Tobacco and Alternative Nicotine Products and Their Regulation

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Abstract

Nicotine is highly addictive, interacts with particulates and infection in respiratory disease and promotes cancer in the lung and other organs. Cardiovascular morbidity and mortality were related to fine and ultrafine particles, free radicals, reactive oxygen species, nicotine and other toxins inhaled by smoking, second hand smoking, use of water pipe, heated tobacco, and to vaping e-cigarettes. Steepest increase of risk is observed in the low dose range, explaining the considerable increase of chronic disease by regular passive exposure and its acute hazards for risk groups like persons with ischemic heart disease or asthma. All forms of tobacco are harmful, and there is no safe level of exposure. Oral nicotine does not expose bystanders, but in users of smokeless tobacco cardiovascular disease, oral cancer and pancreatic cancer may increase and like exposure to tobacco smoke in pregnancy it raised rates of stillbirth and low birth weight. Sudden infant death is associated with prenatal and postnatal exposure of the child and also long-lasting effects of parental smoking were observed on

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respiratory health of children and on the development of their brains. Regulation of all nicotine products should be based on the World Health Organization (WHO) Framework Convention on Tobacco Control. Long-term goal is to raise a nicotine-free generation and to stop selling nicotine products on the free market.

Keywords

Tobacco · E-cigarette · Passive smoking · Nicotine · Health · Disease · Cancer

Introduction

Tobacco kills up to half of its users, more than seven million people worldwide each year as a result of active smoking, and another 1.2 million as a result of involuntary breathing of second-hand smoke (SHS). Compared to earlier reviews (WHO 2008, Fig. 1), annual victims are on the increase and tobacco is projected to kill one billion people this century unless countries take strong action now to prevent it (WHO 2020b).

Tobacco smoke is a complex, dynamic and reactive mixture of hazardous gases and particles, containing thousands of chemicals, including toxic carbon monoxide and highly addictive nicotine. Nicotine promotes cancer growth (Ginzel et al. 2007), initiated by products of pyrolysis (N-nitrosamines, polycyclic aromatic hydrocarbons - PAHs, aromatic amines, volatile hydrocarbons, other organics, heavy metals, and metal compounds). In sidestream smoke (released between puffs from the end of a burning cigarette, cigar, or pipe), particles are smaller and products of pyrolysis higher than in mainstream smoke.

Passive smoking includes inhalation of sidestream smoke and smoke exhaled by smokers. In addition also third-hand smoke deposited on and released from surfaces

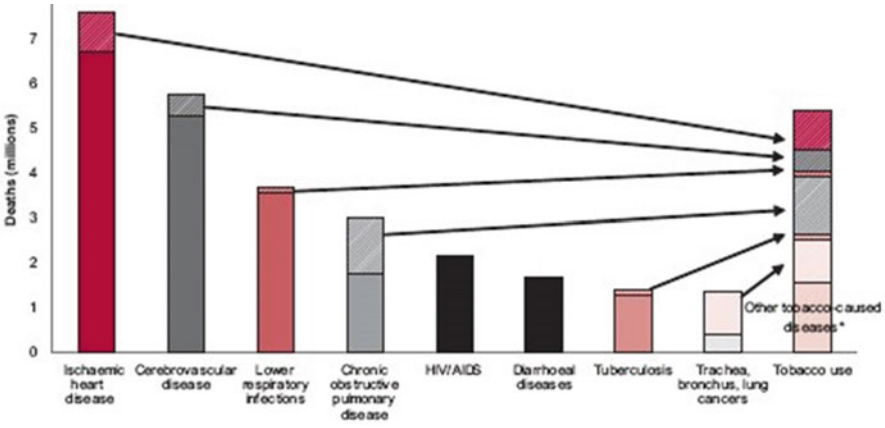

Fig. 1 Eight leading causes of death (2005) and proportions attributable to tobacco smoking © WHO. Reproduced from *WHO REPORT on the global TOBACCO epidemic, 2008* (WHO 2008)

(floor, walls, furniture, house dust) is an involuntary exposure of particular importance for children. Most frequently used are tobacco cigarettes (combustion products), but electronic cigarettes (ecigs) and heated tobacco products (HTPs) are on the increase and many adolescents start their smoking career with these novel products or with water pipe (shisha). Some enter nicotine addiction by oral tobacco like snus^{R} or oral nicotine like skruf^{R}. All these products are not controlled like nicotine products from pharmacies and all are advertised for continuous use and not for limited treatment. Less products of pyrolysis are emitted by HTPs and ecigs, nevertheless nicotine exposure is hazardous, especially in combination with irritant, toxic, and carcinogenic compounds on the large surface of small particles inhaled by "vapers". Oral and dermal applications of nicotine products do not expose the lungs of users and bystanders with aerosols, but like ecigs oral products can serve as a gateway into nicotine addiction, and some increase of cardiovascular and metabolic disease and cancer (oral cavity, esophagus, pancreas) has been observed after long-term use of oral tobacco. Daily maternal use in pregnancy was associated with increased risk of preterm delivery, stillbirth, neonatal apnea, and higher systolic blood pressure in childhood and altered autonomic cardiac control.

Vascular Effects of Tobacco Products and Nicotine

Most frequent causes of death related to tobacco smoking are from cardiovascular and cerebrovascular disease (CVD). Even SHS triggers acute changes of endothelial function, blood coagulability, heart rhythm, and promotes the development of arteriosclerosis (Neuberger 2019). Main driver of vascular effects seem to be fine and ultrafine particles and toxic compounds.

Both outdoor particle pollution from motor traffic and indoor particle pollution from tobacco smoke trigger endothelial dysfunction, platelet activation, and thrombogenesis (Neuberger 2008). In patients with coronary artery disease, active or passive smoking produces acute myocardial ischemia by adversely affecting the balance of demand for myocardial oxygen and nutrients with myocardial blood supply.

Carbon monoxide (CO) – a major constituent of cigarette smoke – binds avidly to hemoglobin, reducing the amount of hemoglobin available to transport oxygen and impeding release of oxygen by hemoglobin to tissues. CO-reduced exercise tolerance in patients with angina pectoris or intermittent claudication (Neuberger 1979).

Cigarette smoke delivers a high level of oxidizing chemicals to smokers, including oxides of nitrogen and many free radicals and reactive oxygen species (ROS) from both the gas and tar phases of cigarette smoke (Church and Pryor 1985). Exposure to oxidant chemicals in smoke was associated with depletion of endogenous levels of antioxidants like vitamin C (Lykkesfeldt et al. 2000), increased levels of lipid peroxidation products, oxidation of low-density lipoprotein (LDL), inflammation, endothelial dysfunction, and platelet activation (Burke and FitzGerald 2003).

