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# Non-Cigarette Tobacco and the Lung

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**Abstract** Cigarette smoking is known to cause a wide range of damaging health outcomes; however, the effects of non-cigarette tobacco products are either unknown or perceived as less harmful than cigarettes. Smokeless tobacco, cigar smoking, and waterpipe smoking have increased in usage over the past few decades. Some experts believe that their use is reaching epidemic proportions. Factors such as a perception of harm reduction, targeted advertising, and unrecognized addiction may drive the increased consumption of non-cigarette tobacco products. In particular, the need for social acceptance, enjoyment of communal smoking activities, and exotic nature of waterpipe smoking fuels, in part, its popularity. The public is looking for "safer" alternatives to smoking cigarettes, and some groups advertise products such as smokeless tobacco and electronic cigarettes as the alternatives they seek. Though it is clear that cigar and waterpipe tobacco smoking are probably as dangerous to health as cigarette smoking, there is an opinion among users that the health risks are less compared to cigarette smoking. This is particularly true in younger age groups. In the cases of smokeless tobacco and electronic cigarettes, the risks to health are less clear and there may be evidence of a harm reduction compared to cigarettes. In this article, we discuss commonly used forms of non-cigarette tobacco products, their impacts on lung health, and relevant controversies surrounding their use.

**Keywords** Non-cigarette tobacco · Smokeless tobacco · Cigar · Waterpipe · Electronic cigarette

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## Introduction

Smoked tobacco has strong associations with lung disease including development of chronic obstructive pulmonary disease (COPD) and lung carcinoma; increased incidence and severity of childhood asthma; worsening control of adult asthma; an accentuated inflammatory response to respiratory tract infections and increased likelihood of developing infections; and interstitial lung diseases [1–6]. Though cigarettes contain the addictive alkaloid nicotine, many of their adverse effects are mediated through the inhalation of various combustion products of tobacco and the chemicals used in its processing. These include polyaromatic hydrocarbons, *N*-nitrosamines (including tobacco-specific nitrosamines, TSNAs), volatile compounds including carbon monoxide, heavy metals, and radioactive elements [7]. Some of these compounds occur when tobacco is burned, and others are generated during the curing process or through additives to the cigarette [8]. An estimated 45.3 million people, or 19.3 % of all adults (aged 18 years or older), in the USA smoke cigarettes [9]. Cigarette smoking is more common among men (21.5 %) than women (17.3 %). Smoking is the leading cause of preventable death in the USA accounting for approximately 443,000 deaths, one of every five deaths, in the USA each year [7]. While smoking prevalence has declined significantly, it remains unacceptably high in industrialized countries and is increasing in developing countries [10].

Recently, consumers worldwide have moved toward non-cigarette forms of tobacco or tobacco smoking including wet and dry oral tobacco, cigars, waterpipes, and electronic cigarettes. A recent US survey of >3,000 subjects estimates that 13.5 % of adults have tried an emerging tobacco product with 5.1 % reporting having tried Swedish-type smokeless tobacco, 8.8 % waterpipe tobacco, 1.8 % electronic nicotine delivery systems (ENDS) products, and 0.6 % dissolvable tobacco products [11]. Reasons for these trends are not entirely clear, though concerns for smoking-related health effects associated with smoking and perceptions of harm reduction may play a role [12–14]. In developed countries, pressures to alter tobacco use from smoked to

non-smoked forms may come from marketing or public health efforts [15–18]. In developing countries, health misconceptions are a suggested reason for not using cigarettes [19], though far less data on this issue exist. Whatever the reasons people choose non-cigarette forms of tobacco, it is important to understand the epidemiology, health impacts including lung disease, and gaps in knowledge concerning these products. By understanding these issues, health care providers will be better prepared for honest discussions with tobacco users and future research agendas can be shaped.

In this article, we discuss non-cigarette forms of tobacco use. Smoked cigarette tobacco, a major and ongoing public epidemic, is summarized in numerous excellent reviews and is not a focus of the present work. We will focus on common types of smokeless tobacco including American and Swedish forms, cigars, waterpipes, and electronic cigarettes. We present relevant data both supporting and refuting calls that alternative tobacco products confer a "harm reduction" compared to smoking.

## Smokeless Tobacco

### Description

Originally described in the English language in 1683 as a preparation of powdered tobacco for inhaling through the nostrils [20], smokeless tobacco (ST) has been used by humans for thousands of years. Previous forms of ST were prepared as a fine powder and sniffed through the nose (a practice giving rise to the term "anatomic snuff box" referring to the base of the thumb where snuff was placed for sniffing). Currently most ST is not sniffed but kept in the mouth either between the lips and gums or in the side of the mouth between the cheek and the gums. There are many preparations of ST including dry and moist, whole leaf, cut leaf, and finely chopped leaf. Additionally, some ST is placed in a small satchel to prevent direct contact between leaves and the oral surface. The exact constituents of ST vary by geographic region, and different preparations are seen in North and South America, Europe, Asia, the Middle East, and Africa. The Centers for Disease Control and Prevention (CDC) has an excellent description of examples from each region [21]. Each preparation is mainly comprised of tobacco which contains nicotine, and, as such, all are considered addictive.

Two products that are of particular interest are American and Swedish ST. These are the best studied in epidemiologic datasets and cohort studies, and they are central to understanding the argument that ST may serve to reduce harm compared to tobacco smoking. The process of making the two is slightly different. American ST is generally made by fire-curing or baking tobacco leaves, chopping them to some degree, and occasionally adding a flavoring agent. Swedish ST (snus, pronounced "snoose") is air-dried or sun-cured tobacco which is finely chopped, mixed with salts and humidifying agents, and kept very moist. The nicotine content of snus is approximately six times that of cigarettes and higher than typical American ST. Often snus is available in a satchel and kept between the upper teeth and gums resulting in less saliva production and consequently less need to spit. The different processes to make American and Swedish ST may create different levels of carcinogens as heating leaves to dry them may engender more *N*-nitrosamines and oxidative species than air-curing and keeping the ST moist [22, 23]. Many other ST preparations exist with known adverse health effects, though less rigorous data regarding these exist.

### Epidemiology

According to a 2002 CDC report, in 2000 6.5 % of US males and 0.5 % of females over 12 years of age reported using ST regularly [21]. More recent prevalence data from the National Youth Tobacco Survey indicates that adolescent tobacco smoking decreased by 18 % from 2000 to 2007, and that the use of non-cigarette tobacco increased by 33 % for ST and 115 % for cigars [12]. Subgroup analysis demonstrated that despite an overall decrease in smoking, over half of the adolescents who still smoked cigarettes also used some form of non-cigarette tobacco. In surprising contrast to US data, approximately 20 % of Swedish men and 2 % of women use snus daily, often for several hours at a time [21]. ST use among Swedish women is rising. Many more of the Swedish ST users are non-smokers compared to ST users in the USA.

Other worldwide data on ST use come from the WHO's Global Adult Tobacco Survey (GATS), a national household survey based in 16 low-to-middle-income countries [24]. Of the 16 countries, data about ST use are available from 7 of them (See Table 1). Bangladesh, India, and Thailand had the highest overall use of ST, which is consistent with the high number of ST products from these areas. The GATS database is derived from a multi-stage geographically clustered

**Table 1** Smokeless tobacco (ST) use in developing countries according to the GATS survey [24]

| Country | Overall ST use (%) | Male ST use (%) | Female ST use (%) |
|---|---|---|---|
| Bangladesh | 27.2 | 26.4 | 27.9 |
| India | 25.9 | 32.9 | 18.4 |
| Mexico | 0.3 | 0.3 | 0.3 |
| Poland | 0.5 | 1 | 0.1 |
| Thailand | 3.9 | 1.3 | 6.3 |
| Ukraine | 0.2 | 0.5 | 0 |
| Russian Federation | 0.6 | 1 | 0.2 |

design to ensure representative national data. One member of each selected household was surveyed, and prevalence data are based on a limited number of respondents. This may under-represent true ST use. Though ST use in parts of Africa and the Middle East is known to be widespread, accurate prevalence data are sparse. One study estimated that 16.1 % of >4,000 South African women surveyed in a 1998 study used inhaled nasal snuff [25].

## Potential Mechanisms of Lung Injury from ST Use

Exactly how ST mediates lung damage is not well defined, but presumably direct contact of the respiratory epithelium with TSNAs, even when not burned or volatilized, can cause inflammatory changes [26]. This effect is likely more pronounced with inhaled snuff than chewed or sucked (i.e., "dipped") ST, though all cured tobacco ST products contain TSNAs [26–29]. Arimilli and colleagues showed that ST extract caused DNA damage and IL-8 production in cultured human cells [30]. The cytotoxic effect was significantly lower than that of products of tobacco combustion, but cytotoxicity was more pronounced than with nicotine exposure alone. The TSNA *N*′-nitrosonornicotine (NNN) is thought to be a particularly carcinogenic compound produced during the tobacco leaf curing process by a nitrosylating enzymatic reaction of nornicotine through nicotine demethylase. In fact, Lewis et al. report that transgenic tobacco strains with reduced expression of nicotine demethylase levels through an RNA-inhibition produce less NNN and may confer decreased carcinogenicity [31]. NNN is a significant substrate for a variant nicotine acetylcholine receptor located on several pulmonary cell lines including alveolar, neuroendocrine, and mixed primary lung cancer cells [32]. Though most of the data identifying this aberrant nicotine receptor come from smokers, the link between NNN/abnormal receptor and NNN found in ST is intriguing. An older report of multiple bacterial strains found in snuff [33] raises the possibility of chronic exposure to infectious agents as a mechanism for the development of chronic lung inflammation (i.e., chronic bronchitis), though this line of investigation has not continued.

