioxidative imbalance and induction of oxidative stress. As a consequence, it activates the inflammation and impairs the immune response [24, 25]. Furthermore, the accumulation of oxidants also affects peroxidation of lipids, proteins and nucleic acids. Moreover, respiratory impairment, such as irradiation, cough, increased mucus production, dyspnea or wheezing may be observed [26]. Finally, smoking tobacco may lead to nicotine addiction [27].

Intensive smoking of tobacco products directly or indirectly contributes to the appearance of further negative health outcomes. Impairment of the immune response may cause increased probability of infectious diseases [28]. Furthermore, smoking tobacco influences asthma-relevant factors, such as airways irradiation, and persistent inflammation, increased production of mucus, dyspnea and wheezing have an impact on asthma exacerbation [29]. In addition, smoking is a significant risk factor of atherosclerosis, the occurrence of which increases likelihood of serious cardiovascular diseases for smokers in the future. Tobacco smokers are characterized by elevated levels of triglycerides and low-density lipoprotein (LDL) particles with a decreased level of high-density lipoprotein (HDL). Furthermore, increased activity of fibrinogen and plasminogen activator inhibitor 1 during smoking has been observed [30]. Moreover, tobacco smoking has an adverse impact on glucose homeostasis, which is associated with decline in glucose uptake due to insulin resistance, which may predispose to diabetes mellitus type 2 [31].

Long-term smoking is the main factor for increasing the possibility of developing chronic obstructive pulmonary disease (COPD) due to chronic inflammation and subsequent remodeling of peripheral airways and emphysematous lung parenchymal destruction [32]. Furthermore, smoking is a major risk factor of cardiovascular disease because of atherosclerosis and possible acute thrombosis activation by tobacco aerosol toxic constituents [33]. These hazardous substances may contribute to activation of biochemical pathways that subsequently affect age-related macular degeneration [34] or rheumatoid arthritis development [35]. In addition, tobacco smoke increases the probability of developing almost 19 different