Acrolein, a reactive aldehyde present at high levels in cigarette smoke, forms protein adducts, implicated in loss of protection by high density lipoprotein (HDL)

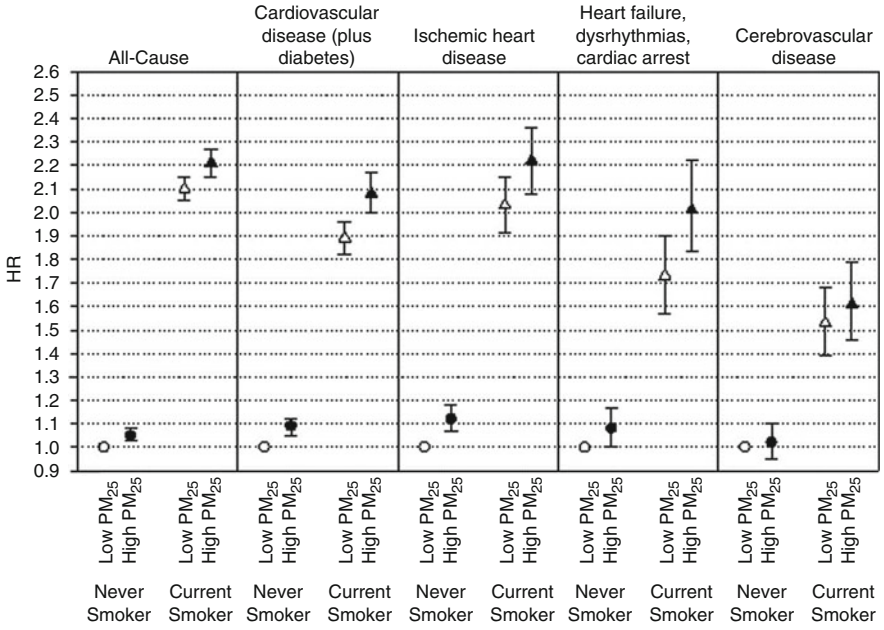

Fig. 2 Cardiovascular mortality: Hazard ratios for active smoking and for ambient air pollution with fine particles – PM2.5 (Turner et al. 2017). ©Elsevier, with kind permission

and in atherogenesis (U.S. CDC 2010). Acrolein also oxidizes antioxidant proteins, which can result in dysfunction and death of endothelial cells, contributing to atherosclerosis. In addition, acrolein inhibits antithrombin activity and could contribute to smoking-induced coronary vasospasm.

Nicotine has a central role in CVD from tobacco use and from SHS. It is a sympathomimetic drug that increases heart rate and cardiac contractility, transiently increasing blood pressure and constricting coronary arteries, which is most risky in persons with preexisting hypertension. Nicotine also contributes to endothelial dysfunction, insulin resistance, and lipid abnormalities. Both tobacco use and SHS are risk factors for diabetes and aggravate insulin resistance in persons with diabetes. The mechanism appears to involve the effects of oxidizing chemicals in the smoke and the sympathomimetic effects of nicotine. Combined effects of smoking and ambient air pollution on CVD are more than additive (Fig. 2): From the hazard ratios for CVD deaths the dominant influence of smoking can be seen, but also additional increases from ambient air pollution with PM2.5, which are higher in current smokers than in never-smokers.

Combined toxins distributed on the large surface of (ultra)fine smoke particles trigger pulmonary reflexes and inflammation, reach the alveoli, some of them cross the alveolar-capillary membrane, elicit acute endothelial dysfunction with inactivation of nitric oxide (mediating vasodilatation), impair the viability of endothelial cells and reduce the number and functional activity of circulating endothelial

progenitor cells. Platelets of non-smokers appear to be susceptible to quick pro-aggregatory changes with every SHS exposure. Apart from vasoconstriction and thrombus formation from sticky platelets, increased fibrinogen and other factors of blood coagulation, further impairment of the myocardial oxygen balance is promoted by nicotine-induced adrenergic stimulation and particle-induced autonomic dysfunction with heart rhythm disturbances and worsening of left ventricular diastolic function. Experiments in healthy men showed that a 30-min exposure to SHS (e.g., the time of a meal in a smoking room) was sufficient to reduce coronary flow velocity reserve (Otsuka et al. 2001) and sustained vascular injury characterized by mobilization of dysfunctional endothelial progenitor cells with blocked nitric oxide production and activation of platelets in blood. Chronic vascular effects of SHS start with endothelial dysfunction in children, arterial stiffness, and the development of a thickening of the intima-media and other signs of early atherosclerosis. Combined effects of tobacco smoke with ambient air pollution with urban aerosols have been detected and complex interactions with nutrition are likely, especially in connection with diabetes. SHS is a risk factor for metabolic syndrome, glucose intolerance, insulin resistance, and the development of type 2 diabetes mellitus. A meta-analysis by Wei et al. 2015 on seven prospective studies investigating the risk for developing type 2 diabetes from SHS found a RR of 1.33 (95% CI 1.20–1.46) and after adjustments for publication bias 1.27 (95%CI 1.16–1.40). After manifestation of diabetes vascular complications are increased by further exposure to tobacco smoke.

Accelerated atherosclerosis from tobacco smoke may result in ischemic heart disease, increased risk of acute myocardial infarction, and sudden cardiac death, stroke, peripheral artery disease with gangrene of extremities, aortic aneurysm, atrial fibrillation, pulmonary embolism, and other sequelae (Banks et al. 2019). The largest smoking-related disease burdens in adults are from CVD, with highest RR at young ages, but continuous increase of risk with pack-years, age, and years of smoking. Over the years also regular passive smokers build up a considerable risk for ischemic heart disease. Classifying male non-smokers in the lowest quarter of serum cotinine (0–0.7 ng/ml) as "light passive smokers" and non-smokers within the upper three quarters of cotinine concentrations (0.8–14 ng/ml) as "heavy passive smokers," Whincup et al. (2004) observed that the risk for major coronary heart disease increased by years of follow-up significantly steeper in heavy passive smokers, comparable to the increase in light active smokers, consuming 1–9 cigarettes per day.

In a European cohort on circulatory mortality a hazard ratio of 1.25 (95%CI 1.04–1.50) was calculated for passive smoking (verified in a subsample by plasma cotinine) per each additional daily hour of exposure (Gallo et al. 2010). A meta-analysis found for SHS a relative risk of 1.35 (95% CI: 1.22–1.50) for stroke and 1.27 (95% CI: 1.10–1.48) for ischemic heart disease, with higher risks in women (Fischer and Kraemer 2015). Many studies underestimated relative risks for CVD, because they compared active smokers with non-smokers, of which many were exposed to SHS. If choosing non-smokers without exposure to SHS as the proper control group (Bonita et al. 1999), the odds ratio of stroke from active smoking increased from 4.14 (95% CI 3.04–5.63) to 6.33 (95% CI 4.50–8.91). Flores et al. (2016) found that the premature mortality hazards of recalled and unconscious

exposure to SHS are comparable and predicted by serum cotinine at beginning of observation. There was a significant increase in years of life lost, adjusted for confounders, across cotinine categories, similar in non-smokers reporting SHS and in non-smokers reporting no SHS exposure.

Dose-response relationships are not linear, but a much steeper increase of cardiovascular risk is observed in the low-dose range, covering SHS and occasional active smoking. SHS increases the risk of coronary heart disease by about 30%. In occasional smokers consuming an average of less than one cigarette per day a hazard ratio of 1.71 (95% CI 1.33–2.21) was found for CVD (Inoue-Choi et al. 2017) and the consumption of 1–4 cigarettes per day raised relative risk of dying from ischemic heart disease to 2.74 (95% CI 2.07–3.61) in men and 2.94 (95% CI 1.75–4.95) in women (Bjartveit and Tverdal 2005). Disproportionately, high risk at low levels of exposure suggest that there is no safe lower limit of SHS exposure for risk groups. Even if reduction of active smoking is sustained, the reduction of daily cigarettes smoked reduces the risk only marginally compared to complete cessation.

