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Review

The Current Status of Cigarette Smoking and Air Pollution Associated Lung Cancer

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Abstract: Cigarette smoking and air pollution (particulate matter) are recognized as two major etiological factors for lung cancer. Of all the risk factors, cigarette smoking is significantly associated with lung carcinogenesis. The main mechanism lies in the metabolically activated carcinogens (majorly polycyclic aromatic hydrocarbons and nitrosamines), which could covalently bind with DNA molecules and lead to irreversible mutations in pivotal cancer genes, such as *TP53* and *KRAS*. Another major etiological factor for lung cancer is air pollution, which is with complex compositions and ubiquitous in daily life, especially in developing countries as China and India. The latest literatures on lung cancer epidemiology and etiology have been briefly summarized and reviewed in this work

Keywords: lung cancer; cigarette smoking; air pollution; epidemiology; etiology

1. Introduction

Cancer is a leading cause for death worldwide, accounting for nearly 10 million deaths in 2020. Specially, lung cancer is one of the most common types of cancer and imposes a huge health burden for humans (1). The five-year survival of lung cancer patients in the United States and developing countries were only 14% and 8%, respectively (2). There are many verified risk factors responsible for lung carcinogenesis. Etiologically, it is believed that cigarette smoking (CS) and extensive air pollutions are the two major risk factors for lung cancer.

The cultivation of the tobacco plant has a very long history that stretches back to 6,000 BC in the Americas. It was thought that tobacco smoking was primarily performed in religious ceremonies and also used for medical purposes in the ancient indigenous American tribes circa 1 BC. In 1912, Adler proposed that CS might be associated with the growing incidence of lung cancer (3). In 1964, the U.S. Surgeon General definitively announced that CS causes lung cancer and laryngeal cancer (4). It is evidenced that cigarette smoking (CS) not only increases the lung cancer risks. In the Human Early-Life Exposome project containing 1,173 children aged 7 years old, it was found that maternal tobacco smoking during pregnancy and CS exposure in childhood could also influence future health and accelerate biological aging from an early age (5). However, the CS associated lung cancer could largely be prevented through smoking cessation. It is never too late to act, quit smoking as early as possible is of much beneficial to you and your children's future.

For a relatively long period of time, ubiquitous air pollution is posing an urgent challenge to worldwide public health. Ambient air pollution was classified as Group 1 carcinogens for lung cancer by the International Agency for Research on Cancer (IARC) in 2013 (6). Substantial evidence, including mechanistic studies, have demonstrated that the air pollution, especially the outdoor particulate matter (PM), is causatively associated with lung cancer (7). More than one-half of lung cancer deaths attributable to air pollution were projected to East Asian countries, especially China (8). However, air pollution is a man-made disaster attributed to everyone. We are an integral part of the environment, and the

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responsibility to curb air pollution and effectively protect the environment lies with all of us.

2. The epidemiology of lung cancer from 1990 to 2020

In the three decades between 1990 and 2020, cancer incidence and mortality continuously grew worldwide (Figure 1A) (1, 2, 9-11). Based on the data from GLOBOCAN, 8.1 million cancer cases occurred in 1990. Thirty years later, the number reached to 19.3 million in 2020. Simultaneously, the number of corresponding cancer related deaths increased from 5.2 million in 1990 to 10 million in 2020 (1, 2). In 2040, the global cancer burden is expected to reach 28.4 million cancer cases, with a 47% increase from 2020 (1). The driving forces behind the curve are complex but reflect aging, social and economic development, and population growth, as well as the changes in the prevalence and distribution of main cancer risk factors, and social and economic development (12, 13).

Lung cancer has been one of the most frequently diagnosed cancers and the leading cause of human cancer death for all humans combined, worldwide (1, 2, 9-11). The incidence and death number of lung cancer for both sexes are still growing (Figure 1B). The incidences of lung cancer were estimated to be 1.04 million (12.8% of the world total) in 1990, 1.61 million (12.7%) in 2008, 1.82 million (13.0%) in 2012, 2.09 million (12.3%) in 2018, and 2.21 million (12.2%) in 2020. The lung cancer associated mortalities were 0.92 million (17.8% of all the cancer caused deaths) in 1990, 1.38 million (18.2%) in 2008, 1.59 million (19.4%) in 2012, 1.76 million (18.6%) in 2018, and 1.80 million (18.2%) in 2020, respectively (1, 2, 9-11). The numbers of new incidences and mortalities for lung cancer continue to increase, whereas the corresponding percentages in all cancer types have peaked and declined since 2012. In 2020, Lung cancer continues to be the leading cause of cancer death for all humans. For both sexes at the national level, lung cancer is the most frequently diagnosed cancer in 37 countries. However, with respect to mortality, lung cancer is the leading cause of cancer death in 90 countries (1). In contrast, the mortality and incidence of lung cancer in the U.S. are dramatically decreased in recent years due to the success of smoking cessation programs (Figure 1C).

