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Risk factors and primary prevention of lung cancer. Cessation of cigarette addiction

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ABSTRACT

Despite the huge knowledge about the risk factors associated with lung cancer, this disease remains the leading cause of cancer deaths in highly developed countries. The reason for this phenomenon is the increasing pollution of the natural environment and, above all, the difficulties in eliminating the addiction to smoking. In large Polish urban agglomerations, the exposure to particulate matter containing hydrocarbons on its surface, to free hydrocarbons, nitrogen and sulphur oxides is constantly increasing. Moreover, almost 25% of the Polish population smoke cigarettes and the elimination of smoking addiction through psychotherapy, nicotine replacement therapy and pharmacotherapy are sometimes ineffective. This article presents that the use of tobacco-burning products other than cigarettes (e.g., cigars or pipes) and products containing marijuana are as dangerous to health as classical cigarettes. Other nicotine-containing products have also appeared: e-cigarettes and tobacco heating systems. These products are highly addictive to nicotine, but the aerosols, that are produced by them, contain fewer toxic substances than cigarette smoke. Therefore, there are reasons to use these products instead of traditional cigarettes in people who are highly addicted to nicotine (after exhaustion of other treatment options) to reduce health risks, including lung cancer risk. However, it must be evoked that only a complete smoking cessation and the use of nicotine-containing products could be effective in reducing the risk of lung cancer.

Key words: lung cancer, environment, smoking, smoking cessation, e-cigarettes, heat not burn products

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Introduction

Lung cancer is the second most common cancer among men and women. According to the National Cancer Register (NCR), in 2018 lung cancer accounted for 16.1% of diagnosed cancer cases in men (after prostate cancer, which accounted for 19.6% of cancer cases in men) and 9.3% of diagnosed cancer cases in women (after cancer breast, which accounted for 22.5% of cancers in women). The NCR estimated that in 2020 there were 22,539 cases of lung cancer in

Poland (13,553 in men and 8,986 in women). On the other hand, Globocan, operating under the patronage of the International Agency for Research on Cancer (IARC) and WHO (World Health Organization), estimated the number of new lung cancer cases in Poland in 2020 at 29,509 (18,277 men and 11,232 women). Lung cancer remains the leading cause of death from malignant cancers in highly developed countries. 28.2% of men and 17.5% of women with cancer die from lung cancer. According to Globocan, the number of deaths from lung cancer in Poland in 2020 was 27,444 patients.

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For comparison, the second most common cause of death in cancer patients was colorectal cancer — 9,382 Poles died of colorectal cancer. The reasons for such a high number of deaths from lung cancer are the high incidence of this cancer due to the high exposure of a quarter of our population to tobacco smoke carcinogens and the still very poor prognosis (less than 20% of patients survive 5 years after diagnosis) [1, 2].

As can be concluded from the above data, it is necessary to conduct intensive lung cancer prevention programs. One of them should be primary prevention aimed at eliminating the addiction to smoking and exposure to other carcinogens. As part of secondary prevention, the use of low dose computed tomography should be developed to detect early asymptomatic cases of lung cancer in a group at high risk of developing this disease (tobacco smokers). The development of new, personalized therapy methods (immunotherapy, molecularly targeted therapies) is also important, as they increase the chance to cure patients after radical treatment (surgery, chemoradiotherapy) and significantly extend the life of patients with advanced cancer (even by over 5 years).

Environmental and occupational factors

The International Agency for Research on Cancer (IARC) recognizes outdoor air pollution as a risk factor for lung cancer. Air pollution data show that lung cancer incidence increases by 30–50% in areas with high levels of ambient air pollution compared to areas with lower levels of ambient air pollution [3, 4].

Particulate matter (PM) can damage various organs and cause many diseases. PM is classified according to particle size. PM₁₀ (particles $\leq 10 \mu\text{m}$ in diameter), PM_{2.5} (particles $\leq 2.5 \mu\text{m}$ in diameter) also called fine particles and PM_{0.1} (particles $\leq 0.1 \mu\text{m}$ in diameter) also called ultrafine particles. Exposure to these particles has various health effects, which are partly due to how these particles travel in the lower respiratory tract and how they affect the lung defence mechanisms [5]. The health risks of PM_{0.1} are very high, but their exact role in many diseases is still unclear. Their high production and rapid redistribution make accidental exposure common in the general population. Many studies have shown that the smaller the size of the particles, the greater their mutagenic potential. The most important carcinogen was considered to be the total surface area of the retained particles, although the dose, particle type and exposure time were also important. The size of the particles depends largely on the size of the internal carbon core on which hydrocarbons and sulphate compounds responsible for the carcinogenesis process are absorbed [6, 7].

A positive correlation has also been observed between various indicators of indoor air pollution and the risk of lung cancer. Indoor air pollution is believed to be a risk factor for lung cancer, especially among female non-smokers and in less developed countries. Indoor air pollution is associated with coal combustion in poorly ventilated homes, combustion of wood and other solid fuels (biomass combustion), and the production of fumes from high-temperature cooking with unrefined vegetable oils. In addition, in airtight rooms in houses built mainly in volcanic areas, radon may accumulate from soil and water. Radon is a radioactive noble gas responsible for the greatest exposure of humans to natural ionizing radiation. It is believed that in some areas, inhalation of radon may be the second cause of lung cancer after smoking [8].