Most at risk for acute effects of SHS are patients with preexisting coronary or cerebrovascular diseases, which in turn are promoted by chronic exposure to SHS. Since Sargent et al. (2004) reported reduced incidence of admissions for myocardial infarction after a public smoking ban, numerous studies confirmed that enforcement of smoke-free laws rapidly reduces admissions for acute coronary syndrome and other cardiac and cerebrovascular diseases (Neuberger 2008). Smoke-free legislation is associated with a lower risk of hospitalization and death from CVD, significantly lower rates of hospital admissions or deaths from coronary events (relative risk, 0.85; 95%CI 0.82–0.88), other heart disease (relative risk, 0.61; 95%CI 0.44–0.85), and cerebrovascular accidents (relative risk, 0.84; 95%CI 0.75–0.94). More comprehensive laws were associated with larger changes in risk. Indoor smoking bans reduced myocardial infarction by 10–20%, in the first year mainly associated with the elimination of passive smoking and followed by sustainable decreases of coronary syndrome, myocardial infarction, stroke, and incident diabetes also in ex-smokers (Tan and Glantz 2012; Akter et al. 2015).

Shisha (water pipe, hookah, narghile) produces similar risks for users and bystanders as tobacco cigarettes, but concentrations of carbon monoxide in charcoal-heated shisha and of heavy metals are higher. Depending on intensity and duration of exposure, acute CO intoxications were reported and in long-term similar CVDs can develop as in cigarette smoking (Waziry et al. 2017). Animal experiments showed hypercoagulability, inflammation, as well as systemic and cardiac oxidative stress (Nemmar et al. 2017). Also the smoking of other pipes and cigars, whether active or passive, carries significant risk of smoking-related CVD (Shaper et al. 2003).

Because less products of pyrolysis are formed by heating than by burning tobacco, HTPs are marketed as less dangerous than conventional cigarettes; however, biomarkers of potential cardiovascular harm did not support this claim (Glantz 2018). HTPs impair vascular endothelial function measured by arterial flow-mediated dilatation in rats to the same extent as by cigarette smoke (Nabavizadeh et al. 2018). An important advantage of all electronic devices over conventional cigarettes

is that SHS or second-hand aerosol is only produced when the user exhales and not continuously like in conventional smoking between puffs. The doses calculated for second-hand uptake of particles, toxins, and carcinogens from electronic devices are usually much lower than from traditional tobacco products, below 1.6×10^8 particles/kg bodyweight, but dosimetry estimates were 50–110% higher for HTPs than for ecigs (Protano et al. 2017). The carrier function of aerosols from electronic devices might be similar, but the clearance of liquid particles is certainly faster than of solid, carbonaceous particles released by conventional cigarettes. On the other hand, some electronic devices release even more ultrafine aerosols carrying tobacco-specific nitrosamines and heavy metals and also volatile organic compounds are released, which are harmful for users and bystanders. In addition hemodynamic changes and adverse effects of nicotine on blood lipids, as well as the induction of insulin resistance contribute to cardiovascular risk of HTPs and ecigs (Zhang et al. 2018; Protano et al. 2020).

Electronic cigarettes (ecigs) have been called "a wolf in sheep's clothing," because they may serve as a gateway drug for youth, prolong nicotine addiction, and the ritual in smokers who would otherwise be willing to quit. So they keep up the handling and use of cigarettes in public and the denormalization of cigarettes is undermined (Neuberger 2015). Even bystanders absorb considerable amounts of nicotine (Ballbè et al. 2014) and inhale particles, which are smaller than in SHS (Schripp et al. 2013). Aerosols exhaled during vaping are less persistent than SHS, nevertheless they are carriers for toxins, which they adsorb on their large surface and transport them to persons in the same room and even to neighboring rooms (Khachatoorian et al. 2018), and into the depth of the lung, where clearance is less efficient and where ultrafine particles can reach the bloodstream. Most dangerous is the contamination of small rooms like passenger cars (Schober et al. 2019). WHO (2020a) clearly stated that ecigs (electronic nicotine delivery systems – ENDS and electronic non-nicotine delivery systems – ENNDS) and other vaping products are dangerous for both users and bystanders exposed to the aerosol. Cohort studies on long-term effects are still missing, but similar cardiovascular risks seem to exist as from tobacco products and HTPs, indicated by a sustained hyperadrenergic effect (triggering arrhythmias and other harmful cardiac reactions), oxidative stress and activation of inflammatory pathways (leading to atherosclerosis, plaque progression and instability, and myocardial ischemia), endothelial dysfunction (leading to impaired nitric oxide release and oxygen supply to tissues), arterial stiffness (caused by nicotine and predicting CVD), and pathological thrombus formation from platelet activation (Middlekauff 2020). The chronic use of ENDS produced platelet aggregation to a similar degree as in chronic users of tobacco products (Nocella et al. 2018). Most worrying are first cross-sectional studies showing associations of ecigs use with myocardial infarction (Alzahrani et al. 2019). Many users of ecigs return to tobacco cigarettes or become dual users and dual use was associated with higher odds of CVD than smoking tobacco only (Osei et al. 2019). Cohort studies on long term risks of use and second hand inhalation of ecigs and HTPs are still lacking, but from the indicators mentioned above it has to be assumed that also passive vaping increases CVD. Because of risks for CVD, respiratory disease, cancer, and addiction

(see below), HTPs and ecigs cannot be recommended as a help for smoking cessation, even though health risks of smoking and SHS are even higher. Some ecigs are labelled "without nicotine," despite of releasing considerable amounts. Adjustable voltage, nicotine salts, and additives were developed to increase nicotine uptake and to mimic the rapid transfer of nicotine to blood and brain like in smoking. For smoking cessation, dermal and oral nicotine products from pharmacies are safer for nicotine replacement and do not contaminate the breathing air of bystanders. Their nicotine content is controlled and can be reduced gradually during cessation. In young and light smokers, preference should be given to cessation aid without any nicotine. Also for pregnant women any form of nicotine is harmful for mother and child (Ginzel et al. 2007). Higher systolic blood pressure in childhood and altered autonomic cardiac control were associated with nicotine consumed by the mother in pregnancy, whether by inhalation or by oral products (Watanabe and Parikh 2019). Stop of oral tobacco (snus) use after a myocardial infarction nearly halved mortality risk, similar to the benefit associated with smoking cessation (Arefalk et al. 2014).

Respiratory Effects of Tobacco Products and Nicotine

Tobacco smoking is the leading preventable cause of death and disability, with important contributions of respiratory diseases (Fig. 1). The earlier smoking is stopped, the better are respiratory outcomes. To end accelerated decline of lung function compared to non-smokers, smokers need complete smoking cessation. Similar to CVD, reduction of daily consumption to below 5 cigarettes is insufficient to stop respiratory function decline (Fig. 3).

In industrialized countries smoking prevalence decreased, nevertheless some studies attributed up to two-thirds of deaths in current smokers to tobacco and an even higher number of diseases, which are not registered as main cause of death (Banks et al. 2019). In respiratory diseases, asthma and chronic obstructive pulmonary disease (COPD) from smoking are most important for disability, early retirement, and invalidity. In 2015, COPD caused 2.6% of global disability adjusted life years (DALYs) and asthma 1.1% of global DALYs, with smoking, air pollution, and SHS as the main risk factors (Soriano et al. 2017). Smokers had a fourfold increase in risk of developing COPD (Bellou et al. 2019), and there are combined effects of active and passive smoking with other environmental and occupational air pollution.