## Lung-Related Problems: Bronchial Obstruction and Chronic Bronchitis

Direct or indirect toxicity to the lung by ST is certainly not at the level caused by smoked tobacco, though there are several clinical associations. Ayo-Yusuf et al. looked at chronic bronchitis associated with inhaled snuff use in South African woman derived from the 1998 South African Demographic and Health Study [25]. Of the 16.1 % of >4,000 women surveyed who used inhaled ST (snuff, not to be confused with snus) regularly, 5.3 % had chronic bronchitis compared to 2.8 % of non-snuff users ($p<0.01$). Additionally, snuff users had lower peak expiratory flow rates (275 vs. 293 L/min, $p<0.01$) and trended towards an increased history of tuberculosis (23.3 vs. 15.9 %, $p=0.06$). Clearly there are potential confounders with these data such as the effects of prior tuberculosis on the development of chronic bronchitis, though the large sample size is highly suggestive of a true association between ST and disease. A study looking at workers exposed to occupational dust in a Nigerian snuff factory showed impaired lung function (mainly pulmonary restriction) and increased symptoms of cough and chest tightness compared to age, weight, and height-matched controls [34].

In 2005, Henley and colleagues examined two US cohort studies, the Cancer Prevention Study I (CPS-I, 1959) and the Cancer Prevention Study II (CPS-II, 1982) to understand the association of a variety of mortality endpoints and ST [35]. CPS-I enrolled 77,407 never-smokers and followed them for a mean of 12 years. CPS-II enrolled 114,809 never-smokers and followed them for a mean of 18 years. The authors compared deaths in those who used (currently or formerly) ST in the chewing or snuff forms to control subjects who never used ST. Results were presented as both age-adjusted and multivariate hazard ratios (HR). In CPS-I death from chronic obstructive pulmonary disease (COPD) was significantly increased in both the age-adjusted and multivariate analyses (HR 2.03 [95 % CI 1.27–3.25] and HR 1.86 [1.12–3.06], respectively). When re-examined in the CPS-II study, death from COPD in ST users was slightly increased over non-ST users, though this did not hold true for multivariate analysis.

## Lung-Related Problems: Lung Cancer

Certainly ST is associated with cancers: in particular oropharyngeal, esophageal, and stomach carcinomas [26, 36]. The association of ST and lung cancer in any form is less clear. Again turning to the 2005 Henley prospective US cohort studies, the risk of death from lung cancer was increased in CPS-II but not in CPS-I [35]. The data from CPS-II show that all-cause mortality was increased in current ST users after adjusting for age (HR 1.29 [95 % CI 1.18–1.40]) and after multivariate adjustment (1.18 [1.08–1.29]). When looking at cancer, mortality was increased for all cancers in ST users (1.19 [1.02–1.40]) and for lung cancer specifically (2.00 [1.23–3.24]) after multivariate adjustment. Interestingly, these associations were true for chewing ST and not for inhaled ST, though the number of subjects who died while using inhaled ST exclusively was low. In contrast, CPS-I did not find a significant association between ST use and cancer death, though all-cause mortality was increased (multivariate HR 1.17 [1.11–1.23]), principally from cardiovascular, non-cancer respiratory, COPD, and digestive system-related deaths. These large,

prospective cohort studies provide compelling evidence of association between ST and lung disease, particularly lung cancer in CPS-II, though there may be several limitations. For example, it is not clear which ST products subjects used in these large studies, and users of multiple types of ST were likely pooled. This may confound the external validity of the results to all forms of ST. Also, unmeasured environmental confounders such as occupational exposures, air pollution, and carcinogenic pesticide use may muddy interpretation. Last, subject recall or reporting bias may undermine associations between ST and lung cancer as the CPS studies were surveys and relied on ICD coding.

Other cohort data emanating from India show an association of intra-thoracic cancer and ST use, though not necessarily lung cancer. In the Mumbai cohort study (MCS), 88,658 males age 35 and older from middle to lower-middle socioeconomic classes were recruited from 1991 to 1997 and followed for an average of 5.5 years [19]. Cancer determination was made based on the Mumbai cancer registry. Approximately 38.6 % population used smokeless tobacco and, of these, 1.4 % ($N$=476) developed any cancer. The HR for developing any intra-thoracic cancer was 1.71 (95 % CI 1.08–2.73), though there was not an increased risk for bronchogenic and lung cancer (1.59 [0.87–2.90]) specifically. The ICD code for intra-thoracic cancers includes nasopharynx, larynx, lung, and mediastinal structures. Though the MCS is a large population study, tobacco use was self-reported and registry data were accessed for the outcomes, all introducing similar biases seen in the CPS cohort studies.

In contrast to the CPS and MCS studies, a large Swedish cohort study of male construction workers assessed the risk of Swedish snus use (a hydrated ST) and oral, pancreatic, and lung cancers [37]. The authors reviewed a large database from 1978 to 1992 including 279,897 construction workers who were seen for at least one clinic visit and provided tobacco use information. They were interested in this group because smoking rates are lower in Sweden than elsewhere allowing isolation of exclusive ST users. Additionally, at the time Swedish snus was being regarded by some advocacy groups as a "harm reduction" product for smokers based on data that fewer TSNAs were present in Swedish versus American ST [38], though this claim was debated [39]. As expected, risks of lung and oral cancers were not increased in the Swedish cohort. However, the risk of pancreatic cancer was increased with a relative risk (RR) 2.00 (95 % CI 1.20–3.30). This was among the first large datasets to support that Swedish ST may reduce the risk of lung cancer compared to smoking, though clearly it is not risk free.

## Lung-Related Problems: All-Cause and Respiratory Mortality

The above-mentioned studies also address the issue of overall mortality associated with ST use. Both CPS studies show an increased all-cause mortality in exclusive ST users after multivariate analysis [35], and data from the Swedish construction workers cohort demonstrated an increased all-cause mortality which appeared to be associated with cardiovascular deaths [40]. Another fairly large Swedish cohort study from Uppsala county, central Sweden, followed over 30,000 participants for about 25 years. A smaller group of 9,976 males from this cohort who smoked, used ST, or both were analyzed for all-cause mortality and mortality due to cancer, cardiovascular disease, or respiratory disease [41]. All-cause mortality was increased in exclusive snus-users [HR 1.23 (95 % CI 1.09–1.40)], but as expected from the other Swedish studies, cancer death risk was not significantly elevated. However, death from respiratory causes in the age >80 group was elevated in ST users who smoked [1.80 (1.20–2.70)] and in exclusive ST users >80 [2.00 (1.20–3.40)]. The subgroup of age >80 was chosen because of a significant interaction between age and respiratory death that did not persist above age 80. The authors remark that excess risk of respiratory death may be due to unmeasured confounding, a required longer cumulative exposure to snus to engender excess respiratory deaths, or older subjects being exposed to ST formulations with larger quantities of TSNAs. Of note, the term "respiratory deaths" was a group of ICD-8, ICD-9, and ICD-10 codes which included many elements of the sino-respiratory tract, lungs, and pleurae making the exact pathological location difficult to discern.

## Controversy Surrounding Snus Use

Lung cancer rates, cardiovascular disease, and tobacco smoking rates are all lower in Sweden compared to other industrialized countries. As indicated above, about 20 % of Swedish men use snus, and snus usage has been increasing among Swedish women [21, 37].

Swedish-style snus has been touted by some groups as a "harm reduction" tool compared to smoking cigarettes [42–45]. Studies and commentaries cite a 95–99 % reduction of most diseases compared to cigarette smoking [42] and the successful use of snus as a smoking cessation product [44]. However, using American ST to quit smoking is associated with an increased mortality compared to quitting tobacco altogether [46]. But the reality of the Swedish and Norwegian experiences and the practicality of recommending snus as a harm reduction tool are far from compatible. Currently no national regulatory agency supports snus for harm reduction, including those in Sweden and Norway. Also, the American Thoracic Society, American Lung Association, American Cancer Society, Centers for Disease Control, US Federal Drug Administration (FDA), and WHO all recommend against using ST including snus, even to help quit smoking. Most groups acknowledge that rates of cancer and all-cause mortality are lower in

snus-users compared to smokers. Concerns center on the uncertain or increased risks of pancreatic cancer and cardiovascular disease, and more recently, type-2 diabetes [37, 40, 47]. Interestingly, oropharyngeal disease (including periodontal disease and cancers) does not show a consistent association with snus use [48, 49].

A 2010 article in the *Journal of the National Cancer Institute* nicely delineates the competing problems which charge the harm reduction debate [50]. On the one hand, snus may lead to increased smoking cessation rates and, consequently, lower attendant health risks. While there are potential risks to snus use (e.g., increased risk of pancreatic cancer), the benefit gained by quitting smoking greatly offsets these risks. On the other hand, a public health effort to promote snus, or any ST, may lead to an increase in snus use among adolescents (even in never-smokers) and an increase in snus-specific health risks. Opponents to the harm reduction argument also suggest that snus use and lower rates of smoking are ingrained in the Scandinavian psyche and would not translate effectively into the US population. They suggest that snus may act as a gateway for dual smoking and ST use. One group modeled the effectiveness of an ST promotion campaign as a part of a harm reduction strategy in the US population [16]. They compared five ST promotion scenarios to a baseline strategy premised on current US smoking prevalence data. Using a Monte Carlo simulation, they concluded that targeting an increase in ST use to decrease smoking would have the same effect as using other methods to decrease smoking in terms of overall harm reduction.