Exposure to several occupational factors carries with it consequences in the form of the development of lung diseases, including lung cancer. The most important occupational carcinogens include asbestos, silica, heavy metals, and polycyclic aromatic hydrocarbons [9, 10]. All forms of asbestos (chrysotile and amphibole, including crocidolite, amosite and tremolite) are carcinogenic, although chrysotile is less potent than other types, possibly because it is more efficiently cleared from the lungs. In many underdeveloped countries, occupational exposure to asbestos remains widespread [11, 12]. Chromium [VI] compounds increase the risk of lung cancer in people employed in the production of chromates, chromate pigments, chrome plating and ferrochrome plating. There was no such risk among workers exposed exclusively to chromium compounds [III]. Workers exposed to nickel salts and workers involved in the production of cadmium batteries using copper and cadmium alloys also have an increased risk of lung cancer. High exposure to inorganic arsenic occurs mainly among workers employed in the steel industry. An increased risk of lung cancer has also been reported among people exposed to high levels of arsenic in drinking water [13]. Other groups with an increased risk of exposure to arsenic are fur handlers (tanners), producers, people employed in the production of sheep fur and pesticide cleaning (bath) mixtures, and vineyard workers [14]. An increased risk of lung cancer has also been reported among patients with silicosis. Many studies have looked at workers exposed to crystalline silica in foundries, pottery, ceramics, diatomaceous earth mining, brickworks and stone cutting [15].

Polycyclic aromatic hydrocarbons are a complex and important group of chemicals formed during the combustion of organic material. An increased risk of lung cancer has been reported in several industries and occupations related to exposure to PAHs, such as aluminium production, coal gasification, coke production, iron and steel foundry, tar distillation, roofing, and chimney cleaning. An increased risk of lung cancer has

also been suggested for those employed in several other industries, including shale oil extraction, wood impregnation, roofing, and carbon electrode production [16].

Vehicle exhaust and other internal combustion engines constitute an important group of PAH mixtures as they contribute significantly to air pollution. Occupational exposure to exhaust fumes from diesel engines is common and the issue of its carcinogenicity has been the subject of many epidemiological studies in recent years. While the results are contradictory, many assessments seem to confirm that high occupational exposure to diesel exhaust over an extended period may be associated with an increased risk of lung cancer.

The SYNERGY project collected information on occupation and smoking in 13,304 lung cancer patients and 16,282 healthy people from 11 studies conducted in Europe and Canada. Exposure to diesel was associated with an increased risk of lung cancer with an Odds Ratio (OD) of 1.31 ($p < 0.01$) and depended on the exposure time and exhaust dose [17, 18]. Dai et al. [19] studied the relationship between exposure to exhaust fumes from diesel engines and the inflammatory response of the body. There was a significant decrease in blood levels of MIP-1 β and IL-8 in people exposed to exhaust gases compared to the control group. Lower levels of these markers were also observed with increasing exposure to PM_{2.5}. IL-8, MIP-1 β are chemokines that play an important role in the recruitment of immunocompetent cells for immune defence and removal of cancer cells [19].

Air pollution is a silent epidemic. However, it is a threat that can be minimized with appropriate actions. Eliminating or at least reducing air pollution will result in an improvement in the health of the entire population. Prevention of lung cancer in this respect should include the control of occupational exposure, as well as indoor and outdoor air pollution [20, 21].

Smoking tobacco and other substances

Smoking is the cause of 90% of lung cancer in men and 80% in women. Smokers are thirty times more likely to die from lung cancer than non-smokers. Cigarette smoke contains over 7,000 chemical compounds, including over 70 compounds recognized as carcinogenic [22]. These compounds are formed during the combustion of tobacco at the end of a cigarette, which takes place at a temperature of over 750°C, and during pyrolysis, which takes place slightly deeper at the temperature of 300–700°C. In addition, the process of tobacco combustion at the end of a cigarette heats the air which is sucked by the smoker through the rest of the cigarette. Due to its high temperature, the air passing through the cigarette evaporates nicotine and other volatile substances contained in the cigarette. This mixture goes as far as to

the alveoli and is then absorbed into the smoker's bloodstream. It contains 93 toxic compounds [Harmful or Potentially Harmful Constituents (HPHCs)] described by the Food and Drug Administration (FDA) in 2012, causing the five most serious health consequences of smoking (cancer, cardiovascular diseases, respiratory diseases, reproductive function disorders, addiction). Tobacco-dependent cancers, apart from lung cancer, include cancer of the larynx, throat, oesophagus, stomach, mouth, kidneys, bladder, and pancreas. Chronic obstructive pulmonary disease is one of the leading causes of premature death in cigarette smokers. Cardiovascular diseases caused by cigarette smoking include ischemic heart disease, lower limb vessel disease, cerebrovascular disease, and arterial hypertension. The number of years of life lost and disability among smokers compared to non-smokers is 10. Giving up smoking reduces the risk of serious diseases, but the risk of lung cancer is halved only 10 years after giving up smoking [23, 24].

The most dangerous substances found in very high concentrations in tobacco smoke include benzo(a)pyrene, nitrosamine, naphthalene, pyrene, naphthylamine, methanol, acetone, hydrogen cyanide, toluidine, ammonia, urethane, arsenic, cadmium, polonium, phenol, butane, vinyl chloride, dibenzo acridine, toluene, carbon monoxide. A highly addictive substance is nicotine, which has not been proven to be carcinogenic, although its metabolites have been established to be highly carcinogenic (this will be described in the chapter on e-cigarettes). The main carcinogenic factors of tobacco smoke are polycyclic aromatic hydrocarbons and volatile N-nitrosamines, which are converted in the body into metabolites of equally high toxicity [25, 26].

Epidemiological evidence of the harmfulness of cigarette smoking began to appear in the 1950s and concerned the association of cigarette smoking with the occurrence of lung cancer and cardiovascular diseases [27]. In 1964, the results of retrospective and prospective studies were announced in the United States which proved a 5- to 20-fold increase in the risk of lung cancer in smokers [28]. Since cigarette smoking has been linked to lung cancer and other diseases, the tobacco industry has started to reduce the content of harmful substances in their products. Filters were gradually added, they were modified with perforations (small spaces to dilute the smoke), tobacco was reconstructed, and the quality of paper and additives was improved. These effects reduced the content of nicotine and tar in cigarette smoke, which, however, remained one of the main causes of civilization diseases.