Other important interactions of tobacco smoke in respiratory diseases occur with infections, especially in childhood. Smokers are touching their face and mouth more often and they can also transfer bacteria causing meningitis or viruses causing respiratory disease by kissing a child. Combined effects of smoking and tuberculosis are a world-wide problem (Fig. 1), especially in the developing world. Smoking and SHS impair mucociliary clearance and lung function. By reducing defense of the respiratory system, weakening and damaging it, tobacco smoke enables viruses and bacteria to invade. Some infectious diseases become more serious or even lethal, e. g., pneumonias in children from SHS or bronchiolitis from respiratory syncytial virus. Higher mortality was also reported in smokers from influenza and corona virus

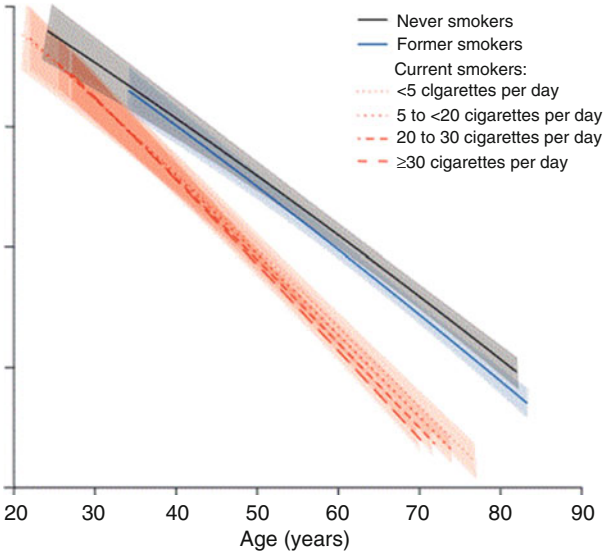

Fig. 3 Decline of Forced Expiratory Volume in first second (FEV1) by age and smoking (Oelsner et al. 2020). ©Elsevier with kind permission

infection (Middle East Respiratory Syndrome and COVID-19), especially in smokers with COPD (Alqahtani et al. 2020).

Also HTPs and ecigs aerosols contain numerous respiratory irritants and toxicants, triggering increased airway hyperreactivity, distal airspace enlargement, mucin production, as well as cytokine and protease expression. Just 15 min of exposure to ecig aerosol induced transient lung inflammation and impaired gas exchange in healthy volunteers. Defense by ciliary function, neutrophils, and alveolar macrophages is impaired and cross-sectional studies found an increase of asthma and of bronchitis symptoms, even in adolescents who had never used tobacco. Long-term observations are still missing, but experiments with animals and with human tissues showed similar structural lung changes from ecigs as in the development of COPD from tobacco, protease release from alveolar macrophages and blood neutrophils, and nicotine dependent elastase release (Gotts et al. 2019). Respiratory toxicity of ecigs is determined by a large number of aromas, nicotine, and the carriers propylene glycol, vegetable glycerin, and other solvents forming aerosols with small particle diameter. Heavy metals (Ni, Cr, etc.) contribute to respiratory risks of ecigs (Fowles et al. 2020). Some ingredients, additives or their decomposition products might cause special respiratory diseases, e.g., diacetyl, which caused bronchiolitis and "popcorn lung" in occupational exposures. In 2019 in the USA, 2558 persons were hospitalized and 60 patients died from acute vaping disease, called "e-cigarette, or vaping, product use–associated lung injury" (EVALI), characterized by gastrointestinal and severe respiratory symptoms with bilateral pneumonia and Acute Respiratory Distress Syndrome (Werner et al. 2020). Days

to weeks after consumption of ecigs also, young people without previous lung disease and without detectable infection developed respiratory failure with pulmonary edema, hypoxemia, diffuse alveolar & endothelial damage, protein-rich inflammatory fluid in alveolar space, and need for mechanical ventilation. The heterogeneity of clinical appearance might resemble the high variety of uncontrolled additives used in ecigs. Most (but not all) cases of EVALI had used ecigs with cannabis or tetrahydrocannabinol (THC). These mixtures contained vitamin E acetate, used as a thickening agent in THC products, which was also found in bronchoalveolar lavage of patients. At temperatures reached in vaping devices the exceptionally toxic ethenone (C_2H_2O) and other ketenes may be formed by pyrolysis of vitamin E acetate (Wu and O'Shea 2020), possibly amplified by metal catalysts. Since the outbreak of SARS-CoV-2 epidemy new cases of EVALI are easily misdiagnosed as COVID-19 (Armatas et al. 2020).

Cancer from Tobacco Products and Nicotine

Tobacco smoke contains dozens of carcinogens, including class 1 carcinogens like benzo[a]pyrene, N′-nitrosonornicotine (NNN), nicotine-derived nitrosamine ketone (NNK), 2-toluidine, 2-naphthylamine, 4-aminobiphenyl, benzene, 1,3-butadiene, ethylene oxide, vinyl chloride, and metals like As, Be, Cd, Cr(VI), and ^{210}Po. Also other products of tobacco pyrolysis contribute to cancer risks in many organs, e.g., benz[a]anthracene, dibenz[a,h]anthracene, formaldehyde, N-nitrosodimethylamine, N-nitrosodiethylamine, 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), acrylamide, glycidol. From these genotoxic compounds or their metabolites cancer can develop in lungs, bronchi, trachea, larynx, mouth, throat, esophagus, stomach, colon, rectum, liver, pancreas, kidney, renal pelvis, bladder, uterine cervix, or blood (acute myeloid leukemia). Combined effects of tobacco smoke with alcohol are of importance in cancer of the upper digestive tract, larynx, colon, liver, pancreas, and female breast, and with chronic infection, e.g., with human papilloma virus (HPV) in cervical cancer and with hepatitis B or C in hepatocellular carcinoma. Increased risk of tobacco smoking was also found for mucinous ovarian cancer, chronic myeloid leukemia, and for breast cancer after exposure (active or passive) during the time when the female breast develops. Frequent and intensive SHS is a verified risk for cancer of the lung and of other locations (breast, pancreas, bladder, etc.), subject to similar combined effects as active smoking.

Smoking of pipes and cigars was found associated with cancer of lung, larynx, oral cavity, hypopharynx, esophagus, pancreas, stomach, and urinary bladder. Waterpipe does not filter carcinogens and the nicotine load of one pipe corresponds to the inhalation of approximately 10 cigarettes. Additional carcinogens enter the smoke of shisha from the burning of coal. Some PAHs, benzene, and heavy metals like Cd, Cr^{VI}, Ni, Co, As are higher in shisha smoke than in cigarette smoke and put users and persons sharing the same room at risk for cancer. In users metabolites of tobacco-specific nitrosamines were detected in urine and in regular shisha users

studies found an increase of cancers of the head and neck, esophagus, and lung (Mamtani et al. 2016).

Cigarette smoking is the number one cancer risk, largely due to lung cancer (Shaper et al. 2003). Cigarette smokers are 15–30 times more likely to get lung cancer or die from lung cancer than people who do not smoke. Even smoking a few cigarettes a day or smoking occasionally increases the risk of lung cancer (Bjartveit and Tverdal 2005). Lung cancer increases with packyears and decreases after smoking cessation much more slowly than the cardiovascular risk. Smoking attributable lung cancer amounts to 70–90%. Other causes are particulate air pollution, other environmental exposures indoors (residential radon, SHS), and occupational exposures. Some combined effects of smoking are overadditive (radon, amphibole asbestos), so that attributable cancer risks sum up to more than 100% and high decreases of lung cancer risk can be achieved by elimination of only one risk factor.