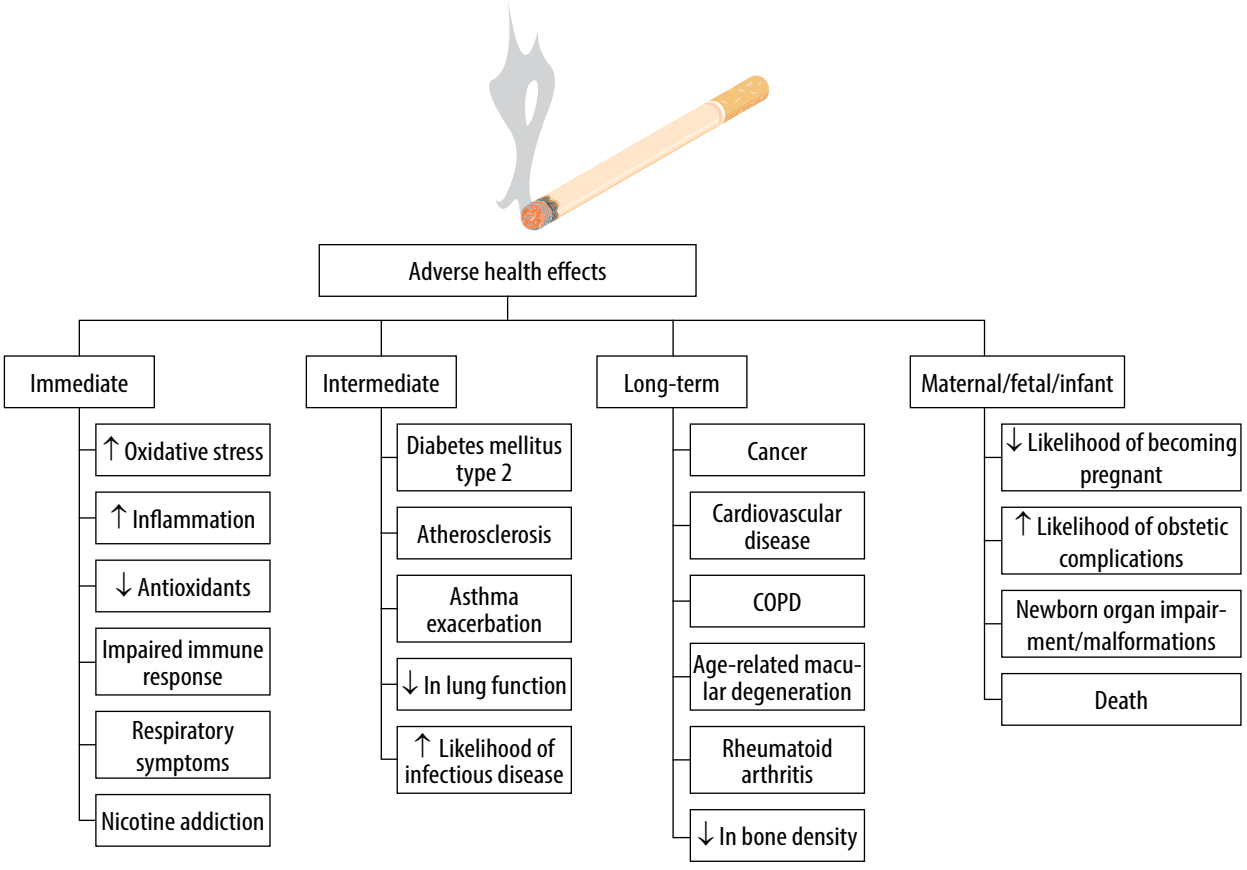

FIGURE 1. The main adverse health effects of conventional cigarette smoking

types of cancer, such as: respiratory system (lung, larynx and oral cavity), genitourinary system (kidney, bladder and uterine cervix), gastrointestinal system (esophagus, pancreas, stomach, colorectal and liver cancer) and acute myeloid leukemia [36]. Finally, cigarette smoke has an adverse health impact on fetus development and for infants (impairment of organ development, malformations or death). Moreover, smoking also negatively affects maternal health and may cause a decline in the likelihood of becoming pregnant or may become a source of some problems during pregnancy [37]. The main health consequences of tobacco cigarette smoking are summarized in Figure 1.

CURRENTLY KNOWN HEALTH CONSEQUENCES OF E-CIGARETTES

E-cigarettes are battery-operated devices with cartridges that generate puffs by heating an element of an atomizer [38]. It was believed that e-cigarettes containing only specific substances (nicotine, flavorings, propylene glycol or vegetable glycerin [15]) may have some positive health effects by reducing the smokers' exposure to dangerous elements present in aerosol from tobacco cigarettes. However, toxicological studies show presence of dangerous substances in their vapors: heavy metals, free radicals (7×10^{11} particles/puff vs. 10^{14}–10^{16} particles/puff for TC) [17, 39] or hazardous ingredients emitted during overheating of propylene glycol or glycerin (e.g. acrolein, formaldehyde). Despite the fact that their values are lower and mostly within limits when compared to conventional cigarettes, the presence of these chemicals in e-cigarette aerosol may have a negative health effect for people who have never smoked [16, 40]. In addition, acute exposure of healthy smokers to e-cigarette aerosol activates oxidative stress (with increased levels of sNox2 and 8-isoprostaglandin F2a) and reduces the amount of antioxidants (non-significant decline in vitamin E) and impairs endothelial function (non-significant decline in flow-mediated dilation) [41].

In a large-scale Internet survey of e-cigarette usage, nearly 60% of respondents noticed occasional undesirable side effects, such as sore and dry mouth and throat, coughing or problems with gums. Consumers who previously smoked conventional tobacco products also noted mitigating reactions of co-existing respiratory diseases (including asthma and COPD). However, a small group of these respondents highlighted worsening in the state of their illnesses [20, 42]. Furthermore, during the investigation of specific symptoms in volunteers ($n = 41$) who wanted to smoke e-cigarettes for the first time, the authors summarized that about 60% of the respondents felt bad after using ECs: they started coughing or had irritated eyes, chest pains, and also an upset stomach [43]. The case report of a 20-year-old male sailor showed shortness of breath, cough and facial flushing after using e-cigarettes. This suggests the development of eosinophilic pneumonitis after exposure to e-cigarette vapor [44]. A case study of a 33-year-old man with germ line tumor showed that after 3 months from switching to e-cigarettes, computed tomography showed presence of new pulmonary changes specific for respiratory bronchiolitis-interstitial lung disease [45]. Prolonged exposure to e-cigarettes also caused enlargement of distal airspace [46].