Comparing the effects of smoking cigarettes with smoking cigars and pipes is quite difficult. The design of the products and the different methods of their use, resulting in a different exposure to smoke, play a significant role here. Size aside, the main difference in the structure of cigars and cigarettes is the lack of

a filter. In cigarettes, the wrapping material for tobacco is paper and for cigars it is a tobacco leaf, increasing the final amount of nicotine and toxic substances released. For comparison, smoking one cigar provides from 100 to 200 mg of nicotine, and one cigarette provides an average of 8 mg. This means that the smoke from one cigar contains at least the same amount of nicotine as there is in one packet of unfiltered cigarettes. However, because cigars are consumed differently, the smoke usually remains in the mouth, rather than being inhaled into the lungs, as is the case with cigarettes. Similar dependencies as in the case of smoking cigars also occur in the users of pipes and water pipes. It should be noted that volatile substances are much better absorbed from the lungs than through mouth tissues, which explains the higher concentration of harmful substances in the blood of cigarette smokers compared to cigar and pipe smokers. At the same time, oropharyngeal cancer is much more common in cigar smokers than in traditional cigarette smokers [29–32].

All highly developed countries have legislation to eliminate smoking in society. In Poland, the Act of November 9, 1995, on health protection against the consequences of using tobacco and tobacco products is in force (Journal of Laws of 2015, items 298 and 1916, and of 2016, item 960). This act was updated on July 22, 2016. Many countries have adopted an endgame strategy to either eliminate tobacco from society completely or to reduce the proportion of smokers to 5% of the population. The first group included Sweden, Ireland and New Zealand (until 2025), Denmark and Finland (until 2030), and Canada and Scotland (until 2035). The second group includes Great Britain and France. Poland is set to become a tobacco-free country by 2030.

The carcinogenic effects of the substances generated during the combustion of cannabis have been studied very poorly. Depending on the species, cannabis contains over 420 chemicals, 61 of which are cannabinoids. More than 2,000 compounds are formed by pyrolysis when smoking cannabis and are represented by different classes of chemicals including nitrogen compounds, amino acids, hydrocarbons, terpenes, and simple fatty acids. Cannabis smoke also contains carcinogenic polycyclic aromatic hydrocarbons as well as other toxic products of combustion. They are similar to tobacco smoke, but the way cannabis is smoked results in higher exposure to smoke. However, the relationship between chronic obstructive pulmonary disease and cannabis smoking has not been fully proven, although chronic bronchitis (coughing, dyspnoea, and sputum production) is often observed in cannabis smokers. The impact of cannabis smoking on lung cancer risk was investigated in a group of 49,321 men aged 18–20 years during conscription in Sweden in 1969–1970. Participants in this study were followed up until 2009 in national medical

registries for lung cancer. Analyses showed that heavy cannabis smoking was significantly associated with more than a twofold increase in the risk of lung cancer [OR = 2.12, 95% confidence interval (CI): 1.08–4.14] over the 40-year follow-up period [33–35].

Electronic cigarettes

E-cigarettes constitute a diverse group of rechargeable electronic nicotine inhalers with several thousand models. The device causes the inhalation liquid in the evaporator to change under the influence of high temperature (150–250°C) into an aerosol inhaled by the user (instead of the smoke inhaled when smoking cigarettes). The inhalation liquid usually consists of propylene glycol, glycerine, flavours, and nicotine in various concentrations (from 0 to 36 mg/mL). In the past, evaporators were disposable. Now, there are also models with liquid in the evaporator that can be refilled when the content of the refill container finishes. Due to the generally low nicotine content of e-cigarettes, e-cigarette users tend to use e-cigarettes frequently. Moreover, the use of e-cigarettes has become fashionable among adolescents, which may lead to nicotine addiction and then to the use of traditional cigarettes later in life. It is estimated that up to 5% of primary school students and over 20% of high school students have regular contact with e-cigarettes. In addition, using e-liquids after purchasing an expensive device is cheaper than buying cigarettes. That is why legal regulations have been created to limit access to e-cigarettes. The pulmonary toxicity of e-cigarettes and their influence on cancer incidence that is discussed with increasing frequency is also important [36].

In art. 20 of the Directive of the European Parliament and of the Council of the European Union (EU) of April 3, 2014, on tobacco products (2014/40/EU), there are provisions for electronic cigarettes sold in the EU. The directive specifies the maximum concentration of nicotine in vaporizers and removable containers and requires the composition of the liquid used in e-cigarettes to be specified, including the exact concentration of nicotine. According to the directive, e-cigarettes should be childproof and easy to handle and have a refilling mechanism that allows leak-free refilling. The ingredients of e-cigarettes must be of high purity, and e-cigarettes should provide a standardized amount of nicotine. Health warnings for e-cigarettes informing consumers that they contain nicotine and should not be used by non-smokers are mandatory in EU countries. The e-cigarette leaflet should contain information about side effects that must be reported and about addictive properties. In EU countries there is a ban on e-cigarette advertising [37]. "Public Health England" found that the use of standardized and certified

electronic cigarettes is 95% less harmful than smoking traditional cigarettes [38, 39].

In August 2016, the WHO recommended a ban on the use of e-cigarettes indoors or where smoking is prohibited [40]. This is because non-users of these products may be exposed to chemicals and e-cigarette aerosols.

In many EU countries, specific regulations are regulating the e-cigarette market. Unfortunately, in Poland, the approval of e-cigarettes for sale is insufficiently controlled by the Bureau for Chemical Substances established in the regulation of the Minister of Health of November 9, 2015 (Journal of Laws of 2015, item 1953). E-cigarettes are admitted to trading in Poland based on a notification, i.e., a notification by the manufacturer. Therefore, the composition of e-liquids is not controlled in any way. This creates a potential risk of interference with the composition of the liquid (so-called premixes). According to Polish legislation, an e-cigarette is not a tobacco product. The nicotine-containing liquid contained in the refill container must not exceed 10 mL or, in the case of single-use containers, 2 mL. The nicotine content in the liquid must not exceed 20 mg/mL. The liquid must not contain vitamins or other additives that give the impression that a tobacco product is beneficial to health, caffeine or taurine, or other additives and stimulants associated with energy and vitality (e.g. legal highs) and additives that in an unburned form have carcinogenic, mutagenic or reprotoxic properties. Despite these limitations, there are several hundred types of e-liquids and e-cigarettes available in Poland without proper authorization of the e-liquid composition [41].