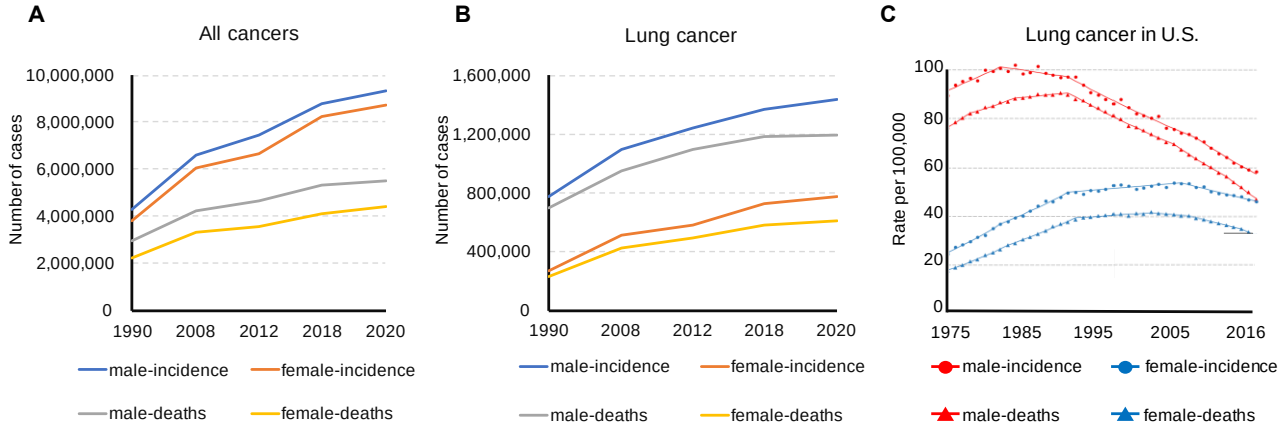

Figure 1. The epidemiology of cancer incidence and mortality from 1990 to 2020 illustrated the growing dynamics in male and female population worldwide. **(A)** The incidence and mortality of all surveyed types of cancer for both sexes are in the process of continuously growing worldwide. **(B)** The incidence and death number of lung cancer for both sexes are still growing. Data source: GLOBOCAN 1990~2020. **(C)** Cancer of the lung and bronchus SEER delay-adjusted incidence and U.S. death rates, 1975-2016, all races, by sex. Source: SEER 9 areas and U.S. mortality files (National Center for Health Statistics, CDC).

2.1. Lung cancer in males

It is estimated that CS accounted for 86% of lung cancer associated mortality in men (2). In 2017, it was estimated that cigarette smoking contributed to 1.19 million lung cancer

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deaths (14). For males, lung cancer ranked as the leading cancer type both in terms of incidence and mortality in the extent of 30 years (1, 2, 9-11). In 1990, male lung cancer was 18.0% of the total male cancer cases and 23.4% of the total male cancer deaths (2). In 2020, the corresponding rates for lung cancer incidence and mortality decreased to 15.4% and 21.7%, respectively (Figure 2A~2B). The time trends of lung cancer incidence and mortality generally reflect the past exposure to cigarette smoking in male population and considerable regional variations (2).

For males, from the perspective of global cancer patterns in 2020, lung cancer is the most frequently diagnosed type of cancer in 36 countries, including Russia, China, Korea, Myanmar, Malaysia, Indonesia, Philippines, Kazakhstan, Iraq, Syria, Turkey, Jordan, Ukraine, Poland, Romania, Greece, Algeria, Libya and Morocco (1). In terms of cancer related mortality, lung cancer is the leading cause of cancer death in men in 93 countries (Figure 2C), half of all the 185 surveyed countries, including all the 36 countries with lung cancer as the most frequently diagnosed cancer, and also Canada, United States, Brazil, Bolivia, Argentina, Uruguay, Paraguay, Japan, Australia, New Zealand, Pakistan, Uzbekistan, Turkmenistan, South Africa, and nearly all the European countries except Sweden (1). For instance, the incidence rate in males from Eastern Europe, Eastern Asia, Western Europe, Southern Europe and Northern America is 49.3, 47.2, 43.3, 43.1 and 39.1 per 100,000 people, respectively (1). The highest incidence rates of lung cancer among both men and women were observed in Hungary. The rate in male was as high as 77.4 in 100, 000 in 2018 (11). In 2020, the leading lung cancer incidences in men occurred in Turkey (Western Asia) (1). If the cancer incidence and mortality patterns are viewed via the perspective of the 4-Tier Human Development Index (HDI), for incidences in men, lung cancer ranks first (39 per 100,000) in higher HDI countries, vice versa for lower HDI countries (10.3 per 100,000) (1). The mortality rate for lung cancer is 31.6 per 100,000 in higher HDI countries and 9.4 per 100,000 in lower HDI countries for men (1).