As a defense against microbes, macrophages react to small particles with the induction of nitric oxide and reactive oxygen intermediates. Like in diesel soot the carcinogenicity of tobacco smoke seems to be less dependent on the mass of carcinogens than on the surface of small particles by which traces of genotoxic substances are transported into the lung. The particle size of SHS is smaller and on its large surface products of pyrolysis are transported, which are formed in higher concentrations in sidestream smoke between puffs than in mainstream smoke. Important for cancer development is also nicotine, which is not only genotoxic on human epithelia of the upper aerodigestive tract (Sassen et al. 2005), mediated through oxidative stress (Bavarva et al. 2004), but is also an important epigenetic risk, promoting cancer cell proliferation by several mechanisms, inhibiting apoptosis and thereby increasing cancer cell survival, stimulating angiogenesis, and thereby vascularization of the growing tumor, and promoting cancer migration (Fig. 4). Possible promotion of a smoking induced cancer by nicotine is one of the reasons, why nicotine replacement therapy after smoking cessation should be limited in time (Ginzel et al. 2007). The potent lung carcinogens NNK and NNN can form during blending of tobacco, but also in the smoker by endogenous nitrosation. Smoking itself increases nitrogen oxides and other nitrosating agents in saliva, stomach, urine, etc. For endogenous nitrosation of nicotine to NNN and NNK, the amount of ingested nitrite and nitrate is less important than chronic infection and diseases with chronic inflammation, which cause continuous increase of NO and peroxynitrite, capable of forming nitrosamines from nicotine and aminoketone (Parzefall et al. 2005).

Cancer risks of HTPs and e-cigarettes are lower than from tobacco products, but not negligible. Certainly the mass of carcinogens in aerosols of HTPs and ecigs is much smaller than in tobacco smoke, but traces of genotoxic agents might be sufficient to induce cancer if distributed on the large surface of very small particles in these aerosols and combined with potent promoters like nicotine (see above). Propylene glycol, glycerol, and flavors in ecigs produce free radicals and reactive oxygen species (Bitzer et al. 2017). Depending on voltage and temperature propylene glycol produces formaldehyde and its hemiacetal in the aerosol (Jensen et al. 2015). Ni, Cr, and other heavy metals were found to be transferred from the heating coils to the e-liquids (Fowles et al. 2020) and some of these carcinogenic metals

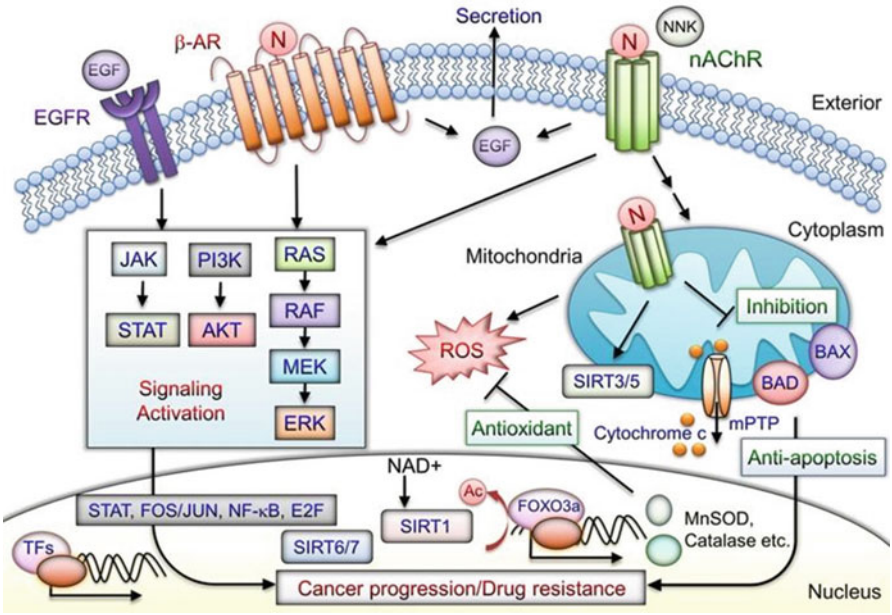

Fig. 4 Lung cancer promotion by nicotine, signaling pathways downstream of nAChRs promoting drug resistance and antiapoptosis (for abbreviations see Cheng et al. 2020). Creative Commons License. Cheng et al. 2020

(from cartridge, fluid, etc.) were higher in e-cigarette aerosols than in SHS (Zhao et al. 2020). N-nitrosamines like NNN and their metabolites were found in saliva and urine of vapers (Bustamante et al. 2018). Also some of the sugars and aromas added to attract children can decompose to carcinogens. Bavarva et al. (2004) found nicotine induced mutations in human breast cells and other epithelial cells across 1,585 genes, of which 49% were associated with cancer, with genes of the mucin family among the top mutated genes. 26% of genes linked to cancer development are deregulated both in buccal mucosa of vapers and of smokers, partly different genes, which are implicated in cancer of lung, esophagus, bladder, ovary, and leukemia (Tommasi et al. 2019). Martin et al. (2016) found decreased expression of immune-related genes in the nasal mucosa of vapers, 53 genes like in smokers (some more suppressed), and 305 genes in vapers only. Damaged DNA and impaired DNA repair from exposure to e-cigarette aerosol was found in mice (lung, heart, bladder) and in human lung cells and bladder cells (Lee et al. 2018).

Oral uses of smokeless tobacco have the advantage that there is no inhalation risk for users and bystanders, but carcinogens like tobacco-specific nitrosamines are a cancer risk for betel quid chewers and for users of oral tobacco. Overall, there is sufficient evidence that smokeless tobacco causes oral cancer and pancreatic cancer in animal studies and in humans (Cogliano et al. 2004), possibly also esophageal cancer. Levels of cotinine and metabolites of tobacco-specific nitrosamines in urine

were found higher in smokeless tobacco users than in smokers (Hecht et al. 2007). Most risky is the combination of oral tobacco with tobacco smoking.

All nicotine products promote carcinogenesis and may interfere with cancer therapy. By example human pharyngeal cancer cells became resistant to Cisplatin by exposure to ecigs aerosol (Manyanga et al. 2019). Figure 4 shows some of the pathways by which nicotine, the primary addictive constituent of cigarettes, contributes to cancer progression through activation of nicotinic acetylcholine receptors (nAChRs), which are membrane ligand-gated ion channels. Activation of nicotine/nAChR signaling is associated with lung cancer risk and drug resistance (Cheng et al. 2020).

Other Important Diseases Promoted by Tobacco and Nicotine Products

Numerous other diseases leading to disability were associated with smoking tobacco and with exposure to SHS. For newly developed nicotine products, there is still a lack of epidemiological data on their effects on chronic diseases, but from animal experiments and bioindicators in humans, there is sufficient evidence for metabolic effects of tobacco smoke and of nicotine (see chap. ► "Other Important Diseases Promoted by Tobacco and Nicotine Products"). HTPs showed no difference in most biomarkers of potential harm from conventional cigarettes (Glantz 2018), possible hepatotoxicity and a potential for unexpected organ toxicity not previously associated with cigarettes (Chun et al. 2018).