Investigation of the effects of propylene glycol and glycerine for lung function in healthy volunteers ($n = 20$) and asthmatic patients ($n = 10$) indicated incidences of cough, mucosal secretion and chest pains for both groups (healthy vs. asthmatic). However, the authors did not report any significant reduction in lung functions (FeNO or CRP) in asthmatic patients [47]. Studies on healthy smokers showed that 5-minute vaping increases lung flow resistance and decreases fractional exhaled nitric oxide (FeNO) concentration. An increase of peripheral flow resistance is connected with narrowing of smooth muscles in airways and can lead to the appearance of specific symptoms [48]. Similar studies detected that e-cigarette smoke (after 5-minute vaping) is responsible for reduction of forced expiratory volume in 1 s (FEV1) and forced expiratory flow at 25% (FEF25) [49], and a decrease in FeNO (for healthy e-cigarette smokers and e-cigarette smokers with mild asthma) [50]. Investigation of the effect of tobacco- and cherry-flavored e-cigarettes compared to tobacco cigarettes for basic respiratory parameters in 105 participants indicated that e-cigarette usage reduced exhaled CO, but for dual users this level was significantly higher. Moreover, for users of both tobacco- and cherry-flavored e-cigarettes, the authors observed an increased forced vital capacity (FVC) and increased FEV_1 for cherry-flavored EC smokers and dual users [51]. Other studies involving smokers and non-smokers showed that active and passive smoking of e-cigarettes also causes small changes in airways, when compared with TCs [52]. A huge observational study on about 4 500 current and former smokers at risk/with COPD symptoms revealed that for about 350 of the participants possible negative symptoms connected with e-cigarette usage, such as increased chronic bronchitis prevalence (connected with elevated probability of COPD development) and a decrease in some basic lung functions, were observed [53].

Short-term vaping may increase heart rate (up to 17.2 beats per minute) and diastolic blood pressure and reduce oxygen saturation. However, the results differ between types of e-cigarette device, used e-liquids and nicotine doses [54–56]. Moreover, current findings are inconclusive, as some studies only showed effects of vap-

ing on elevated oxygen saturation, without any changes of heart rate or blood pressure [57]. In addition, as the data suggest, acute smoking of e-cigarettes increases the level of oxidized low-density lipoprotein (LDL) (compared to never-smokers) [58], and may also affect epithelial dysfunction [41]. Finally, e-cigarette liquids contain high concentrations of nicotine, which may lead to developing addiction. There is some evidence of nicotine poisoning (by ingestion or through the skin) among e-cigarette smokers [59]. The literature provides several case reports of burns caused by e-cigarettes. Most often they were caused by overheating and battery explosion in the devices [60–62].

CURRENT KNOWN HEALTH CONSEQUENCES OF HEAT-NOT-BURN PRODUCTS

Heat-not-burn products, such as the IQOS system, are electric devices which comprise an electronic heating mechanism and a plug impregnated with glycerine. Using a metal flange allows the tobacco to be heated at lower temperature (up to 350°C) without combustion. This solution allows the smokers' exposure to toxic components of tobacco smoke to be reduced [63]. However, as current findings suggest, even this lower temperature of aerosol production is enough to melt the polymer-film filter and release potentially hazardous substances such as formaldehyde cyanohydrin, 1,2-diacetin or ε-caprolactone [19]. In addition, HnB cigarettes may contain similar nicotine content as conventional tobacco cigarettes [64]. Another study highlighted the presence of some carbonyl compounds and nitrosamines in their aerosol [65]. Despite the fact that heat-not-burn products reduce exposure to harmful or potentially harmful constituents when compared to tobacco cigarettes (up to 70–95%), presence of the aforementioned substances in their aerosol may be dangerous for never-smokers in particular [66].

IQOS heat-not-burn products were introduced to the market in 2014 (Japan and Italy), and therefore there is only a limited number of trials researching the health consequences of using this novel type of cigarettes. In addition, the available data focus mostly on determination of chemical composition or some basic mechanisms, such as oxidative stress or inflammation, potentially activated by the aerosol of these products (*in vivo* and *in vitro* studies). There are only a few clinical trials which compare basic health parameters of smokers of conventional cigarette smokers and those who switched to HnB products. Additionally, most of the assessments are carried out by the manufacturer of IQOS. There is also lack of data about the long-term effects of these products on health outcomes. For this reason, it is difficult to clearly determine the health consequences associated with using HnB cigarettes.