The large variation in regional lung cancer incidences across the world is attributable to the maturity of tobacco epidemic, varied patterns of smoking exposure, including intensity and duration of smoking, type of cigarettes consumed, and degree of inhalation (2). Based on 1990 estimates, the incidence of lung cancer in males in regions of Eastern Europe, North America, Northern Europe, Southern Europe, Western Europe and Australia were 75.85, 69.62, 59.12, 58.81, 54.1, and 47.55 per 100,000 population, respectively (2). In 2008, the incidence of lung cancer in these areas decreased to 57, 48.5, 39.3, 49, 44.7, and 32.4, respectively (9). In 2020, the incidence rates furtherly reduced to 49, 35.7, 33.3, 43.1, 41.7, and 28.1 per 100, 000 population, respectively (1). The motivation behind the decreasing male lung cancer incidence is largely attributed to the decreasing CS epidemic. The United States (US), Northern and Western Europe, and Australia have now passed the peak of the tobacco-related epidemic in the middle of last century, and incidence rates and death rates of lung cancer are declining (2). The decreasing CS prevalence, followed by a peak and decline in lung cancer rates in the same generation, was also observed in developed nations such as the UK, the US, Finland, Australia, New Zealand, the Netherlands, Singapore, and (more recently) Germany (15, 16). After analyzing the Nordic cancer registries of Denmark, Finland, Norway and Sweden from the NORDCAN database, it was found that the approaching of incidence rates for lung and bladder cancer can be expected in the course of the abating smoking epidemic (17).

On the contrary, in Southern and Eastern European countries, the incidence rates of lung cancer continues to increase, where smoking prevalence have not peaked (2, 18-20). Additionally, in many developing countries such as China and Indonesia, the epidemic of tobacco smoking has just been recently established and has either peaked or continues to grow. Therefore, lung cancer rates are likely to increase for the next several decades in these countries (21). Especially in China, the most populous country in the world, with more than 4.5 million new incidences of cancer and 3 million cancer deaths China also tops first in cancer burden worldwide. In which, active smoking is the leading cancer risk in men. It was found that, in 31 Chinese provinces, the highest population-attributable fraction among men was smoking (22). In total, Chinese men now smoke more than a

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third of the world's total cigarettes. It is estimated that smoking caused about 20% of all adult male deaths in China during the 2010s. The tobacco-attributed proportion of mortality is still increasing. Although overall adult mortality rates are falling, as the adult population of China grows and the proportion of male deaths due to smoking increases, the annual number of deaths in China that are caused by tobacco will rise from about 1 million in 2010 to 2 million in 2030 and 3 million in 2050, unless there is widespread cessation of CS (23). The above epidemiological data shows that barring intervention measures to accelerate smoking cessation and reduce the number of new adopters are desperately required for the purpose of lung cancer prevention.