Unlike Polish legislation, since August 8, 2016, the FDA ordered e-cigarettes to be subject to tobacco product regulations. As in the EU, in the USA there is a ban on selling e-cigarettes to minors. The FDA has classified e-cigarettes as stimulant delivery devices and they are therefore regulated under the Federal Food, Drug and Cosmetic Act (FDCA). After the detection of serious respiratory diseases related to the inhalation of untested substances from e-cigarettes, which resulted in the death of six people in the USA, in September 2019 the US government began working on introducing a complete ban on e-cigarettes [42].

In April 2019, there were reports of severe respiratory failure due to lung damage in e-cigarette users in the United States. There were more patients with this syndrome in Great Britain and Japan [43, 44]. By January 21, 2020, a total of 2,711 hospitalized patients and 60 deaths due to respiratory failure after the use of e-cigarettes were reported to the Centres of Disease Control and Prevention (CDC) [15]. Most of the cases concerned young people. 80% of patients reported the use of tetrahydrocannabinol (THC) in e-liquids, approximately 55% of patients reported THC added to nicotine-containing products, and 13% of patients

reported exclusive use of nicotine-containing products. Symptoms of respiratory failure developed within days to weeks of exposure. THC is an organic chemical compound of the cannabinoid group and is the main psychoactive substance found in the cannabis plant. The CDC and the FDA, as part of the investigation carried out in 2019 and 2020, confirmed the presence of THC in vaporization products. Most vaporization liquids also contained significant amounts of Vitamin E Acetate (tocopherol), which was used in street sales to dilute flavours and THC [45]. Previously, vitamin E was used in low concentrations in e-liquids (up to 20% of the volume of the cartridge or was prohibited). Due to the limited availability of illegal marijuana, as well as the high demand for this type of e-cigarette, illegal vendors used about 50% or more of diluents in e-liquids [45]. For these reasons, the use of e-cigarettes, especially from an uncertain source, should be considered risky.

Concerns about the carcinogenicity of e-cigarettes result from both inhalation of nicotine [46] and other chemicals that may be contained in the aerosols [42]. The interaction of nicotine with nicotinic acetylcholine receptors (nAChR) activates signalling pathways that trigger several responses such as increased cell proliferation and survival. There is evidence from *in vitro* studies (breast, colorectal and lung cancer cell cultures) and in animal models (lung cancer) that nicotine may be carcinogenic and may accelerate tumour growth and promote metastasis [46]. *In vitro* studies have shown that nicotine increases cell proliferation, induces cell resistance to apoptosis, causes Epithelial-Mesenchymal Transition (EMT), which increases the migration and invasiveness of cancer cells and induces neoangiogenesis [47]. The pro-angiogenic effect of nicotine, resulting from the activation of endothelial cell proliferation and increasing the production of nitric oxide, which is a strong angiogenic factor, seems to be of the greatest importance for tumour progression. In high concentrations, nicotine damages DNA and can induce necrosis of normal cells, but also the formation of new somatic mutations and promotion of the carcinogenesis process with a decrease in the expression of suppressor genes such as CHEK2 (Checkpoint Kinase 2) [48]. Moreover, in *in vitro* cultures (lung cancer cell lines: H460 and A549), nicotine has been shown to reduce the antiproliferative and pro-apoptotic effects exerted by cytostatics and radiotherapy, which may result in a worse response to cancer treatment in patients who smoke or use other nicotine-containing products. This effect can be eliminated by the use of inhibitors of the alpha nAChR subunit, e.g., α -bungarotoxin. The products of nicotine metabolism proved to be very carcinogenic in *in vitro* cultures and in animal models. These are N-nitrososnicotine (NNN), responsible for the occurrence of stomach and oesophageal cancers, and nitrosamine ketone (NNK),

which is one of the most carcinogenic substances, as well as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), which is a metabolite of the carcinogenic NNK in the lungs. All these substances have been found in the urine of people who smoke traditional cigarettes and use e-cigarettes. Nicotine may inhibit the anti-cancer immune response by influencing the antigen presentation and activity of dendritic cells, increasing the production of pro-inflammatory cytokines, and intensifying oxidative stress [48].

In addition, there is evidence that some substances found in e-cigarette fumes, such as formaldehyde and acrolein, certain flavour additives, vitamin E acetate, and even propylene glycol, can cause DNA damage and carcinogenesis, or be irritating to the respiratory tract, which may increase the risk of lung, mouth, and throat cancer. It is because e-liquids containing nicotine isolated from tobacco can contain contaminants such as nicotine oxides, cotinine, anabasine, anatabine, myosmine, acrolein and beta-nicotyrine, and even in small amounts toluene, and heavy metals such as cadmium, tin, nickel, and lead. Propylene glycol used in e-cigarettes can be contaminated with diethylene glycol and transform into propylene oxide. Some of these substances can form adducts with DNA, which leads to activating mutations in oncogenes (most often in the *KRAS* gene) and deactivating mutations in suppressor genes (most often in the *p53* and *RBI* genes). However, it should be noted that compared to traditional cigarette smoke, the levels of toxic substances identified in e-cigarette aerosols were 10 to 450 times lower [48–55].

Despite the risk of carcinogenesis and respiratory damage associated with the use of e-cigarettes, a 2014 report by the Surgeon General of the United States concluded that there was insufficient evidence of carcinogenic effects of nicotine alone *in vivo* in humans. However, further studies were recommended to check whether exposure to the nicotine contained in, for example, e-cigarettes does not increase the risk of oropharyngeal, oesophageal, lung and pancreatic cancer [56]. Moreover, the health consequences of inhaling aerosol from e-cigarettes are unknown because no reliable safety study has been carried out on e-cigarette use due to the variety and a large number of manufacturers. The content of hazardous substances in e-liquids has not been thoroughly tested, nor has their permissible level been determined [57]. Therefore, as early as in 2009, the FDA issued a warning that the use of e-cigarettes may pose a health risk [51]. In turn, the United Kingdom has introduced a procedure under which medically tested e-cigarettes can be registered as medicinal products indicated for the reduction of abstinence syndrome in the treatment of nicotine dependence [58].