### Conclusions Regarding ST

ST use is widespread in several parts of the world, and all ST products studied contain harmful substances including TSNAs. Inhaled snuff is associated with more direct lung toxicity than is chewed or sucked ST, though non-inhaled ST is associated with a possible increase in pancreatic cancer and cardiovascular effects. Newer formulations of snus utilize air- and sun-curing rather than fire-curing, and modern snus probably contains lower levels of TSNAs than older forms of ST and possibly American ST. Arguments to include snus in a harm reduction strategy center on lower rates of smoking-related diseases in Sweden, and counterarguments center on a persistence of harm with snus use and a less than ideal implementation in the US population.

## Cigar Smoking

### Description

Cigars are made from tobacco rolled in a leaf of tobacco, as opposed to cigarettes which are tobacco rolled in non-tobacco paper. They come in a variety of sizes: large cigars which typically contain >1/2 ounce of tobacco—as much as a whole pack of cigarettes; cigarillos which contain ~3 g of tobacco and no filter; and small cigars which are the size of a cigarette and often contain a filter [8, 51, 52] (See Fig. 1). Small cigars are often flavored with fruit, chocolate, and other essences;

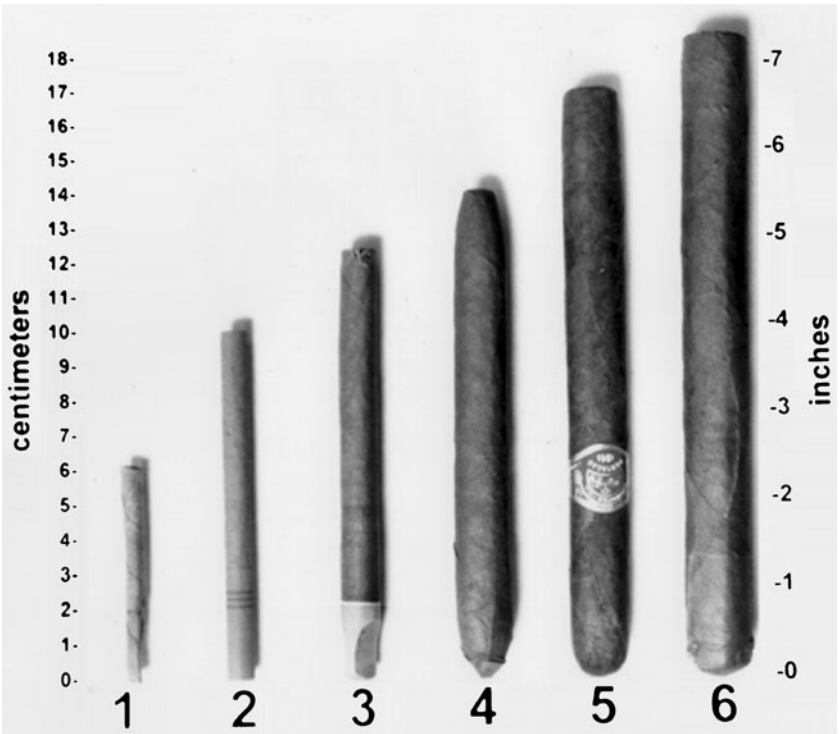


**Fig. 1** Cigars on the US market by size. *1*, hand-rolled "bidi" from India; *2*, little cigar with a filter tip; *3*, small cigar with a plastic mouthpiece; *4*, regular cigar; *5* and *6*, premium-sized cigars. Reproduced courtesy of the National Cancer Institute, ref. [8]

consequently, they may appeal to children and adolescents. Early records of cigars came from the Maya civilization on the Yucatan peninsula in present-day Mexico [8]. Initial cigars were smoked in religious rituals, though in the sixteenth century cigars, and other tobacco, debuted in Europe. Modern cigars are made of either *Nicotiana tobacum* (in North America, Western Europe, and Africa) or *Nicotiana rustica* tobaccos (Eastern Europe, Asia, and South America). Most cigars, regardless of size, contain almost all air-cured and fermented tobacco in various amounts.

## Epidemiology

Though cigars have been smoked for centuries, they made a resurgence in the USA in the 1990s. According to the CDC, 5.4 % of all American adults smoked cigars in 2009 [53]. This was mainly comprised of males (9.1 % males vs. 1.9 % females), and was most prevalent in non-Hispanic blacks (7.7 %), followed by Native American/Alaskan Native (7.2 %), non-Hispanic whites (5.3 %), Hispanic-Americans (4.9 %), and Asian-Americans (1.5 %). Interestingly, the major US manufacturers of cigars are Swisher International and Middleton, which both market small cigars with flavoring that may be particularly attractive to youth and to certain ethnic groups [53–56]. Despite this, though, premium large cigars make up the bulk of cigars smoked in the USA today [57].

Two large tobacco use surveys from California describe cigar smoking prevalence in 1990 and 1996. These data illuminate interesting trends: cigar use increased in younger, more educated, and higher-earning males and females (though overall use in females remained low) [57]. Much of this increase was in never-tobacco smokers who used cigars some days of the week and overall smoked less than 50 cigars. Prior epidemiologic studies included established cigar smokers (i.e., those who had smoked >50 cigars overall), and these studies may have missed the target group in whom current cigar smoking is increasing. Compared to cigarette smoking trends (i.e., decreasing use with educational level attained), the prevalence of cigar smoking is increased in those who are educated and affluent.

In the 2000s, American youth stopped smoking as many cigarettes and turned towards alternative tobacco products including ST and cigars. In 2009 the CDC estimated that 10.9 % of high school students, grades 9–12, smoked cigars [53]. Alarmingly, children in grades 6–8 had an overall 3.9 % cigar smoking prevalence. As described previously, the National Youth Tobacco Survey shows that from 1999 to 2009 there was an 18 % decrease in cigarette consumption by adolescents, and a 115 % increase in cigar smoking [12]. In 2009, over half of continuing adolescent cigarette smokers used some form of alternative tobacco, and over 39 % of these were cigars. Those who smoked both cigarettes and cigars tended to be male and >16 years of age. Non-Hispanic whites were more likely to smoke cigars than Hispanics or Non-Hispanic blacks. Early use of cigars is associated with a propensity to smoke cigarettes later, though cigar use is not as often assessed in adolescent smoking surveys [58]. Unfortunately, under-reporting of cigar use may occur on surveys even when asked, particularly from blacks and youth diagnosed with asthma [59].

Why there has been a resurgence of cigar smoking since the 1990s is not entirely clear. Historically, cigars were smoked early in the twentieth century until the 1920s when cigarette smoking became popular [60]. From the 1930s to 1950s, cigar smoking remained low until reports about the harmful effects of cigarettes and the introduction of small cigars in the 1960s increased cigar sales. Following a ban of cigar ads on television in 1973, cigars again lost favor until 1992. From 1993 to 1997 there was a 50 % increase in cigar consumption which may have resulted, in part, from advertising efforts and high-profile celebrity endorsements of cigar smoking [51, 57, 60]. One of the reasons for increased use, as suggested by multiple authors, is public perception of a decreased risk associated with cigar smoking than cigarettes, perhaps due to lower inhalation depth. DH Jolly suggests that black college students may smoke smaller cigars not only due to perceived status and social acceptance but also because they believe smaller cigars are less harmful than cigarettes [55]. Additionally, the prestige and glamor conveyed by celebrities smoking cigars on magazine covers likely accelerated cigar use in the 1990s and made it socially acceptable [56]. This may explain why younger, more educated, and affluent males had the largest increase in cigar consumption in the 1990s to present.

## Potential Mechanisms of Lung Injury from Cigar Smoking

Like cigarettes, cigars contain over 3,000 compounds, many of which are carcinogenic [8]. In contrast to most cigarette tobacco and like some ST, cigar tobacco is cured *and* fermented. This is the process of drying leaves and then humidifying them to allow bacterial conversion of tobacco carbohydrates to polyphenols and other compounds. The curing and fermentation processes engender N-nitrosation of nicotine leading to TSNAs, including NNN and others [1, 61]. In cigars, these TSNAs are often present in higher amounts than seen in cigarettes because there are more nitrates produced in tobacco during fermentation [62, 63]. Though there is a claim that cigar smokers do not routinely inhale deeply compared to cigarette smokers, small cigars are often inhaled more deeply than large cigars [8]. Alarmingly, even small cigars contain higher levels of TSNAs, and deep inhalation (i.e., that of filtered cigarettes) may expose cigar smokers to more TSNAs than cigarettes.

As with smoking, carcinogenic characteristics of cigar tobacco increase with the duration of time burned/smoked, the width of the burning cone, and the absence of a filter [8]. Additionally, nicotine delivery from cigars compared to cigarettes differs. Due to slow burning time, cigars develop a higher pH than cigarettes, which creates an un-protonated form of nicotine. Un-protonated nicotine, present only in the vapor phase of smoke, absorbs quickly into the oral mucosa [64]. Thus, even if cigar smokers do not inhale deeply, they are still exposed to higher nicotine levels and any untoward effect this may cause.

Like that of cigarettes, cigar smoke causes an array of toxic effects on human cells. Cigar smoke contains high levels of carbon monoxide (CO), especially in sidestream smoke, which leads to elevated levels of carboxyhemoglobin (COHgb) in primary (i.e., only cigar smokers) and secondary (i.e., cigar and cigarette) smokers [65]. Though there are few specific studies, COHbg levels are expected to be increased in secondary cigar smokers compared with cigarette smokers. The elevated CO levels are thought to result from a non-porous tobacco leaf wrapping and less oxygen exposure of the center of the cigar. The health effects of elevated COHgb levels in cigar compared to cigarette smokers has not specifically been studied. In addition, cigar smoke also acts as a likely ciliatoxin [8], a genotoxin [66], and a carcinogen [67]. It is evident that cigar smoke is no safer, and perhaps more harmful, than cigarette smoke.