Smoking is linked to the development of rheumatoid arthritis and their severity and exacerbation. Animal experiments proved that nicotine causes specific alterations in the disease-related cellular and humoral immune responses and exacerbate inflammatory arthritis (Lee et al. 2017). Smoking has also been identified as a major risk factor for osteoporosis, resulting bone fractures and impaired healing. Nicotine affects estrogen and calcium metabolism, osteocyte development and bone lamellar structure, inhibits catalase and glutathione reductase activity, contributing to an accumulation of ROS by cigarette smoke exposure, and induces apoptosis in human osteoblasts (Marinucci et al. 2018).

Smoking or heavy exposure to SHS increase the risk of blindness, macular degeneration, and a number of other eye diseases (dry eye, cataracts, uveitis, diabetic retinopathy, glaucoma with optic nerve damage). For some of these diseases, impairment of microcirculation by nicotine plays an important role, which can be triggered also in healthy subjects by oral nicotine (Cınar et al. 2019).

Effects of Tobacco Products and Nicotine on Fetus and Child

Maternal smoking during pregnancy is associated with numerous adverse offspring outcomes (Horak et al. 2012). Complications of gravity, birth, and reduced birth weight are mainly seen if pregnant smokers continue to smoke into the last trimester,

but the problem of tobacco smoke exposure starts with conception since active smoking reduces the sperm count, male and female fertility. Impairments of fetal life cannot only be measured by higher rates of abortion and stillbirths, but also by increased fetal heart rate, limb movements, and fetal activity associated with later infants' attention and self-regulation (Stroud et al. 2019). Neonatal morbidity and mortality and malformations (orofacial clefts) are increased, and birthweight is decreased by an average of 200 g. The leading cause of death in the first year is sudden infant death syndrome (SIDS), which doubles when the mother smokes one cigarette per day and increases ninefold if she smokes more than 20 cigarettes per day. Also long-term neurobehavioral deficits develop more frequently, in particular attention deficit hyperactivity disorder, but also addictive behavior, and disruptive behaviors/conduct disorder. Also lung development of children is impaired by maternal smoking during pregnancy and afterwards by parental smoking (Pattenden et al. 2006) and the risk for infectious and allergic respiratory disease and asthma increases. A meta-analysis on parental smoking and the risk of congenital heart defects concluded, that maternal active smoking was significantly associated with risk of atrial septal defect and right ventricular outflow tract obstruction and that also maternal passive smoking as well as paternal smoking increased the risk of congenital heart defects in offspring (Zhao et al. 2019). Many effects of prenatal exposure to tobacco smoke have been attributed to nicotine (Ginzel et al. 2007), with adverse perinatal outcomes associated to placental syndromes and direct toxic effects on arteries supplying the fetus and his heart. Prenatal exposure to constituents of tobacco smoke can also have long lasting effects on children like metabolic disease and visceral adiposity, but only few epidemiological studies were able to disentangle them from effects of postnatal exposure. Transgenerational effects of smoking in pregnancy seem to be related to altered DNA methylation patterns in cell nucleus and mitochondria, which are gender-specific and tissue dependent. Epigenetic impacts of in utero exposure to maternal smoke, e-cigarette aerosol, and maternal SHS on fetal respiratory development may persist across subsequent generations, regardless of the smoking habits of the second generation, so that asthma in grandchildren was associated with the smoking habit of the grandmother in pregnancy (Zakarya et al. 2019).

Also passive smoking of the mother puts the fetus at risk of growth retardation and shortening of gestational age. Individual risks for mother and child from mothers' passive smoking are substantially lower than from her active smoking. But since the number of exposed pregnancies are higher, the number of attributable cases is in the same order of magnitude as for active smoking in pregnancy. Postnatal exposure of children to parental smoking was estimated to cause approximately 10% of children's respiratory and middle ear diseases (Moshammer et al. 2007).

SHS leaves accumulating contaminants on surfaces like carpets, wallpapers, upholstery, blankets or soft toys and these remnants called "Third Hand Smoke (THS, Cold Smoke)" endanger in particular children by oral, dermal, and inhalation uptake from house dust, etc. (Neuberger 2018). Even parents omitting contamination of indoor air nevertheless bring toxins and carcinogens to indoor spaces and to their children by clothes, hair, skin, and breath, but the highest contamination is found on

surfaces of rooms used for smoking. From these surfaces toxins are released back into the air and by aging and chemical transformations more toxic pollutants are formed, e.g., residual nicotine from tobacco smoke adsorbed to indoor surfaces reacts with ambient nitrous acid to form carcinogenic nitrosamines. Animal experiments demonstrated numerous effects of THS: hyperactivity, persistent changes in the immune and hematopoietic system, lung cancer, liver damage, increased thrombogenesis, and metabolic effects, including elevated triglycerides, increased LDL, decreased HDL, and insulin resistance through oxidative stress. Estimates of harm from THS are all by inference, since direct evidence of human health problems arising from THS is still missing (Neuberger 2019).

Tobacco cigarettes carry the highest risk for parents and child, but any use of nicotine in pregnancy should be discouraged, because for many of the fetal hazards described above (SIDS, brain development, lung development, etc.) nicotine plays an essential role (Ginzel et al. 2007). Rodent and primate studies found that the effects of maternal SHS exposure on developmental outcomes are comparable to effects seen with isolated nicotine, including effects on number of neurons, neuronal and synaptic damage, and cognitive dysfunction. The motivation to stop smoking during pregnancy should be supported, but nicotine replacement was unsuccessful and has adverse effects on fetal development. Even more dangerous are ecigs without proper control of nicotine dose and problematic additives. Maternal smokeless tobacco use increased rates of stillbirth, low birth weight, and altered the male/female live birth ratio (Ratsch and Bogossian 2014).

Nicotine exposure during adolescence altered development of cerebral cortex and hippocampus and was associated with deficits in working memory, attention, and auditory processing, as well as increased impulsivity and anxiety (England et al. 2017). First nicotine exposure of children is usually by SHS, which could lead to later active smoking not only by imitation of parent's behavior and easy access of cigarettes, but also by providing a molecular basis for later nicotine addiction and possibly other addictions (Kandel and Kandel 2014).

Addiction

Nicotine is a highly addictive drug, by smoking rapidly absorbed into the blood and delivered quickly to the brain, so that nicotine levels peak within 10 s of inhalation, releasing the neurotransmitter dopamine in the brain and activating reward pathways which regulate reinforcement and feelings of pleasure. This happens with every puff in cigarette smoking, but the smoker adapts by increasing nAChRs and as a result needs to increase the number of cigarettes and the depth and duration of inhalation in order to sustain slight, brief euphoria. Even after this euphoria had disappeared completely over the years, the smoker still longs for the next cigarette, which quickly relieves withdrawal symptoms like irritability, craving, depression, anxiety, cognitive and attention deficits, sleep disturbances, and increased appetite. These withdrawal symptoms may begin within a few hours after the last cigarette, quickly driving people back to tobacco use, which has also been learned meanwhile to be

used as a coping strategy for stress and – like in classical conditioning – prompts associations with all kinds of environmental stimuli and things we desire.

Given the rapid rise of nicotine and associated psychoactive effects, smoking of combustible cigarettes allows the smoker to titrate the level of nicotine and related effects during smoking. This makes smoking the most reinforcing and dependence-producing form of nicotine administration. Nicotine products absorbed more slowly are less addictive, but the tobacco industry attempts to achieve a quick rise in brain nicotine concentrations also by other products, e.g., nicotine salts with organic acids like benzoic acid, which make ecigs taste milder, so that users can inhale deeply and reach nicotine levels in blood and brain within 5 min, which are comparable to combustion products. This way ecigs can become a gateway drug into nicotine addiction for young non-smokers, and for smokers ecigs make it more difficult to leave nicotine addiction, frequently resulting in dual use of ecigs and tobacco cigarettes. Replaceable podstyle nicotine cartridges have also become popular ecigs among youth because of efficient nicotine delivery, appealing flavors, sleek designs, ease of concealment, and social media marketing (Lee et al. 2020).