Heat-not-Burn systems

Heat-not-Burn (HnB) devices heat tobacco to 200–350°C, releasing aerosols. The devices consist of a ceramic blade with electric wires connected to a battery with the possibility of charging from an external power source. The blade is located inside an acetate tube with a cellulose acetate mouthpiece. The polymer filter is designed to cool the resulting aerosol. The compressed tobacco rod is made of a suspension of dried tobacco, 70% of which is tobacco, and humectants (water, glycerine, propylene glycol) to generate an aerosol. In comparison to e-cigarettes, tobacco heating systems are subject to more rigorous procedures of standardizing the content of various substances in the inhaled aerosol [59, 60].

Tobacco heating systems are not subject to the Directive of the European Parliament and the EU Council of April 3, 2014, on tobacco products, like e-cigarettes, because the first HnB products were created in 2014. Therefore, there is no official position of EU agencies regarding HnB products. In November 2020, a document aimed at assessing and introducing regulations on tobacco heating systems, as well as new regulations governing the approval of e-cigarettes for sale was subjected to social discussion [60].

Some EU countries have internal regulations for HnB products. The German Federal Institute for Risk Assessment and the Dutch National Institute for Public Health and the Environment have carried out appropriate tests, finding a reduction in the content of toxic substances in aerosols from HnB devices ranging from 80% to 99% compared to cigarette smoke. However, it has been found that the use of heat-not-burn products is harmful to health, but most likely carries a significantly lower risk of disease than smoking [61, 62]. Public Health England found that, compared to cigarettes, heat-not-burn products may present less exposure of users and bystanders to particulate matter and harmful and potentially harmful chemicals. In turn, the British Committee on Toxicity (COT) stated that although heat-not-burn products are still harmful to health, they are probably less dangerous than smoking traditional cigarettes [38, 39, 63].

In Poland, HnB products, like e-cigarettes, are subject to registration by the Chemical Substances Office. However, unlike electronic cigarettes, the market for heat-not-burn devices is better controlled. The procedure for submitting heat-not-burn devices to the Office requires authorization (i.e., not only determining the aerosol composition, but also presenting test results for each new device), and not an only notification, as is the case with e-cigarette registration. Therefore, in December 2020, the Office stated that, like e-cigarettes, heat-not-burn products are often seen as an opportunity to give up smoking regular cigarettes. Declarations of

respondents affected by this situation may indicate that the effectiveness of heat-not-burn products in this respect is much higher than that of e-cigarettes, although due to the small size of the studied groups, this data requires confirmation in further studies [41].

In October 2019, the FDA issued the first-ever decision to award a Modified Risk Order to eight tobacco products that do not burn or produce smoke. These products were based on the snus technology (cellulose bags containing powdered, moist tobacco, usually placed behind the upper lip). In turn, in July 2020, as part of the MRTP (Modified-Risk Tobacco Product) procedure, after nearly 4 years of research analysis, the FDA decided to authorize the first tobacco heating system as a tobacco product that ensures lower exposure to harmful and potentially harmful substances compared to classic cigarettes. The registration process considered the state of scientific knowledge about these products, as well as the data of the manufacturer and independent researchers and the comments raised in the public debate [64, 65].

The content of harmful substances, including carcinogens, in tobacco heating systems, is usually comparable to the content of these compounds in certified and standardized e-cigarettes (however, as described in the previous chapter, not all e-liquids can be subject to such control). The nicotine content in HnB products is 0.5–1.3 mg per cartridge. The aerosol also contains glycerol, propylene glycol and water. Since the aerosol is made of real tobacco, when it is heated to a temperature of over 300°C, it may contain small amounts of toxic substances, such as compounds resulting from the chemical transformation of nicotine (similarly to e-cigarettes), nitrosamines, benzene, benzo(a)pyrene, 4-aminobiphenyl, acrolein, acetone, 2-butanone, methyl glycol, pyridine, hydroxyacetone, diacetyl, isopentane and numerous aldehydes (e.g. formaldehyde, acetaldehyde, propionic aldehyde, crotonic aldehyde, pentanal, benzaldehyde, heptanal, furfural). However, the content of toxic substances in the aerosol from HnB products is at the level of 8% to 3% of their content in the smoke of traditional cigarettes. The content of group 1 carcinogens from the IARC list in HnB aerosols is reduced compared to cigarette smoke by 97%, and of carcinogens identified by the FDA by 93%. The reduction of factors damaging the respiratory and cardiovascular systems and disrupting reproduction ranges from 92 to 94%. The levels of carbon monoxide, pyrene, acrylonitrile and aminophthalenes in aerosols from HnB products are reduced to almost zero, which is associated, among others, with a significant reduction in the content of carboxyhaemoglobin in the blood of people using HnB products compared to smokers of traditional cigarettes [66].

Due to the short presence of HnB products on the market, no retrospective observations are determining

the level of reduction in the incidence of tobacco-related cancers compared to smoking. Therefore, attempts were made to estimate the carcinogenicity of the aerosol of the HnB product based on detailed toxicological data. In a study published in Tobacco Control BMJ, the carcinogenic potency was defined as at least one order of magnitude lower than that of cigarette smoke [67]. Public institutions in some countries also performed their own detailed oncological risk assessment of the use of tobacco heating systems. In studies conducted by the Ministry of Health of Japan and the National Institute of Public Health in the Netherlands, the risk of cancer resulting from the use of HnB was estimated to be about 10 times lower compared to smoking, and the reduction of cumulative exposure to the main carcinogens of tobacco smoke was 10 to 25 times lower [68, 69]. The risk of cancer induction in the case of passive exposure to HnB aerosols was estimated to be approximately 3,000 times lower than that of cigarette smoke.