## General Health Effects

Methodological problems and the fact that cigar smoking is much less prevalent than cigarette smoking make large-scale epidemiologic studies of the health effects of cigar smoking difficult to perform. As cigars come in many different sizes and depth of inhalation varies, quantification of use (i.e., amount smoked) is a particular problem. Despite this, there are abundant data to strongly suggest that cigar-only smoking (and certainly cigar and cigarette smoking) confers substantial health risks. These risks include malignancies of the aero-digestive tract, pancreas, and urinary systems; ischemic heart disease; cerebrovascular disease; aneurysmal disease; and pulmonary disease. Here, we will discuss lung-specific health effects, though keeping in mind that, like cigarette smoking, cigar smoking has protean and widespread effects.

## Lung-Related Problems: Airflow Obstruction

While it is well-established that cigarette smoking increases the risk for COPD, less is known about cigar smoking. In a cross-sectional study, Rodriguez et al. looked at a subset of 3528 subjects ages 48–90 from the Multi Ethnic Study of Atherosclerosis (MESA) who did not have clinical cardiovascular disease—the MESA Lung Study [68]. About 11 % of subjects reported smoking cigars (median 6 cigar-years), and 52 % smoked cigarettes (median 18 pack-years). Cigar smokers had significantly decreased FEV1/FVC ratios (−0.3, $p<0.001$) and reduced FEV1 (−11 mL, $p<0.005$) for each 10 cigar-years. If they were primary cigar smokers, their odds ratio (OR) of airflow obstruction was 2.31 (95 % CI, 1.04 to 5.11); and if they were secondary cigar smokers, the OR was higher at 3.43 (1.75 to 6.71). Depth of inhalation was not reported in this study. Urine cotinine levels were significantly associated implying a dose–response relationship. This cross-sectional study provides powerful association data between cigar smoking and airflow obstruction, though causality cannot be determined.

Several large cohort studies support an association between cigar smoking and COPD. Lange and colleagues looked at 13,584 men and women from 1976 to 1989 in the Copenhagen City Heart Study [69]. They assessed mortality from any cause and specific causes, including COPD. For men, the RR of COPD death was 3.7 (1.1–12) and women 10 (2.3–48) compared to never-smokers. However, compared to cigarette smokers, the risks were lower. When taking depth of inhalation into account, the RR of a COPD death in cigar smokers was the same as cigarette smokers. Another cohort study conducted in Britain failed to show an increased risk of COPD-related death in cigar smokers despite an increase in overall mortality [70]. The CPS-I indicates a trend towards increasing COPD death with cigar inhalation depth, and an increased risk of COPD in secondary cigar smokers [71]. It is unclear how long the secondary cigar smokers smoked cigarettes before cigars, and this may confound interpretation of the increase in COPD death risk.

A large cohort study from the Kaiser Family Foundation followed 17,777 males from northern California who reported no cigarette or pipe tobacco smoking from 1971 to 1976 [72]. Of these, 1,546 men smoked cigars with varying frequency, and these were compared to never-smokers. Women were not included due to the low numbers of cigar-smoking females. The RR of hospitalization for COPD was 1.45 (95 % CI 1.10 to 1.91) and the RRs for coronary heart disease (1.27, 1.12 to 1.45), upper aero-digestive cancers (2.02, 1.01 to 4.06), and lung cancer (2.14, 1.12 to 4.11) were also observed. There was a dose–response relationship for many of these outcomes with outcomes of COPD and lung cancer being significant in subjects who smoked >5 cigars per day. Depth of inhalation was not reported in the study. These data provide strong evidence that cigar smoking is associated with COPD. It does not demonstrate causality, however, because baseline lung function tests were not provided and subjects were smoking cigars at time of enrollment.

In summary, cigar smoking is associated with COPD based on available data, especially the Kaiser and Copenhagen cohort data. There are scant data published regarding the effects of cigar smoke on other obstructive lung diseases such as

asthma. Future studies may need to address these, especially asthma, as cigar smoking is prevalent in younger age groups.

## Lung-Related Problems: Lung Cancer

It is reasonable to assume that most of the health effects attributed to cigarette smoking, including lung cancer, are also caused by cigars. Key differences are that cigarettes generally have a stronger association with lung cancer and cigar inhalation depth corresponds to the risk of cancer.

Some early studies demonstrate a much lower risk of lung cancer in cigar compared to cigarette smokers [73, 74], though several others show an increased rate in both [75–79]. One of the earlier large reports of cigar smoking and lung cancer came from Hammond and Horn in 1958 [80, 81]. The authors followed 187,783 white male subjects ages 50–69 from 1952 to 1955 and ascertained the causes of death of 11,870 men. As expected, there were high rates of death in cigarette smokers from cardiovascular disease and lung cancer. There was an increased rate of death from lung cancer associated with cigar or pipe smoking with a RR of 1.50 compared to non-smokers. This rate was lower than among cigarette smokers. Depth of inhalation and quantity of cigars smoked were not mentioned.

A case–control study performed in Cuba compared cigar smokers to matched hospitalized and local controls who did not smoke (or were not hospitalized for a smoking-related reason) [82]. The OR for lung cancer was 4.4 (2.3–8.2) compared to non-smokers. This risk increased for mixed cigarette and cigar smokers, and there was a trend towards a significant association between inhalation depth and an elevated risk of lung cancer. In another case–control study from Europe, 6920 lung cancer cases were matched to 13,460 controls (again, hospitalized patients for non-smoking-related problems) and the RR for lung cancer in cigar smokers ($N$=37) was 2.90 (2.1–4.0) [83]. This was higher in mixed cigar and cigarette smokers, and the RR increased to 8.93 (6.8–11.1) for those smoking over seven cigars per day. This was one of the early studies to show that reported inhalation depth was increased for mixed cigarette and cigar smokers compared to cigar-only smokers.

Higgins et al. were the first to look at cigar smoking cessation and the risk reduction for lung cancer [84]. Their study examined 2,085 lung cancer cases and 3,948 matched hospital controls. Lung cancer cases had an OR of 3.1 (1.8–5.6) for cigar smoking compared to controls. The OR fell to 2.5 (1.3–4.8) for those who had quit smoking cigars for a year more. When looking at cigarette smokers who quit compared to those who switched to cigars, lung cancer cases were more likely to have switched to cigars. As an example, 10–19 years after changing their smoking habits, the OR of lung cancer cases quitting cigarette smoking was 6.1 versus an OR of 9.9 for those who switched from cigarette to cigar smoking. Further, this study showed that lung cancer was more strongly associated with inhalation versus non-inhalation [OR 12.3 (4.0–37.7) vs. 2.3 (1.4–3.8)] and >10 cigars smoked per day [OR 25.1 (7.2–87.4)].

This was echoed in the 1997 Wald and Watt study looking at the reduction in mortality of cigarette smokers who switch to cigars versus those who quit all together [85]. As anticipated, this study showed that switching to cigars does reduce risks of dying from lung cancer, ischemic heart disease, and COPD. However, the risk of death is elevated compared to smoking cessation, primary cigar smoking (i.e., never having smoked cigarettes), and never-smoking. The authors point out that elevated levels of COHgb in secondary cigar smokers indicates deeper inhalation, and this may contribute to the elevated mortality risk. These conclusions are fully supported by a large multi-European study cohort study [86].

As reported previously, the Copenhagen City Heart Study was a large cohort study which showed a strong association between cigar smoking in both men and women and lung-specific diseases [69]. Lung cancer-specific mortality was increased with an age-adjusted RR of 6.0 (2.2–17) for men and 4.9 (3.0–12) for women cigar-only smokers. When compared to cigarette smokers, lung cancer mortality was reduced in cigar smokers of both sexes. The large CPS-I cohort demonstrated elevated risks of both lung cancer-specific and all-cause mortality in cigar smokers [71]. As detailed in the "Lung-related problems: all-cause mortality" section below, risks for lung cancer mortality increase from primary to secondary cigar smoking, and with depth of inhalation.

Some of the most compelling data linking cigar smoking to lung cancer come from two large cohort studies. In the large Kaiser Family Foundation cohort study, approximately 1,546 of 17,777 men smoked cigars at various frequencies [72]. As stated above, the RR for a diagnosis of lung cancer after multivariate analysis was 2.14 (1.12 to 4.11), which is lower than most reported risks from cigarette smoking. There was a dose–response element to this with the significant association between cigars and lung cancer coming from those who smoked >5 cigars per day. The RR in this groups was 3.24 (1.01–10.4), though there were only three cases of lung cancer in this "heavy smoking" group. Still, this risk is lower than comparable cigarette smoking, but, unfortunately, inhalation depth was not reported. Shapiro et al. looked at the CPS-II dataset to determine lung cancer risk from cigar smoking [87]. They followed 137,243 men who never-smoked cigarettes or pipes and compared those who smoked cigars to non-smokers over 12 years of follow up. The RR for lung cancer was 5.1 (4.0–6.6), and there were increased rates of oropharyngeal cancers (4.0, 1.5–10.3) and laryngeal cancers (10.3, 2.6–41.0) after controlling for age, alcohol consumption, and ST use. These large cohort studies provide strong data for the association of cigar smoking with lung (and other) cancers.