Six-month trials by Philip Morris International showed significant improvements in high-density lipoprotein cholesterol (HDL-C), haemoglobin with irreversibly bound carbon monoxide (COHb), white blood cells (WBC), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and FEV_1 biomarkers for smokers who switched from tobacco cigarettes to IQOS [67]. Pre-clinical studies by the IQOS manufacturer indicated less chemotaxis and reduced integroty of human coronary arterial endothelial cells (HCAEC) monolayer [68]. In addition, exposure to IQOS aerosol leads to reduced adhesion of monocytic cells to HCAECs and a decline in molecular changes for both of those cell types, which may suggest reduced risk of atherosclerosis and cardiovascular disease when compared to tobacco cigarettes [69]. However, there is no independent clinical trial on the effect of HnB products on atherosclerosis/cardiovascular diseases in humans.

Current literature findings suggest that HnB cigarette aerosol may enhance oxidative stress and the inflammatory response due to increased amounts of free radicals and other toxic compounds [65]. Single use of an IQOS cigarette causes activation of oxidative stress (increased level of Nox2, H2O2, 8-iso-PGF2a), reduction of antioxidants (reduction of HBA) and increased levels of platelet activation markers (sCD40L, sP-selectin) in healthy smokers. In addition, acute exposure to IQOS smoke increases systolic blood pressure and endothelial dysfunction [70]. Furthermore, other clinical data show that acute exposure to IQOS aerosol increases levels of bilirubin and ALT for IQOS smokers (compared to tobacco cigarettes and non-smokers), which may suggest hepatotoxicity of these products [71]. Finally, there are two case reports of 20- and 16-year-old men in whom smoking HnB cigarettes caused acute eosinophilic pneumonia (AEP) [72, 73]. Table 1 summarizes the currently known consequences of smoking conventional tobacco cigarettes (TCs), e-cigarettes (ECs) and heat-not-burn cigarettes (HnB).

CONCLUSIONS

Collected literature data indicate that short-term exposure to smoke from conventional cigarettes, e-cigarettes and HnB products affects the occurrence of respiratory symptoms, i.e. dry mouth, cough, and increased mucus secretion. In addition, oxidative stress is activated in healthy smokers in each of the cases, which can contribute to inflammation, remodeling, and chronic respiratory symptoms. In addition, TCs, ECs and HnB may contain comparable concentrations of nicotine, the use of which may have an influence on the occurrence of addiction, which has been noted in each case.

TABLE 1. Comparison of main health consequences of tobacco cigarette, e-cigarette and heat-not-burn cigarette smoking

Health consequence	Tobacco cigarette (TC)	Electronic cigarette (EC)	Heat-not-burn cigarette (HnB)	Comments
Immediate:				
Oxidative stress	↑	↑	↑	Increased oxidative stress markers for TC, EC, HnB smokers
Inflammation	↑	↑ ?	↑ ?	Increased markers of inflammation for TC smokers Increased markers of inflammation (investigated on pre-clinical studies) for EC and HnB smokers
Antioxidants activity	↓	↓	↓	Decreased antioxidant activity markers for TC, EC and HnB smokers
Immune response	↓	↓ ?	?	Immune response impairment for TC smokers Reduced host defense against bacterial/viral infection for EC and HnB smokers
Respiratory symptoms:				
Irradiation	↑	↑	↑	Increase of respiratory symptoms for TC, EC and HnB smokers
Cough				
Mucus production				
Dyspnea				
Wheezing				
Nicotine addiction	↑	↑	↑	Nicotine addiction; cases of nicotine poisoning for TC, EC and HnB smokers
Intermediate:				
Infectious disease	↑	↑ ?	↑ ?	Impairment immune response, increased likelihood of infectious diseases for TC smokers Reduced host defense against bacterial/viral infection for EC smokers (pre-clinical studies) Acute eosinophilic pneumonitis cases for EC and HnB smokers
Lung function	↓	↓ ?	↓ ?	Reduced lung function parameters for TC smokers Enlargement of distal airspace and cases of respiratory bronchiolitis-intestinal lung disease, decreased eCO, increased FVC for EC smokers Decrease in basic lung parameters for HnB smokers
Asthma exacerbation	↑	↑ ?	?	Increased asthma-relevant factors for TC smokers 5-min EC vaping increases lung flow resistance and reduces FeNO, FEV_1 and FEF25 No direct findings about asthma development or exacerbation for HnB smokers
Atherosclerosis	↑	?	No data	Increased triglycerides, LDL, fibrinogen, PAi-1, decreased HDL for TC smokers Inconclusive findings; impairment of oxygen saturation, increased heart rate and systolic blood pressure (data differ among EC types and methodologies) for EC smokers No direct data about atherosclerosis development for HnB smokers
Diabetes mellitus type 2	↑	No data		insulin resistance, reduced glucose uptake for TC smokers No direct data about DMT2 development for EC and HnB smokers