There are many *in vitro*, animal, and human studies that have compared the effects of substances in an aerosol produced when tobacco is heated and that of tobacco smoke. A team of researchers from the Institute of Experimental Biology of the Polish Academy of Sciences showed a much greater effect of inhibiting oxygen consumption by the mitochondria of bronchial epithelial cells exposed to cigarette smoke in culture compared to an aerosol from the HnB device. Moreover, cigarette smoke had a much stronger effect on oxidative phosphorylation and expression of genes involved in the response to oxidative stress compared to an aerosol from the HnB device [70]. In a 6-month clinical trial Ludicke et al. [71] showed greater disorders of lipid metabolism (decrease in HDL cholesterol and increase in LDL cholesterol and triglycerides), increased inflammation (increase in the number of white blood cells, C-reactive protein and pro-inflammatory cytokines), impaired vascular endothelial function, blood clotting, oxidative stress (increase in the concentration of 8-epiprostaglandin F₂, 8-epi-PGF₂), the level of carboxyhaemoglobin in smokers compared to people using HnB products. In people who switched from traditional cigarettes to HnB products, after 6 months of observation, the above-mentioned biochemical parameters and respiratory function improved, expressed by increasing spirometric parameters, such as FEV₁ (Forced Expiratory Volume in 1 second) [71].

Tobacco dependence therapy

Smoking tobacco causes a strong pharmacological addiction to nicotine and is at the same time the most important carcinogenic factor of lung cancer. When nicotine levels drop in blood, clinical withdrawal symptoms develop, forcing the smoker to continue smoking

and thus maintain adequate levels of nicotine in the blood. After a certain period of smoking, nicotine tolerance develops, which makes it necessary to take increasingly higher doses of nicotine to obtain the desired effect. Tolerance arises by increasing the activity of nicotine metabolising enzymes and by increasing the number of nicotine receptors in the central nervous system. In addition to pharmacological addiction, smoking causes a behavioural addiction that consists of complex psychological, environmental, cultural, and social factors [72].

Non-pharmacological treatments for tobacco dependence consist of three components. The first is education on the harmful effects of tobacco smoking, conducted through specialist telephone consultations, educational brochures, radio, and television programs and on the Internet. The next stage is anti-smoking counselling conducted in a doctor's office, among others, at a general practitioner and a specialist pulmonologist. The key to properly conduct anti-smoking counselling is a thorough interview, which can be used to assess the degree of nicotine addiction (including Schneider and Fagerström tests). The Fagerström questionnaire consists of 6 questions concerning the period from waking up to smoking the first cigarette, difficulties in refraining from smoking in forbidden places, the number of cigarettes smoked daily, the degree of difficulty in giving up the first cigarette, the time of the day when more cigarettes are smoked, smoking during a disease. The maximum number of points obtained in the Fagerström test is 10. The sum of points above 6 indicates a strong degree of nicotine addiction and is an indication for replacement treatment when giving up smoking [72]. On this basis, the type of the most appropriate medical advice and the frequency of subsequent appointments can be planned. The third stage of addiction treatment is behavioural therapy, consisting of comprehensive medical and psychological counselling and short personal consultations, including learning to eliminate pro-tobacco stimuli as well as relaxation and motivational techniques [72].

The pharmacological treatment of nicotine addiction includes nicotine replacement therapy (NRT), psychotropic drugs (bupropion) and nicotinic cholinergic antagonists (varenicline and cytisine). The use of tobacco heating systems as a method of treating tobacco addiction is still debatable [72].

Nicotine replacement therapy (NRT), introduced in the late 1970s, supplies the addicted smoker with nicotine, which eliminates acute withdrawal symptoms and reduces the number of nicotinic receptors, making it easier to abstain from smoking. Before starting replacement treatment, one should be ascertained whether they are dealing with pharmacological dependence based on the results of the Fagerström questionnaire [72].

Various forms of NRT are available: transdermal systems (patches), chewing gums, lozenges, sublingual tablets, aerosols, and oral inhalers. These products are available in Poland without a prescription.

Patches provide stable levels of nicotine in the blood, making it easier to stop smoking, but when using them, in the event of nicotine craving, it is necessary to use emergency oral products. The nicotine contained in a patch gradually penetrates the skin and subcutaneous tissue into the blood and the brain. Patches come in different doses (7, 14 and 21 mg of nicotine in 24-hour patches and 5, 10 and 15 mg in 16-hour patches). Patches are applied to dry and hairless skin, on the upper body (chest, back, arms). To reduce the risk of a local skin reaction, patients should change the application site. Nicotine patches are generally well tolerated, especially in those most addicted to nicotine. Full treatment usually lasts about 10 weeks, during which the nicotine dose is gradually reduced [72].

Oral nicotine replacement therapy delivers nicotine on demand. Nicotine is absorbed through the oral mucosa, satisfying short-term nicotine cravings. Chewing gum with nicotine and nicotine lozenges are available in doses of 2 mg and 4 mg. They are usually used as an addition to patches. The acidic environment of the oral cavity reduces the absorption of nicotine, therefore gums and lozenges should be used at least 15 minutes after eating or drinking [72].

The nicotine inhaler delivers nicotine in an aerosol to the oral mucosa where it is absorbed. The inhaler is not an e-cigarette (the liquid is not heated and no aerosol imitating smoke is produced). The device consists of a plastic tube in which a replaceable cartridge containing nicotine, often enriched with menthol as a fragrance, is placed. Nicotine is released as air flows through the inhaler. The inhaler is used as a cigarette and is especially useful for smokers with a behavioural addiction. Inhaler cartridges usually contain 10 mg of nicotine and are sufficient for four 20-minute inhalations [72].

Oral aerosols allow for the fast delivery of nicotine to the central nervous system. A dose contains 1 mg of nicotine. Usually, 1 or 2 doses are used every 30 minutes to 1 hour. The maximum allowable dose is 2 administrations at the same time or 4 administrations per hour. The maximum daily dose is 64 administrations over 16 hours. A gradual reduction in the number of doses is recommended. The recommended duration of use of this form of NRT is 3 to 6 months. Side effects of inhaler use include hiccups, headache, nausea, and throat irritation [72].