### Lung-Related Problems: All-Cause Mortality

Several lines of evidence detail an increase in all-cause mortality among cigar smokers in population studies. Hammond and Horn described a RR of death in 187,783 white male subjects of 1.20 in cigar and pipe smokers compared to non-smokers [80]. Other large studies conducted in the 1960s and 1970s support increased death rates, though rates were higher in mixed cigar and cigarette smokers and exclusive cigarette smokers [88–90].

Carstensen et al. looked at a Swedish cohort study of >25,000 males from 1963 to 1979 [91]. Cigar smokers were self-identified as cigar-only smokers, though they may have previously smoked cigarettes. The RR of death in the cigar-only group was 1.39 (95 % CI 1.16–1.65), and this was close to the cigarette smoking group, RR 1.45 (1.36–1.54). The number of cigar-only smoking deaths, though, was small at 131. The Copenhagen City Heart Study identified cigar smokers at the time of survey and likely included secondary cigar smokers [69]. RR of death in this cohort of cigar smokers compared to never-smokers was 1.6 (1.3–2.0) for men and 1.8 (1.4–2.2) for women. These RRs were slightly lower than cigarette smokers compared to never-smokers. When cigar smokers were compared to cigarette smokers, there were no appreciable differences in mortality (i.e., both were associated with increased mortality). However, when comparing those cigar smokers who did not inhale deeply to cigarette smokers, RRs of death were decreased in the cigar groups [RR 0.7 (0.6–0.8) men; RR 0.6 (0.5–0.8) women].

A British cohort study looked at primary and secondary cigar smokers to address the question if cigar-only smoking confers a different mortality effect than either mixed cigar/cigarette smoking or cigarette smoking alone [85]. Twenty-one thousand five hundred twenty (21,520) London professionals were followed between 11 and 18 years (mean 14.3), and they were assessed for mortality, COPD, cardiovascular disease, and lung cancer. Regarding mortality, primary cigar smokers actually had no increased risk of death compared to never-smokers after age adjustment. Secondary cigar smokers had a slight increased RR of 1.33 (1.03–1.73) compared to never-smokers, and cigarette smokers had the highest RR of 2.26 (1.97–2.58). Secondary cigar smokers reported inhaling more deeply than primary cigar smokers, and they had higher associated COHgb levels. This study not only indicates that cigar use in former cigarette smokers is deadly, but that depth of inhalation is greater in former cigarette smokers who switch to cigars. Interestingly, overall mortality was not increased in cigar smokers who were not previous cigarette smokers. Two other large British cohort studies support an increased RR of all-cause death in primary and secondary cigar smokers [70, 92].

The largest cigar use dataset with mortality outcomes is from the CPS-I, described previously in the ST sections above. This dataset includes both primary and secondary cigar deaths stratified by age and amount of cigars smoked per day [71]. Primary cigar users made up 3,580/19,667 deaths. The associated risk of death increased based on level of inhalation (ranging from none to deep), with the overall RR 1.08 (1.04-1.11). Secondary cigar smokers made up 1,400/19,667 deaths with an overall RR 1.11 (1.05–1.07). Interestingly, there was no overall increased risk of death with the "none" inhalation level for either primary or secondary cigar smokers. When smokers used both cigars and cigarettes or just cigarettes, the RR of death was significantly elevated regardless of self-reported inhalation depth.

The above studies clearly associated cigar smoking with an increased risk of all-cause mortality. The risk appears to vary with depth of inhalation, and is thus greater for secondary cigar smokers.

### Controversies Surrounding Cigar Use

Unlike ST where the point is controversial, there is broad agreement that cigar use is not an appropriate strategy for harm reduction from cigarette smoking. Even though several studies show reduced rates of lung disease and death in cigar smokers compared to cigarette smokers, the rates are still elevated compared to never-smokers. Even if cigar smokers do not inhale, there are other very significant health risks [71]. Also, studies are quite limited in adolescent populations where small cigar use and, perhaps, increased depth of inhalation may confer the same, if not elevated, risks of lung disease and death as cigarette smoking. In addition, there is evidence that early cigar smoking may increase the propensity for later cigarette smoking [58].

### Conclusions Regarding Cigar Use

There is no doubt that cigar smoking causes a number of the same adverse health effects as cigarette smoking. Key differences between smoking cigars and cigarettes are inhalation depth, nicotine delivery, carbon monoxide formation, and smoking frequency. Some of these factors correlate with lower rates of lung-related problems for cigar smokers compared to cigarettes. However, cigars are not safe and certainly they are not a good alternative to cigarettes. Alarmingly, there is a growing trend of cigar smoking in adolescents and school children, and surveys used to determine cigar smoking prevalence may underestimate true values because of reporting bias in younger populations. In addition, younger groups tend to smoke small cigars which are flavored and often inhaled. Current and future efforts to understand cigar use in younger populations are critical to inform disease prevention efforts.

## Water Pipe Smoking

### Description

Waterpipe tobacco smoking dates back over 400 years and, until recently, was largely restricted to use in Middle Eastern countries, the Arabian peninsula, Turkey, and Northern Africa [13]. There has been a recent increase of waterpipe tobacco smoking in western Europe and the USA, particularly in younger populations. Waterpipes go by many names: argileh, goza, narghile, hookah, shisha, sheesha, and hubbly-bubbly are a few [93]. They consist of a small bowl into which specially prepared tobacco is placed and burned, often by a lump of coal or wood embers. The smoke generated is drawn through a pipe connecting the bowl to a base filled with liquid that is often water or wine. The smoke passes through the liquid into the headspace where it is drawn, by oral suction, into a tube, mouthpiece, and then into a person's lungs (See Fig. 2). The tobacco used in waterpipes (called shisha, Massell, and other names) is almost always flavored with fruit, chocolate, mint, or spices. Waterpipe smoking is often a communal activity; several smokers in a single session pass a mouthpiece from person to person, and these sessions can last much longer than the time taken to smoke a cigarette. Additionally, waterpipe tobacco is considered "smoother" than other forms of tobacco, and as a result smokers tend to inhale deeply [94].

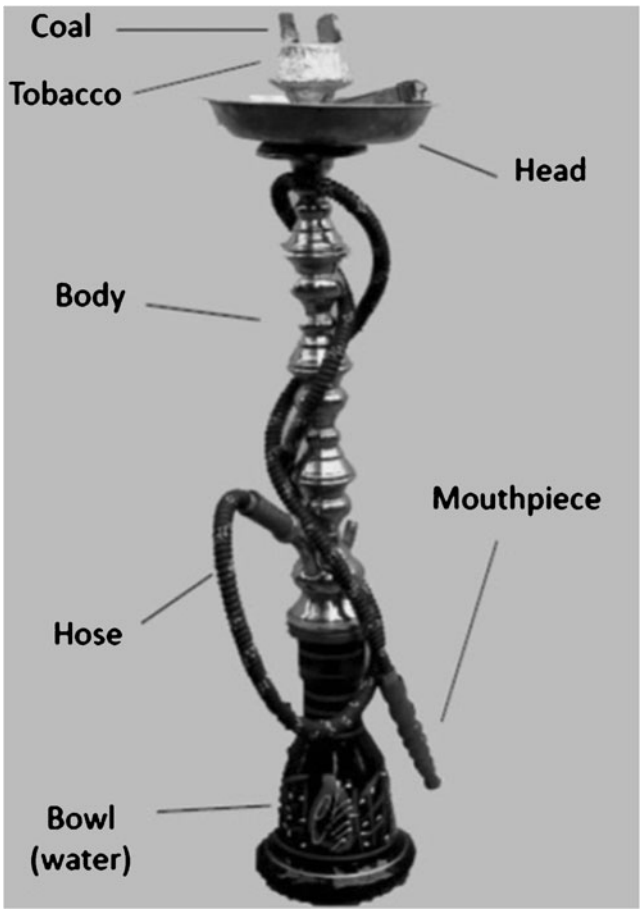


**Fig. 2** Waterpipe picture showing the components described in the text. Reproduced with permission from Oxford University Press, ref. [95]

### Epidemiology

Many authors cite a rapidly increasing use of waterpipes both in the USA and abroad. Maziak, who writes extensively about waterpipe smoking, describes the increasing use as "perhaps … the second global tobacco epidemic since the cigarette," especially among adolescents [94].

Abundant data come from the Global Youth Tobacco Survey (GYTS) about patterns of tobacco use over time in a large number of countries [96]. Adolescents ages 13–15 were chosen by clustering from representative schools in 95 WHO countries and 5 other areas. Response rates to surveys were fairly high as was the percentage of female respondents. The highest rate of waterpipe smoking was in the Eastern Mediterranean region, reaching 34 % among 13–15 year olds (See Table 2). Interestingly, in the GYTS waterpipe smoking did not increase in the USA from 1998 to 2008, though estimates show 10–19.9 % of US boys and 8 % of girls ages 13–15 using tobacco products other than cigarettes, including waterpipes. Other investigators have shown increased use in Pakistan to levels between 17 and 27 % among school-aged children [97, 98] and Australia where 11.4 % of youth smoke or smoked waterpipes [99]. A large report from Estonia reveals a prevalence of 25 % for boys and 16 % of girls ages 11–15 from a national sample in 2006 involving over 13,000 respondents [100]. Alarmingly, but intuitively, waterpipe smoking is a gateway to cigarette smoking among youth as indicated by a Danish study of 762 14–16 year olds [101].