In smokeless tobacco products nicotine is absorbed through mucous membranes in the mouth and reaches peak blood and brain levels more slowly than from inhalation, why they are less addictive. Nevertheless also smokeless tobacco products proved to cause addiction and are most dangerous if combined with tobacco cigarettes. Products for skin application are absorbed much slower, are much less addictive, and should therefore be preferred, if nicotine replacement is needed at all. Only for heavy smokers, fast absorbed nicotine products like a gum are necessary, usually in combination with a nicotine patch, but for a limited time only. Help in smoking cessation is possible without nicotine (varenicline, bupropion, cytisine, etc.) and all pharmaceutical help must be accompanied by professional counseling, because motivation is the most important part in the treatment of smokers.

Though nicotine exerts a priming effect on illegal drug use through global acetylation in the striatum, creating an environment primed for the induction of gene expression (Kandel and Kandel 2014), only a small part of nicotine addicts turn to illegal drugs; however, most persons addicted to marihuana (cannabis), cocaine and similar drugs are also addicted to nicotine and the majority started with nicotine in their career of addictions. These addicts also continue to use nicotine, which may enhance the physiological effects of other drugs.

From animal research, a number of additives in combustible cigarettes and ecigs are known to increase the reinforcing properties of nicotine, e.g., acetaldehyde created by the burning of sugars (added as sweeteners for children) or monoamine oxidase inhibitors (Hogg 2016). Cooling of the smoke like in shisha or adding of aromas like menthol makes deep inhalation easier, resulting in higher nicotine concentration in blood and brain and speeding the transition from occasional to regular smokers.

Guidelines and Regulation on Tobacco Products and Nicotine

The most important guidelines are connected to the WHO Framework Convention of Tobacco Control (FCTC), an evidence-based global treaty signed and ratified by 181 nations and the European Union. This convention was adopted during the 56th World Health Assembly in 2003, entered into force in 2005 and is supplemented by details at regular meetings of the meanwhile 182 parties. A key element is article 5.3, which states that there is a fundamental and irreconcilable conflict between the tobacco industry's commercial interests and public health policy interests. FCTC is raising awareness of international instruments that governments should use to protect tobacco control policies from tobacco industry interference. Politicians and officials need to limit interactions, communications, and contacts with the tobacco industry to those necessary for effective regulation and to make them transparent for civil society. This is an essential prerequisite for reduction of the demand for tobacco (Art. 6, 7), for protection from SHS (Art. 8), for regulation of constituents and emissions of tobacco products (Art. 9) and their packaging and labelling (Art. 11), as attempted in the EU Tobacco Products Directive (TPD) 2014/40/EU. The TPD was a progress for public health limiting the sale and merchandizing of tobacco and related products in the EU, but was weakened because FCTC Art. 5.3 had not been implemented before in member states. Also a comprehensive ban of all tobacco advertising, promotion, and sponsorship (Art. 14) is still missing in many countries and very limited budgets are available for promotion of non-smoking by media campaigns and educational programs (Art. 13), compared to the huge amounts of money the international tobacco industry is investing in direct and indirect tobacco advertising. FCTC also recommends a number of measures to reduce the supply of tobacco, e.g., elimination of all forms of illicit trade in tobacco products (Art. 15). An own protocol on illicit trade tracking, tracing, etc. entered into force in 2018, was ratified by 61 nations meanwhile and details are updated regularly. Youth protection from commercial interests of the tobacco industry and retailers (Art. 16) is still insufficient in many countries and several surveys showed that the age control by tobacconists is insufficient and the electronic age control by vending machines is unreliable (Berger and Neuberger 2020). Unacceptable are also the serious risks posed by tobacco growing to human health and to the environment (Art. 17). Child labor in tobacco growing is aggravated by nicotine poisoning, because during harvesting nicotine of the wet, green leaves gets absorbed through the skin of the children. Common agricultural practices in tobacco farming, especially in low- and middle-income countries, lead to deforestation and soil degradation, agrochemical pollution, destruction of ground water resources, sedimentation of rivers, reservoirs, and irrigation systems, which in turn lead to ecological disruptions that cause a loss of ecosystem services, including land resources, biodiversity, and food sources, all of which negatively impact human health (WHO 2017). All phases of cigarette production, from leaf cultivation through cigarette manufacture to transportation, contribute to environmental hazards and greenhouse gas emission responsible for global climate change. Cigarette butts are toxic waste, endangering playing children, polluting water and air, and finally ending as microplastics in the ocean. E-cigarettes

and their batteries are a new and growing environmental threat, which would need regulation.

Besides FCTC and policy options convened at the "conferences of the parties," there have been a number of other important guidelines from WHO and the World Bank. In 2008, WHO released the strategy MPOWER: Monitor tobacco use and prevention policies, Protect people from tobacco smoke, Offer help to quit tobacco use, Warn about the dangers of tobacco, Enforce bans on tobacco advertising, promotion and sponsorship, Raise taxes on tobacco. The success of the adoption and implementation of MPOWER on national level was analyzed in later WHO reports, in particular on decreasing smoking prevalence and consumption and estimated smoking-attributable deaths (Ngo et al. 2017). As early as 1999, the World Bank published that tobacco tax should be increased to 80% of retailed price and that increase of tax and price, which is the most powerful tool to reduce smoking, should be supplemented by comprehensive advertising bans, smoke-free public places and work places, support of smoking cessation and intensive information on health effects including prominent warning labels (The World Bank 1999). Also later reports of the World Bank came to very similar conclusions.

In Europe, the Tobacco Control Scale of the European Cancer Leagues made use of recommendations by WHO and World Bank, granting a maximum score of 30 for a high average price of cigarettes (adjusted for purchasing power), a maximum score of 22 for smoke-free legislation and enforcement in work places, other public places and private cars, of 13 for comprehensive bans on direct and indirect advertising and promotion of tobacco products and cigarettes, of 10 each for spending on public information campaigns, for large pictorial health warnings with plain packaging, and for smoking cessation support. To reach a total maximum score of 100 also ratification of the Illicit Trade Protocol and compliance with its track and trace system (score 3) and enforced measures to restrict tobacco industry interference (score 2) were necessary (Joossens et al. 2020). Table 1 shows best ranks for United Kingdom, France, and Ireland, followed by Scandinavian countries. It has to be acknowledged, however, that tobacco control is more advanced in several countries outside of Europe, e.g., Australia, where tobacco prices are much higher, nicotine containing fluids are banned for ecigs, and smoking prevalence is much lower than in UK, especially in children. Australia introduced plain packaging in 2012 already.

In Europe, poor tobacco control and lowest progress was seen in Germany, still allowing tobacco advertising on billboards and in cinemas, and smoking is allowed in the hospitality industry in 11 of 14 federal states; in Switzerland hosting the headquarters of the international tobacco companies, probably the cause for the weak tobacco advertising legislation and why this country has not ratified the FCTC; and in Luxembourg, which has very low taxes on tobacco products, in order to attract cross-border shopping from neighboring countries. Prices of cigarettes adjusted for purchasing power are also too low in Central and Eastern Europe (Neuberger 2019a).