The results of a Cochrane systematic review of a meta-analysis of 133 randomized trials of 64,640 smokers smoking at least 15 cigarettes a day indicate a significantly greater likelihood of smoking cessation in the NRT groups compared to the placebo groups (OR = 1.55;

95% CI: 1.49–1.61) [23]. The effects were significant for all types of NRT: for users of nicotine gums, the odds ratio was 1.64, for users of nicotine patches — 1.52 and for users of nicotine inhalers — 1.90 [73].

Antidepressants can help in the fight against the addiction to smoking for several reasons. Withdrawal from nicotine can cause depressive symptoms, and antidepressants can relieve them. In addition, some antidepressants may have specific effects on the receptors and messenger pathways underlying nicotine addiction. Bupropion is an antidepressant that inhibits the postsynaptic uptake of dopamine and norepinephrine, reducing the feeling of pleasure from nicotine. Bupropion also blocks nAChR, alleviates withdrawal symptoms, including the urge to smoke, and reduces weight gain after giving up nicotine use [72].

Smokers should start using the drug one week before the planned smoking cessation date with an initial dose of 150 mg a day for 3 days, and then 150 mg twice a day for 6 to 12 weeks. A smoker can suddenly stop taking the drug without having to gradually reduce the dose. The most reported side effects of bupropion include insomnia, dry mouth, nausea, and skin allergic reactions [72].

Based on a meta-analysis of 45 randomized trials (17,866 participants) from a Cochrane systematic review that assessed the frequency of giving up smoking in a long-term follow-up with bupropion versus placebo, the drug effectiveness was demonstrated (OR = 1.64, 95% CI: 1.52–1.77) [25]. In comparison to the placebo group, smokers treated with bupropion more often resigned from participation in the study due to adverse events (OR = 1.37, 95% CI: 1.21–1.56; 25 studies, 12,340 participants). Those in the bupropion group were also more likely to report psychiatric adverse effects compared to those in the placebo group (OR = 1.25, 95% CI: 1.15–1.37; 6 studies, 4,439 participants). The meta-analysis did not provide sufficient evidence for the greater effectiveness of the combination therapy with bupropion and NRT compared to NRT alone (OR = 1.19, 95% CI: 0.94–1.51; 12 studies, 3,487 participants) or the advantage of combining bupropion and varenicline compared to varenicline alone (OR = 1.21, 95% CI: 0.95–1.55; 3 studies, 1,057 participants). A meta-analysis of 6 studies provided evidence that bupropion was less effective than varenicline (OR = 0.71, 95% CI: 0.64–0.79; 6 studies, 6,286 participants). In contrast, the likelihood of giving up smoking when using bupropion was similar to that with NRT (OR = 0.99, 95% CI: 0.91–1.09; 10 studies, 8,230 participants) [74].

Varenicline is a partial $\alpha 4\beta 2$ nAChR antagonist. It shows a strong antagonistic effect against nicotine. It is a partial competition agonist of nAChR, which reduces their availability for nicotine, decreasing the satisfaction with smoking and the feeling of reward after smoking a cigarette. Varenicline, although it is less agonist than

nicotine on nAChR, leads to a reduction in the feeling of craving and withdrawal symptoms in people who give up smoking [72].

The 12-week treatment should be started 2 weeks before the planned smoking cessation date. In the initial phase, 1 tablet of 0.5 mg should be taken once a day for 3 days, for the next 4 days 2×1 tablet of 0.5 mg, and for the next week 2×1 tablet of 1 mg. In the treatment continuation phase after giving up smoking, it is recommended to take 1 tablet twice a day. If the attempt to give up smoking is unsuccessful, treatment continues, and the patient tries to stop smoking on the next day until successful. The most common side effects of varenicline include nausea, usually of moderate intensity, and intense dreaming with restlessness, insomnia, headache, arrhythmias, and mood changes. Cautious use of varenicline is recommended in patients with depressed mood, although a meta-analysis of 10 randomized, placebo-controlled studies on the effectiveness and safety of varenicline when giving up smoking showed similar rates of new symptoms and mental illness in the placebo (9.7%) and varenicline groups (10.7%) (OR = 1.02, 95% CI: 0.86–1.22) [74].

Based on a meta-analysis of 27 randomized trials (12,625 participants) included in the Cochrane systematic review, it was indicated that treatment with standard-dose varenicline more than doubled the chance of long-term smoking cessation compared to placebo (OR = 2.24, 95% CI: 2.06–2.43). A meta-analysis of 5 studies (5,877 participants) comparing the effectiveness of varenicline and bupropion, and a meta-analysis of 8 studies (6,264 participants) comparing the effectiveness of varenicline and NRT showed the superiority of varenicline in long-term smoking cessation (OR = 1.39, 95% CI: 1.25–1.54 and OR = 1.25, 95% CI: 1.14–1.37) [75].

Cytisine is a quinolizidine alkaloid extracted from the seeds of the golden chain (*Laburnum anagyroides*). It is a competitive, partial agonist of $\alpha 4\beta 2$ nAChR, and its mechanism of action is similar to varenicline. For several decades, cytisine has been available in Poland as an oral drug in the treatment of nicotine addiction [72]. Cytisine treatment should be started up to 5 days before the planned smoking cessation date. For the first 3 days, 1 tablet of 1.5 mg is used 6 times a day, for the next 9 days 1 tablet 5 times a day, from the 13th to the 16th day 1 tablet 4 times a day, from the 17th to the 20th day 1 tablet 3 times a day and from the 20th to the 25th day 1 tablet once or twice a day. The most common side effects during treatment include nausea, vomiting, diarrhoea, tachycardia, and an increase in blood pressure [76, 77].