Wapterpipe smoking among school-age youth in the USA and Canada has increased as well [102, 103]. Authors cite increased availability and affordability of waterpipe tobacco as one of the reasons. Chan et al. accessed a large Canadian dataset on smoking habits in Canadian youth, and

**Table 2** Global Youth Tobacco Survey results showing increasing waterpipe tobacco smoking over 10 years among youth (13–15 years old) by geographic region [96]

| Geographic region | Waterpipe smoking increasing (no. of countries) | Total countries surveyed (no. of countries) |
|---|---|---|
| African | 5 | 20 |
| Eastern European | 8 | 17 |
| Americas | 9 | 30 |
| Southeast Asian` | 3 | 6 |
| Western Pacific | 3 | 8 |

they found that prior cigarette smoking and alcohol use were associated with an increased likelihood of smoking waterpipes [103]. US Statewide surveys including large numbers of respondents indicate high usage: 7 % of 12 graders in Arizona, 11 % of Florida high school students, and 9.7 % of New Jersey high school students used or currently use waterpipes to smoke tobacco [102, 104, 105].

Increased waterpipe smoking is very prevalent in university-aged adults, in part reflecting the social nature of the practice. A study of about 550 Jordanian university students found a prevalence of current waterpipe smoking of 42.7 % [106]. In a study involving British university students, 38 % of 937 students surveyed had experimented with waterpipes [107]. Cobb et al. identified that the prevalence of waterpipe smoking in US universities ranges from 7 to 20 %, and Primack and colleagues sampled over 8,000 US university students and identified a 29.5 % ever-use and 7 % current use of waterpipes [108, 109]. More recent prevalence data suggest that concomitant cigarette and waterpipe smoking is fairly common among US university students. In a cross-sectional analysis of smoking among 2,998 university students, Cobb et al. noted a cigarette-only prevalence of 22 %, waterpipe only use of 6.1 %, and combined use of 9.3 % [110]. It is unclear based on the nature of the study if waterpipe use potentiated cigarette consumption. A recent review of literature regarding US college students indicates that one in five students has used or currently uses waterpipes [111]. Consequent to increased waterpipe smoking among young people, or perhaps in parallel with the social phenomenon, hookah lounges are increasing around US universities [94].

A central question regarding the increased prevalence of waterpipe smoking is what fuels it? Clearly waterpipe tobacco contains the addictive substance nicotine [112], but why is the practice increasing when cigarette smoking is on the decline? There are probably several reasons waterpipe smoking appeals to youth [113]. First, the practice is inexpensive and involves flavored tobacco. As with flavored cigar smoking, it is clear that youth prefer tobaccos that do not have a strong tobacco taste. Next, many younger waterpipe smokers falsely presume that the water that filters the tobacco smoke makes it less harmful [114] (see section on "Potential Mechanisms of Lung Injury from Waterpipe Smoking" below). Primack et al. surveyed 647 US university students, of whom 40.5 % smoked waterpipes, to identify perceptions of harm [115]. Of the smokers, 52.1 % perceived that waterpipe tobacco smoking was less addictive than cigarette smoking. In an adjusted multivariate model, waterpipe smoking for 1 year was associated with low perceived harm (OR 2.54, 95 % CI 1.68 to 3.83), low perceived addictiveness (4.64, 3.03 to 7.10), perception of high social acceptability (20.00, 6.03 to 66.30), and high perception of popularity (4.72, 2.85 to 7.82).

In contrast, other studies have demonstrated that waterpipe smokers know about associated health risks, but they choose not to stop smoking. Ahmed et al. surveyed 50 students in the San Francisco Bay Area about their perceptions of waterpipe smoking [116]. Though 88 % of smokers knew of the risks, over half, 52 %, did not intend to quit. This alarming trend may relate to the invincibility of youth, though it is in direct opposition to trends with cigarette smoking. Wray and colleagues looked at survey data from 67 young adults about their perceptions about tobacco use [117]. Most were familiar with alternative tobacco products including ST and waterpipes, though there was wide disagreement about the harms of such products. Interestingly, if participants resided in a state with smoke-free policies, there was less disagreement about risk. Sutfin and colleagues examined 3,770 college students in North Carolina to assess factors associated with waterpipe smoking [118]. Among the 40 % of students who were ever-smokers and the 17 % current smokers, associated factors included male sex, freshman status (younger), other risk behaviors (cigarette smoking, marijuana use, and other illicit drugs), a belief that waterpipe smoking is less harmful, and having access to a hookah bar. These data underscore the need for a concerted and focused public awareness about waterpipe smoking.

The above epidemiologic data illustrate that despite overall decreasing rates of cigarette smoking, waterpipe tobacco smoking is increasing in many world regions, particularly among young smokers. This increase is fraught with misperceptions about harm, and in some cases, disregard for the damaging effects of waterpipe tobacco smoking. As with ST and cigars, waterpipe smoking at an earlier age may predispose to cigarette smoking later, though more study in this area is needed. In sum, waterpipe smoking is prevalent, on the rise, particularly affects younger people, and should stimulate aggressive public health efforts to educate the public.

## Potential Mechanisms of Lung Injury from Waterpipe Smoking

Since waterpipe tobacco is burned and the smoke is inhaled, it is reasonable to assume that waterpipe smoking has many of the same cytotoxic and carcinogenic effects as smoking cigarette tobacco. Unfortunately, this has not been well studied. In 2003, Shihadeh et al. described the components of mainstream waterpipe smoke derived from a smoking machine [119]. Although the nicotine content from a single aliquot of waterpipe smoke was lower than cigarette smoke, nicotine-free dry particulate matter was similar. Interestingly, levels of arsenic, chromium and lead were higher. The authors suggest that characteristic particulates derived from the heating process are difficult to predict given the extreme temperature gradients from the tobacco burning site and the water through which the smoke is "filtered." Later work

demonstrated many similar compounds in waterpipe smoke as in cigarette smoke: polycyclic aromatic hydrocarbons (PAH), nicotine, CO, VOCs, and chrysene, phenanthrene, and fluoranthene, the latter of which are known carcinogens [120, 121].

Many of the harmful compounds in mainstream waterpipe smoke have also been identified in sidestream smoke [122]. Though data are nowhere near as abundant as for cigarette or cigar smoke, the specter of environmental tobacco smoke from waterpipes leading to harm is becoming clear [121, 122]. The charcoal used to heat the tobacco may lead to many of the dangerous chemicals and VOCs seen in waterpipe sidestream smoke [123]. Cobb et al. performed an interesting study assessing the fine particulate matter in hookah cafés and in restaurants that allow cigarette smoking [124]. They identified that the PM(2.5)—the measure of particles 2.5 μm or smaller, as would be produced in tobacco smoke—was highest in waterpipe smoking rooms (PM[2.5]=374 mcg/$m^3$) followed by waterpipe café non-smoking rooms [PM(2.5)=123], cigarette smoking rooms [PM(2.5)=119], non-smoking rooms in cigarette-permitted restaurants [PM(2.5)=26], and lowest in smoke-free restaurants [PM(2.5)=9]. Other studies support the increase emission of small-sized particulate matter in waterpipe smoke compared to cigarette smoke [125].

Nicotine and smoke-product delivery is efficient in waterpipe smoke as demonstrated by Mazak et al. in 2011 [126]. The investigators measured nicotine levels and exhaled CO in 61 waterpipe smokers after a washout period. They noted that after one smoking session, plasma nicotine increased 5-fold and correlated with session time, puff duration, and total smoke inhalation. Alarmingly, exhaled CO increased from 4 to 35.5 ppm, which is significantly higher than the boost seen from a cigarette. Elevated urinary PAH levels have also been reported after waterpipe smoking indicating an efficient systemic absorption of smoke products [127]. Other work supports 3–9 times the CO and 1.7 times the nicotine exposure from waterpipe smoking compared to cigarette smoking [128, 129]. Unlike in cigars where CO production is a function of non-porous leaf wrapping and poor oxygen exposure, CO production in waterpipe smoke may come from the charcoal used to heat it [130].

The cellular effects of waterpipe smoke exposure have been studied in limited quantities. An early study by Yadav and Thakur in 2000 assessed the effects of waterpipe smoke on somatic cells of 35 hookah smokers compared to age, sex, socioeconomic, and drug intake-matched controls [131]. They found an increase in mitotic index, chromosomal aberrations, sister chromatid exchanges, and satellite associations in smokers compared to controls (each $p<0.01$). Additionally, there was a dose–response relationship to the degree of cytologic abnormality. Other studies have shown that micronuclei in buccal mucosal cells in waterpipe smokers are increased—a measure of tobacco-related toxicity [132], and lymphocytes sustain higher levels of sister chromatid exchanges when waterpipe-smoke exposed [133]. In a model of waterpipe tobacco smoke condensate exposure, Rammah and colleagues showed accelerated cell cycle arrest and cellular senescence mediated by the p53-p21 pathway in exposed type II pneumocytes [134]. In this model there was increased expression of matrix metalloproteinases MMP-2, MMP-9, and Toll-Like Receptor-4, all of which are implicated in COPD pathogenesis.

Though the evidence linking waterpipe tobacco smoke to cellular damage is limited to small studies, available data support a connection. Waterpipe smoke contains harmful chemicals; some of these chemicals are absorbed and excreted; and there is both in vitro and in vivo evidence of cytologic changes in several cell lines.

## General Health Effects

Unlike cigarettes, cigars, and ST, waterpipe tobacco smoking has not been extensively studied. Since waterpipe smoking was, until recently, mainly performed in rural eastern Mediterranean and Middle Eastern countries, its adverse health effects have not been closely evaluated. Beginning in the late 1990s and early 2000s, waterpipe smoking has exploded as an alternative tobacco product mainly consumed by youth and young adults.