Progress in tobacco control was slower in Europe than in Australia or North America and average smoking prevalence is considerably higher. International comparisons of tobacco control legislations including country laws regulating

Table 1 Ranking of Tobacco Control by European Cancer Leagues (Joossens et al. 2020). © Association of European Cancer Leagues. With kind permission

Ranking 2019 (ranking 2016)		Country	Price (30)	Public place bans (22)	Budget (10)	Ad bans (13)	Health warning (10)	Treat-ment (10)	Illicit trade (3)	Art 5.3 (2)	Total (100)
1 (1)	–	United Kingdom	25	22	0	12	9	9	2	1	80
2 (4)	▲	France	22	18	4	11	9	7	2	1	74
3 (2)	▼	Ireland	18	22	1	13	9	8	1	1	73
4 (3)	▼	Iceland	23	17	9	13	4	4	0	0	70
5 (5)	-	Norway	22	17	1	13	8	4	1	0	66
6 (6)	-	Finland	18	18	2	13	5	5	1	0	62
7 (new)		Israel	27	15	1	11	1	6	0	0	61
8 (28)	▲	Slovenia	12	16	2	13	9	6	1	0	59
8 (9)	▲	Hungary	15	21	0	11	5	6	1	-	59
10 (8)	▼	Spain	15	21	1	9	5	5	2	0	58
10 (17)	▲	Belgium	16	16	1	8	9	6	2	0	58
12 (7)	▼	Romania	16	21	0	8	5	6	1	0	57
13 (31)	▲	Greece	18	20	-	7	5	3	1	0	54
14 (9)	▼	Netherlands	14	15	1	9	5	7	1	1	53
15 (9)	▼	Sweden	14	15	0	9	5	7	2	0	52
15 (13)	▼	Italy	15	16	0	9	5	6	1	0	52
17 (9)	▼	Turkey	10	15	0	8	10	6	2	0	51
17 (13)	▼	Malta	16	12	0	11	5	5	2	-	51
17 (23)	▲	Croatia	16	11	0	12	5	5	2	-	51
20 (15)	▼	Portugal	18	11	-	10	5	4	2	0	50
20 (35)	▲	Austria	11	20	0	7	5	5	2	0	50
20 (17)	▼	Ukraine	17	15	-	11	4	3	0	0	50
23 (15)	▼	Poland	14	11	0	11	5	7	1	0	49
23 (26)	▲	Latvia	14	12	2	10	5	4	2	0	49
23 (31)	▲	Czechia	12	15	0	8	5	7	2	0	49
23 (21)	▼	Estonia	13	14	1	11	5	3	2	0	49
27 (19)	▼	Bulgaria	15	11	-	11	5	5	1	0	48
27 (26)	▼	Cyprus	15	10	0	11	5	5	2	-	48
29 (17)	▼	Russian Fed.	8	15	0	13	4	6	1	-	47
29 (28)	▼	Lithuania	12	13	1	10	5	4	2	0	47
29 (23)	▼	Denmark	13	11	2	8	5	7	1	0	47
32 (30)	▼	Slovakia	12	12	-	9	5	6	2	0	46
33 (23)	▼	Serbia	19	11	0	9	1	4	1	0	45
34 (33)	▼	Luxembourg	5	16	0	9	5	7	2	0	44
35 (21)	▼	Switzerland (-1)	13	11	4	2	5	7	0	0	41
36 (33)	▼	Germany	14	11	0	4	5	4	2	0	40

ecigs and HTPs are provided, e.g., by the Johns Hopkins Bloomberg School of Public Health at https://globaltobaccocontrol.org. This site helps to keep up with rapid changes in laws and policies from across 98 countries. This policy bank has been verified by public health professionals in the respective country and is separated into domains so that users can compare various national policies for minimum age, sale, marketing, packaging, product regulation, reporting, clean air, and taxation. Similar comparisons within Europe are made by the European Network for Smoking and Tobacco Prevention at http://ensp.network/. Binding regulations as given in the TPD can be found at https://ec.europa.eu/health/sites/health/files/tobacco/docs/dir_201440_en.pdf and a commentary on its revision at https://tobaccotactics.org/wiki/eu-tobacco-products-directive-revision/.

Even more diverse than the regulation of ecigs and HTPs is the legislation on other nicotine products. Oral tobacco has been banned in the EU except for Sweden, but oral nicotine has not been regulated yet. The problem with nicotine is that it is easily imported and that it can be mixed with just about anything. The historical mistake to sell tobacco products on the free market should not be repeated with other nicotine products. A positive example is Australia, which banned import of vape liquids with nicotine. For buying nicotine you need a prescription. In most countries, however, nicotine products are not subject to pharmaceutical law, but are sold without proper control of dose, additives, etc. and even provided in vending machines, which are not "child-safe" (Berger and Neuberger 2020), disregarding their high addictive potential.

The European Cancer Leagues in 2020 recommended 10 priorities to be fulfilled by all EU member states: to spend a minimum of €2 per capita per year on tobacco control, to implement at least the six World Bank priority measures in line with FCTC (Art. 4, comprehensive tobacco control policy), to address tobacco industry interference in public health policy making (Art. 5.3), to implement significant tax increases for cigarettes, hand rolled tobacco, etc. and a comprehensive smoke free legislation (Art. 8), including private cars carrying minors, to introduce standardized/plain packaging for all tobacco products, to ban the display of tobacco products at the point of sale, to accelerate implementation of tobacco cessation support (Art. 14), to ratify the FCTC Protocol to eliminate illicit trade and adopt tracking & tracing standards, and to invest in research to monitor and measure the effect of tobacco control policies (Art. 20).

The EU allows member states to go beyond the TPD (e.g., by requiring plain packaging) and also Art. 2.1 FCTC states "In order to better protect human health, Parties are encouraged to implement measures beyond those required by this Convention and its protocols, and nothing in these instruments shall prevent a Party from imposing stricter requirements that are consistent with their provisions and are in accordance with international law." Progress in tobacco control in some countries have led to plans of ending the tobacco epidemic completely, often called the "endgame". Usually the envisaged goal is to reduce smoking prevalence to below 5% in the population. Up to now only Bhutan banned tobacco sales and production, however, an increasing number of governments formulated long-term goals. In Finland a strategy was proposed to become not only smoke-free, but nicotine-free.

Denmark's goal in 2016 was: "none of the children born today smoking in 2030." Australia, New Zealand, Sweden, Iceland, Norway, Ireland and multiple other nations might reach this goal in the next decade. Endgame strategies have to build on existing tobacco control measures that have proved effective. In countries where tobacco industry and retailers still influence policy, the phasing out of cigarettes sales will take longer, but should be possible by applying the principles of consumer protection and human rights in a fair and equitable way to halt the sale of a deadly product (Smith and Malone 2019).

Cross-References

- ▶ Designer Drugs and Their Regulation
- ▶ Do Carcinogens Have a Threshold Dose? Pro and Contra
- ▶ Epidemiological Methods in Regulatory Toxicology
- ▶ Examination of Organ Toxicity
- ▶ Extrapolation-Procedures for Carcinogenic and Noncarcinogenic Compounds
- ▶ Nanoparticles and Their Regulation
- ▶ Specific Toxicity Tests for Neurotoxicity, Immunotoxicity, Allergy, Irritation, Reprotoxicity, and Carcinogenicity

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