TABLE 1. Cont.

Health consequence	Tobacco cigarette (TC)	Electronic cigarette (EC)	Heat-not-burn cigarette (HnB)	Comments
Long-term:				
Cancer	↑	?	no data	Increased likelihood of 19 different types of cancer for TC smokers Some cancer occurrence in animal models for EC smokers No direct data about cancer occurrence for HnB smokers
Cardiovascular disease	↑	↑ ?	?	Increased atherosclerosis occurrence, acute thrombosis, increased blood pressure for TC smokers Inconclusive findings of impairment in oxygen saturation, increased heart rate and systolic blood pressure for EC smokers Increased systolic blood pressure for HnB smokers
Liver disease	↑	↑ ?	↑	Toxic, immunologic and oncogenic effects on liver for TC smokers Non-alcoholic fatty liver disease (mice model) for EC smokers Increased bilirubin and ALT for HnB smokers
Chronic obstructive pulmonary disease	↑	↑ ?	?	Chronic inflammation, remodeling of peripheral airways, emphysematous lung parenchymal destruction for TC smokers Endothelial dysfunction for EC and HnB smokers
Age-related macular degeneration	↑	No data		Activation of molecular changes, increased likelihood of age-related macular degeneration for TC smokers No direct data about age-related macular degeneration occurrence for EC and HnB smokers
Rheumatoid arthritis	↑			Activation of molecular changes, increased likelihood of rheumatoid arthritis for TC smokers No direct data about rheumatoid arthritis occurrence for EC and HnB smokers
Bone density	↓			Decreased in bone density for TC smokers no direct data about effect on bones density for EC and HnB smokers
Maternal health:				
Pregnancy likelihood	↓	↓ ?	No data	Decreased likelihood of becoming pregnant and health consequences during pregnancy for TC smokers Only pre-clinical animal models for EC negative effect on maternal health No direct data about HnB effect on maternal health
Pregnancy complications	↑	↑ ?		
Fetus/newborn:				
Organ impairment	↑	↑ ?	No data	Impairment of organ development, organ dysfunction or malformations, infant death for TC smokers Only pre-clinical animal models for EC negative effect on fetus or infants health No direct data about HnB effect on fetus health
Malformations	↑	↑ ?		
Death	↑	↑ ?		

In the case of novel smoking devices – e-cigarettes and HnB products – compared to standard cigarettes, they reduce smokers' exposure to HPHCs from cigarette smoke, which may reduce the risk of smoking-related diseases. However, these products are not free of toxic substances, which can negatively affect non-smokers' health. In addition, we do not have enough clear evidence to comprehensively determine the health consequences of

smoking e-cigarettes and HnB products. Current findings are based on assessing short-term effects of smoking those products on basic health parameters, mainly compared to TCs or after switching to these novel alternative smoking products. The existing studies were carried out mainly on small groups of smokers, using various products and research methodologies, which makes it difficult to precisely compare their results. In addition, there is no analysis of the long-term use of such products on the health of their consumers.

In the future, long-term studies regarding the effects of smoking e-cigarettes and HnB products on the health of smokers, pregnant women and the development of the fetus and the newborn should be carried out. Additionally, scientific research should focus on determining the relationship between smoke exposure of these products and the development of cardiovascular, respiratory or cancer diseases. In particular, we should investigate the determination of the subsequent impact of individual smoke components on the activation of individual signaling pathways and structural changes that contribute to the development of specific diseases. Also, in the conducted research it would be necessary to harmonize the methodology used and the compared tobacco products.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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