In 2010, Akl and colleagues performed a meta-analysis of 10 studies selected from 23 reports in a systematic review pertaining to the health effects of waterpipe smoking [95] The authors used Cochrane criteria to select appropriate studies, and they graded the quality of the studies according to the GRADE system. Overall, the meta-analysis identified that there are few quality studies assessing health outcomes in waterpipe tobacco smokers. With respect to non-lung processes, they found a significant increase in periodontal disease (OR 3–5, $p=0.001$) and alveolar osteitis ("dry socket"; OR 3.7, $p=0.001$); low birthweight (OR 2.12, 95 % CI 1.08–4.18) and newborn lung problems (OR 3.65, 1.52–8.75); and a trend towards infertility. All studies were judged to be of low quality, and very few studies were included in each category.

More recent studies have looked at the cardiovascular effects of waterpipe smoking. Cobb et al. evaluated heart rate variability (HRV) in response to waterpipe smoking [135]. A loss of HRV is associated with adverse cardiovascular outcomes, and the authors designed a cross-over study among 32 subjects who smoked either tobacco or a tobacco-free product through a waterpipe. Tobacco smoking produced increases in plasma nicotine, blood pressure, and heart rate (all $p<0.01$), and both tobacco and the non-tobacco product increased exhaled CO and reduced HRV ($p<0.01$). Hakim et al. assessed a variety of parameters after

45 subjects smoked from a waterpipe for 30 min [136]. Compared to baseline, waterpipe smoking significantly increased blood pressure (systolic, 119.52±12.07 mmHg versus 131.98±17.8 mmHg; diastolic, 74.84±7.89 mmHg versus 82.98±12.52 mmHg; both $p<0.001$) and heart rate (80.39±9.92 beats/min to 95.59±17.41, $p<0.001$). In addition, there was a significantly increased COHgb level after smoking which was mostly in the female group. These studies are some of the first to show a negative impact of waterpipe smoking (regardless of product smoked) on the cardiovascular system.

## Lung-Related Problems: Airflow Obstruction

As they both involve inhalation of tobacco, it is reasonable to assume that waterpipe smoking would engender similar lung-related problems as cigarette smoking. However, there are few studies to support this. Raad and colleagues performed a Cochrane-based systematic review and meta-analysis on waterpipe smoking and lung function [137]. The authors compared waterpipe smokers to non-smokers and cigarette smokers, and they reported standardized mean differences (SMD) in lung function (FEV1, FVC, and FEV1/FVC ratio) from the pooled results. Though the meta-analysis involved only six cross-sectional studies, there was significantly lower lung function in waterpipe smokers compared to non-smokers in terms of FEV1 (SMD −0.43 L, 95 % CI −0.58 to −0.29; equivalent to a 4.04 % lower FEV1). There were non-significant but trending reductions in FVC and the FEV1/FVC ratio. Compared to cigarette smokers, waterpipe smokers had similar reductions in lung function. Though the cross-sectional nature of the component studies precludes determination of causality, the pooled results strongly implicate waterpipe smoking in the development of COPD.

In the study by Hakim et al. cited above, the authors also evaluated the short-term effects of waterpipe smoking on lung function and lung inflammation [136]. After smoking from a waterpipe, the mean results from 45 subjects showed significant decreases in FEF 25–75 % (mid-expiratory flows), PEFR, FENO, and 8-isoprostane levels in the exhaled breath condensate. Again this supports the link between waterpipe smoking, lung inflammation, and airflow obstruction.

More recent data derived from a large telephone-based survey in the Middle East and North Africa assessed smoking habits and determinants of lung disease [138]. Of the 61,551 respondents who provided useable data, 2,173 were waterpipe-only smokers and 42,923 were non-smokers, the rest being cigarette or combined smokers. The ORs adjusted for cigarette smoking showed an increase in productive cough (OR 1.29, 95 % CI 1.09–1.51), chronic bronchitis (1.42, 1.12–1.80), and breathlessness (1.18, 1.04–1.34) for waterpipe smokers. Standard epidemiologic definitions for chronic bronchitis were used and lung function was not measured. Salameh et al. performed a case–control study in Lebanon (274 cases, 559 controls) to determine if waterpipe smoking was associated with chronic bronchitis [139]. This survey-based study showed that previous waterpipe smoking (OR=6.4), previous mixed cigarette and waterpipe smoking (OR=38.03), and current mixed smoking (OR=7.68) were significantly associated with chronic bronchitis ($p<0.001$ for all). Curiously, current exclusive waterpipe smoking was not associated with chronic bronchitis (OR=1.87, 95 % CI 0.74–4.72), though current waterpipe dependence (defined as a high score on the authors' independently validated Lebanese Waterpipe Dependence Scale) was significantly associated with chronic bronchitis (OR=3.74, $p<0.001$). After adjustment for confounders, ever waterpipe smoking >20 waterpipe-years was significantly associated with chronic bronchitis ($p<0.001$).

The above evidence supports a link between waterpipe smoking and obstructive lung disease, namely COPD and chronic bronchitis. Though the studies are survey based and meta-analyses and, as such, have inherent flaws, the data provide a compelling platform to justify larger studies. At the very least, questions about waterpipe use should be included on any longitudinal tobacco use study, especially pertaining to younger people.

## Lung-Related Problems: Lung Cancer

One of the earlier reports of waterpipe smoking and its relation to lung cancer came from a small study in India [140]. The authors examined cases of lung cancer and identified that 22 of 25 cases smoked waterpipes (called "hukkah" or "Indian hubble bubble"). This is one of the first reports to acknowledge that waterpipe smoking has carcinogenic potential. In the systematic review by Akl et al., lung cancer was addressed in six studies of low to very low quality [95]. Five of the studies were a case–control design and involved tobacco which was un-processed. This is important because most of the tobacco used in waterpipes today is processed, making generalization of the results difficult. Nevertheless, the pooled risk for waterpipe smoking in lung cancer cases was increased (OR 2.12, 95 % CI 1.32–3.42) and the relative risk of mortality from lung cancer was elevated (RR 4.39, 3.82–5.04).

More recently, Koul and colleagues assessed 251 lung cancer cases and 500 age-matched controls [141]. They identified an almost sixfold increase of hookah-smoking in cases compared to controls (OR 5.83, 95 % CI 3.95–8.60). Though there are several limitations to this study, namely controlling for other potential exposures, the results are intriguing.

Though data showing causality between waterpipe smoking and lung cancer are scant, the biologic plausibility of such a connection is logical. As addressed by Maziak,

"waterpipe smoking bears all the signs of burgeoning global epidemic with grave outlook for tobacco-related morbidity and mortality" [142].

### Lung-Related Problems: Infections

One of the concerns of waterpipe smoking is that it is a social practice which involves sharing smoking equipment in a confined space, thus, potentially exposing people to communicable infectious diseases [94]. Data substantiating this are minimal, though some do exist. A Danish study looked at public health data from Storstroem County where there was an increase in tuberculosis starting in 1990 [143]. The investigators found that contacts of TB-infected patients were more likely to be infected if they shared a waterpipe than if they were simply a household contact. Whether this infection risk is due to sharing smoking equipment, volatilization of mycobacteria, or immunologic derangements is unclear, though it is in-line with reported data of increased risk of tuberculosis infection in cigarette tobacco smokers [1]. Regarding fungal infections, a case report of a 46-year-old man with acute myelogenous leukemia who smoked mixed tobacco and marijuana from a waterpipe linked his death from an overwhelming *Aspergillus* infection to waterpipe smoking [144]. These data address concerns that waterpipe smoking may carry a risk of infectious disease transmission.

### Public Health Concerns and Controversies

As detailed above, waterpipe smoking is increasing among young people. This may be fueled by nicotine addiction, though there appear to be unique social aspects to waterpipe smoking that add to its appeal. People perceive waterpipe tobacco smoking as less harmful than cigarette smoking [113, 114, 118]. There are false beliefs that the water that filters the tobacco smoke renders it less harmful, and the smoothness of the smoke seems to belie its risk. Also, tobacco smoke is not the only substance inhaled since it is known that the charcoal used to heat the tobacco also emits chemicals during its combustion [123]. Unfortunately, it is unlikely that most young smokers are aware of this fact. Second, waterpipe smoking requires prolonged, deep inhalation (>500 mL per puff) to keep the tobacco lit, and the smooth smoke facilitates such inhalation [128, 145]. This may expose young smokers to more noxious particles in deeper portions of the lung. Whether this translates to increased rates of lung cancer and COPD for a shorter duration of exposure compared to cigarettes remains unclear. Additionally, if waterpipe exposure is one of the first modes of tobacco smoking in young people, this may potentiate cigarette smoking later [94]. Third, waterpipe tobacco is accessible, especially around universities where hookah bars concentrate [118]. Regulations appear to be less stringent regarding waterpipe smoking compared to cigarette smoking, and future public health efforts should focus on informing the public of the harms of waterpipe tobacco and reducing waterpipe access among minors.

In sum, it is clear that there is a long way to go regarding education and regulation of waterpipe smoking. Though the issue is complex and beyond the scope of this review, we have some general recommendations. One is targeted education to youth in whom waterpipe smoking is most prevalent. To do this, public health professionals will need to understand the unique aspects of waterpipe smoking (image, social contexts, and misperceptions of harm) [94]. To date, there is some evidence that targeted education may lead to reduced waterpipe smoking [146]. This education should be coupled with tighter regulation of waterpipe tobacco including clear labeling of risks, enforcement of smoking bans in restaurants and bars, and restricted access to waterpipe tobacco.