A systematic review published in the Cochrane Library includes 3 studies on the effectiveness of cytisine in the treatment of smoking addiction. In two studies (937 participants) it was found that patients treated

with cytosine were four times more likely not to smoke after 6 months of follow-up in comparison to placebo (OR = 3.98, 95% CI: 2.01–7.87). One study compared the effectiveness of cytosine with NRT (1,310 subjects) and showed the advantage of cytosine six months after the start of treatment (OR = 1.43, 95% CI: 1.13–1.80) [75].

The use of e-cigarettes or heat-not-burn devices in the fight against smoking addiction is still debatable. All scientific societies dealing with this issue and agencies assessing medical technologies, such as the National Institute for Health and Care Excellence (NICE) or the FDA, emphasize that there are no completely safe products containing tobacco, and the most effective method of reducing health risk in tobacco smokers is to give up smoking completely. Both agencies state, however, that in people who are highly addicted to nicotine and who smoke cigarettes, reduction of health risk is possible thanks to the temporary or long-term use of licensed nicotine-containing products instead of traditional cigarettes [63–65].

Based on a toxicological analysis by the Committee on Toxicity [38], the NICE concluded that licensed nicotine products, approved by the MHRA, contain significantly less harmful substances compared to traditional cigarettes and under certain conditions can be used as an aid in reducing addiction to tobacco smoking if smokers decide to switch completely to smokeless products containing nicotine. However, the NICE made a reservation that strict control over the use of these products, the composition of an aerosol and the prohibition of access to them for children and adolescents, as well as further clinical and scientific research on their safety are required (e.g., NCT03569748 study aimed at comparing the safety and effectiveness of using e-cigarettes and HnB products in reducing tobacco addiction is in the process) [63, 78].

The use of e-cigarettes to reduce tobacco addiction is most controversial. As mentioned above, the e-cigarette market is not sufficiently controlled, resulting in the appearance of contaminated products, including THC-containing products, on the market-leading to serious and life-threatening pulmonary toxicity. Moreover, e-cigarettes are a fashionable and attractive product eagerly bought by children and adolescents, which leads to nicotine addiction and more frequent use of traditional cigarettes by people in this age group [46]. The results of a study conducted in 2020 by the National Institute of Public Health - National Institute of Hygiene showed that the products initiating nicotine consumption were traditional cigarettes for 52% of teenagers, electronic cigarettes for 32%, and HnB products for 0.2% [79]. Similar results were obtained in a study commissioned by the European Commission (Eurobarometer 2021), according to which in 87% of cases, traditional cigarettes and roll-your-own tobacco are responsible for the ini-

tiation of nicotine use. The remaining products played a much smaller role in the initiation of addiction (water pipes with tobacco — 4%, e-cigarettes — 2%, snus and HnB products < 1%) [80].

The FDA has issued an opinion on the use of tobacco heat-not-burn devices (but not e-cigarettes) as a way to reduce health risks in smokers, granting HnB products an MRTP status. The FDA opinion was based on 30 analyses and reports, the results of 10 clinical studies, 8 non-clinical studies, 141 independent scientific studies and 340 peer-reviewed articles. They have shown that a complete transition from traditional cigarettes to a tobacco heat-not-burn system significantly reduces exposure to harmful or potentially harmful substances, which can help addicted adult smokers give up smoking and reduce their exposure to harmful factors. In addition, the FDA has made a reservation that it will closely monitor how tobacco heating systems are used by consumers and whether they do not adversely affect their health and that the use of these products by adolescents is not increasing, which would lead this age group to nicotine addiction. It was emphasized that HnB products are not completely safe and people, especially young people who do not currently use tobacco products, cannot start using them [64, 65]. Similar recommendations were also issued by the Dutch National Institute of Public Health and the Environment (RIVM), the Belgian High Council for Health, the German Federal Institute for Risk Assessment (German Bundesinstitut für Risikobewertung, BfR) and the Japanese National Institute of Public Health [61–63, 79, 81].

In Poland, there are no such recommendations issued by state organizations. There are, however, expert opinions. One of them is the opinion of Szymański et al. [82], in which the authors state that HnB products may potentially be helpful in the treatment of tobacco addiction and in reducing the adverse health effects associated with this addiction. They also state that HnB products may be a safer alternative to cigarettes in people in whom all, including pharmacological, treatments for tobacco dependence have failed [82]. Polish guidelines for the management of lower limb artery disease by Jawień et al. [83] also emphasize that replacing traditional cigarettes with heat-not-burn products may be an alternative in the treatment of smoking addiction.

Summary

Lung cancer risk factors are largely known and well characterized. Therefore, primary prevention of this disease seems to be easy to implement by eliminating environmental threats and smoking. Nevertheless, lung cancer remains the leading cause of deaths among malignant cancers in all developed countries.

The reasons for this phenomenon should be sought for in the growing problem of environmental pollution, but above all in the difficulties in eliminating the addiction to smoking in the Polish population. Due to the lack of adequate education, young people still turn to nicotine-containing products, first e-cigarettes and then traditional cigarettes. On the other hand, nicotine addiction is extremely strong in many people and its elimination using traditional methods (psychotherapy, nicotine replacement therapy, pharmacotherapy) turns out to be impossible. In these people, reducing the health risks associated with smoking can be achieved by replacing cigarettes with smokeless nicotine-containing products. Many scientific studies have shown that aerosols from e-cigarettes and heat-not-burn devices contain over 90% fewer carcinogens than cigarette smoke. However, it should be remembered that while the composition of aerosols in heat-not-burn devices is known, in the case of e-liquids it may be modified by e-cigarette owners or companies producing them (this was the cause of many cases of acute lung damage in people using e-liquids containing THC and vitamin E acetate). Therefore, many countries (the USA, the Netherlands, Belgium, Germany) have identified HnB devices as products with a reduced health risk compared to traditional cigarettes, and experts from many countries issue cautious recommendations on the possibility of reducing the health risk in people smoking cigarettes by replacing them with heat-not-burn products.

Conflict of interest

The authors report no conflicts of interest.

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