### Conclusions Regarding Waterpipe Use

Though the data are not as abundant for waterpipe smoking as for cigarettes, cigars, and ST, waterpipe smoking is emerging as a deadly trend in tobacco smoking. Available evidence shows all the necessary ingredients for a harmful practice including volatilized carcinogens and cellular toxins in both mainstream and sidestream smoke; evidence of cytologic damage and precursors to malignancy; and prospective clinical data showing effects of waterpipe smoking on lung function. Though many more studies are needed, perhaps it is time to amass the available data and work towards educational and policy changes.

## Electronic Cigarettes

### Description

Electronic cigarettes are defined by the tobacco industry as electronic nicotine delivery devices, or "ENDS", and they have been on the market since 2007. Numerous manufacturers market ENDS, but the devices share key design features. They utilize a battery-operated heating device that vaporizes a nicotine-containing solution from a replaceable cartridge in a process triggered by the pressure drop that occurs when the user inhales from the device. They resemble cigarettes, and, in addition to providing nicotine in inhaled form, replicate some of the behavioral aspects of cigarette smoking (see Fig. 3). Cartridges come with varying concentrations of nicotine, and refill solutions containing large amounts of nicotine are available [147]. The most common vehicle in which the nicotine in such cartridges is contained is propylene glycol, though other chemicals may be used. The efficiency of systemic nicotine delivery with the e-cigarette is highly variable [148] and the pharmacokinetics of nicotine delivery appear to more closely

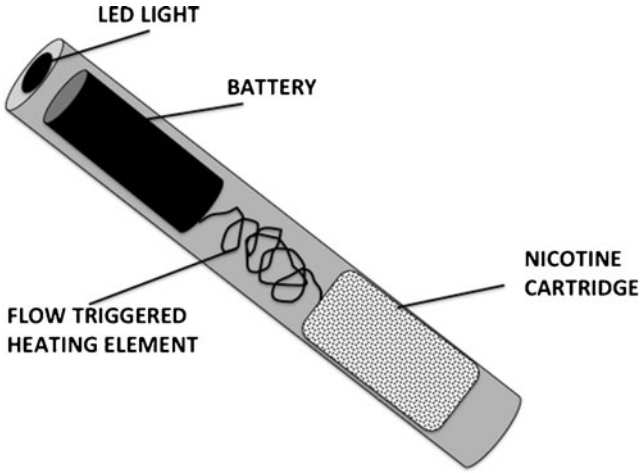


**Fig. 3** Typical E-cigarette device. Represented are the basic mechanics of most e-cigarette devices. The individual places their mouth on the end containing the nicotine solution. The flow created triggers activates a heating element that in turn vaporizes the nicotine-containing cartridge producing a vapor that is inhaled by the user. Each inhalation attempt also activates an LED light that gives the visual impression of a typical cigarette

resemble those of nicotine replacement therapies than that of cigarettes [149]. ENDS are marketed as a "safer cigarette," but many use the product as a bridge to quitting smoking. Some manufacturers flavor the ENDS products.

## Epidemiology

Users of ENDS tend to be former or current smokers who choose ENDS for a variety of reasons, including markedly reduced cost compared with cigarettes, the ability to use the devices in settings in which cigarette smoking is prohibited, curbing nicotine cravings, and perceived lower toxicity compared to traditional tobacco cigarettes [150]. Given the relatively short time that ENDS have been available, long-term patterns of use are not clear, and it is plausible that as with cigarettes and other forms of nicotine, some users will use the devices for prolonged periods. ENDS appear to be most commonly used by current smokers as an alternative to cigarettes rather than cessation tools, though some ENDS users do reduce or eliminate cigarette use [151].

There has been some concern that these devices may be the first nicotine product young people would try because of the unique technology of the device itself. Once introduced to nicotine, the user may then move on to the more traditional cigarette. Studies aimed at looking at the awareness of the e-cigarette among adolescents and young adults have discovered that the majority have heard of ENDS but only 1–7 % reported that they had tried them before [152, 153]. In these same studies, the researcher did find that the participants that we willing to try ENDS or had tried ENDS were more likely to do so if they were already smoking traditional cigarettes, were male or had friends who smoked traditional cigarettes. In one European study, however, the use of ENDS among 15–19-year-old high school students was almost 25 % and, similar to the American surveys, more common among previous tobacco users, males, and those who live with cigarette smokers.

## Potential Mechanisms of Lung Injury from ENDS Use

An e-cigarette vaporizes nicotine and vehicle solutions that contain propylene glycol and glycerin so the pathogenic effect of e-cigarette would be derived from the vapor aerosol of these substances. Studies have established that nicotine from an e-cigarette is systemically absorbed to a similar degree as a traditional tobacco cigarette [154]. These studies have demonstrated that nicotine is absorbed systemically in both active and passive e-cigarette smoking sessions. However, the effect of active and passive e-cigarette smoking had no effect on complete blood count markers which was statistically different than active and passive tobacco cigarette smoking [155]. The e-cigarette produces ultrafine particulate matter (PM) but when compared to traditional tobacco cigarettes it is statistically much less [156]. A recent study looked into the concentration of pollutants compared to the traditional tobacco cigarette. Pollutants included VOCs, carbonyls, PAHs, nicotine, TSNAs and glycols, all of which were found to be clinically insignificant amounts for the e-cigarette and "significant risk" amounts for the traditional cigarette [157].

## Lung-Related Problems

There have been very few studies that have focused on the acute effect of e-cigarettes on lung function and virtually no studies that have evaluated the long-term effects of these products on lung function. In a study on the short-term effects of e-cigarettes on lung function, Vardavas and colleagues demonstrated that a 5-min e-cigarette session increased respiratory impedance and respiratory resistance with a drop in exhaled nitric oxide that was significantly different from baseline [158]. A more recent study showed no difference in the degree of airflow obstruction as measured by FEV1/FVC ratio after active and passive smoking of on an e-cigarette [154]. Studies to evaluate the long-term effect of e-cigarettes on lung function particularly in people with preexisting lung disease have not been performed.

## Public Health Concerns and Controversies

The biggest controversy around the e-cigarette is how they should be regulated. Currently, the FDA regulates e-cigarettes as nicotine delivery devices, the same way they regulate tobacco cigarettes. There was a push to regulate e-cigarettes marketed for therapeutic purposes as drug delivery devices,

the way the nicotine patch or nicotine gum is regulated [159]. However, since most sellers of these products are careful not to make therapeutic claims, the devices are largely unregulated in the USA. This has been the source of debate and controversy, with some groups advocating less regulation and others raising concern over unproven safety. Recently, the CDC reported that the use and awareness of the e-cigarette is on the rise. Their report, published in "Nicotine and Tobacco Research," highlights that the e-cigarette can be a tool for smoking initiation, that many companies indirectly market these products for cessation without proof of efficacy, and that there may be adverse effects from the chemical products present in the e-cigarette vapor that need to be studied [160]. There have been no large-scale studies on the efficacy of the e-cigarette as a smoking cessation aid but a few smaller studies have attempted to evaluate their potential. A recent study focused on the smoking habit of 14 smokers with schizophrenia. The researchers monitored smoking cessation over the course of 1 year. There was 50 % reduction in total cigarettes with 2 of the 14 patients staying abstinent for the entire 52 weeks. There were no adverse effects on the patient's schizophrenia symptoms [161]. However, without more substantial evidence of efficacy as well as more extensive analysis of safety, it is currently difficult for physicians to comment on e-cigarettes for their patients.

### Conclusion Regarding Electronic Cigarette Use

The e-cigarette is gaining popularity in the general population. The likelihood of using the e-cigarette is associated with having previous contact and exposure to tobacco. There are chemical byproducts from the e-cigarette that differ from the traditional tobacco cigarettes. The safety of firsthand and secondhand exposure to these byproducts has not fully been established but small preliminary studies suggest that their safety profile is favorable compared to traditional tobacco cigarette. The delivery of firsthand and secondhand nicotine is similar to that of the traditional tobacco cigarette. There is enthusiasm surrounding the potential of the e-cigarette to be used a cessation aid but studies evaluating their efficacy and safety are not available. It is reasonable to hypothesize that an increase in the use of the e-cigarette could significantly reduce the use of traditional tobacco cigarettes; however, it is equally reasonable to be concerned that the e-cigarette could be used to initiate the user to tobacco product consumption. Oversight focused on establishing the safety profile and efficacy as a smoking cessation aid is needed and appropriate.

## Overall Summary and Conclusions

Non-cigarette forms of tobacco have gained popularity in the past few decades, though users do not appear to fully understand their health risks. The increased use of these products is fueled by many factors. First, people may choose non-cigarette tobacco products due to a perception of harm reduction. This may be true for e-cigarettes and snus compared to cigarette smoking, though each may have other, unappreciated, health risks. Clearly, cigar and waterpipe smoking do not confer a harm reduction compared to cigarette smoking. Second, users of non-cigarette tobacco products may be swayed more by cultural or social aspects than health risks. Cigar smoking is a good example of how targeted advertising can encourage smoking. Waterpipe smoking carries with it the allure of a convivial and highly social practice, one to which young people are particularly susceptible. Third, non-cigarette tobacco products are often addictive and evidence supports that they may potentiate cigarette smoking, especially in the cases of ST, cigar, and waterpipe smoking, and possibly in the case of e-cigarettes.

If some non-cigarette tobacco products truly reduce harm compared to cigarette smoking, then efforts should focus on a detailed risk–benefit analysis to prepare healthcare providers for accurate, rational conversations with patients who smoke cigarettes. If, however, some non-cigarette tobacco products are as harmful as cigarettes, then efforts to increase public awareness should increase. Either way, non-cigarette tobacco products are used by many people in the USA and abroad, and they deserve intensive study to ensure public safety.

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