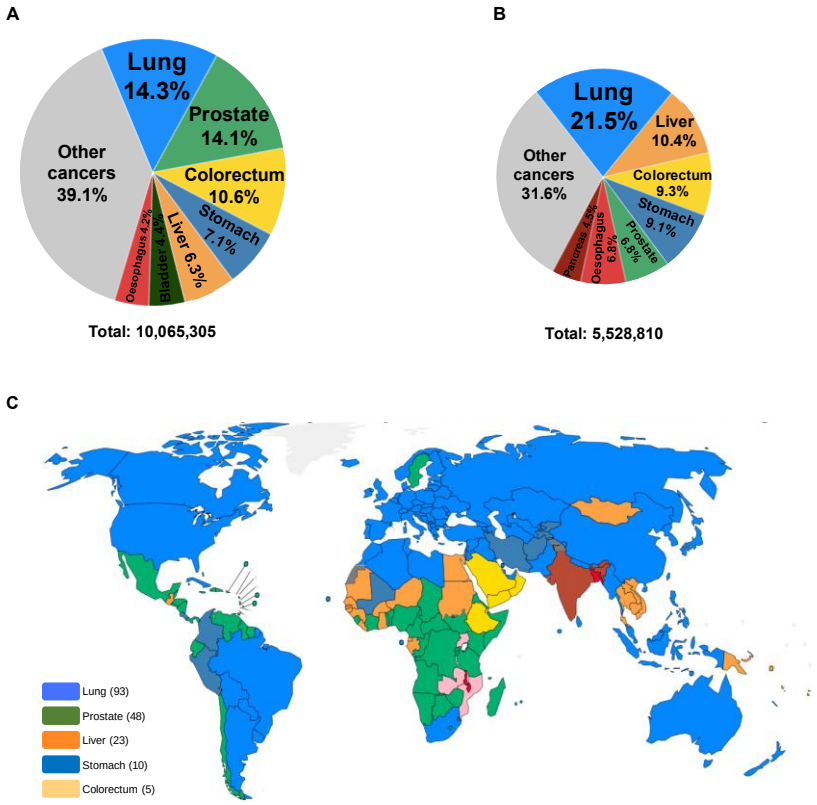

Figure 2. The proportions of top types of cancer in GLOBOCAN 2020. **(A)** shows the estimated percentage of new cancer cases in 2020, worldwide, males, all ages. (**B)** shows the estimated percentage of cancer deaths in 2020, worldwide, males, all ages. **(C)** Globally, the world map shows the top cancer per country, estimated number of deaths in 2020, only males, all ages. For mortality, female lung cancer as the top cancer in one country would be presented in blue color. Lung cancer was estimated as the leading cause of male cancer death in 93 countries showed in the world map. Data source: UNDP. World Health Organization. GLOBOCAN 2020.

2.2. Lung cancer in females

It is estimated that CS accounted for 49% of lung cancer associated mortality in women (2). For females, in the thirty years from 1990 to 2020, the percentage of lung cancer incidence in all cancers increased from 7.0% to 8.8%, and corresponding mortality percentage increased from 10.2% to 13.8% (1, 2, 9-11) (Figure 3A~3B). In 1990, lung cancer ranked fifth in incidence and third in mortality in all cancer types in females (2). The ranking increased to the fourth in incidence and second in mortality in 2008. Afterward, lung cancer consecutively ranked third in incidence and second in mortality in 2012, 2018 and 2020 (1, 10, 11). However, the most marked change is that, in 2020, female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases (1). Lung cancer incidence in females are of high variety among global regions in 2020. At the national level in females population, lung cancer was the most frequently diagnosed cancer only in

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North Korea (1). However, lung cancer was the leading cause of cancer death for females in 25 countries, such as China, Korea, Australia, Canada, the United States, Norway, Sweden, Finland, Iceland, the United Kingdom, Ireland, Denmark, Netherlands, Belgium, Poland, Czech Republic, Hungary, and Slovenia (1) (Figure 3C). The highest incidence rate is in Northern America (30.7 per 100,000), followed by Northern Europe (26.9), Western Europe (25.7), Australia (24.0) and Eastern Asia (21.9) (1). From the perspective of HDI, lung cancer incidence ranks third (18.2 per 100,000) in all cancers in higher HDI countries, vice versa for lower HDI countries (4.2 per 100,000) (1). The corresponding mortality rate for female lung cancer in higher HDI countries is 13.7 per 100,000, and the rate in lower HDI countries is 3.8 per 100,000 (1).

The trends of lung cancer incidence in females are also of high variety, globally. For example, the corresponding female lung cancer incidence in North America, Northern Europe, Southern Europe were 32.91, 20.21, and 7.26 per 100,000 females, respectively in 1990 (2). In 2008, the incidences increased to 35.8, 21.8, and 10.4, respectively (9). In 2020, the rates were 30.1, 26.8, and 16.4 (1). Except Northern America with the continuously decreasing rate of lung cancer incidence from 2008, the rates from Northern Europe and Southern Europe both generally increased from 2008 to 2020 (1, 9-11). Actually, only a few female populations, such as the US and the UK, are showing signs of plateau and decline. In many other countries, the lung cancer incidence rates are increasing in women (24). The trend convergence in the men and women in several European countries is possibly resulted from the sex-specific differences in the distribution of histologic subtypes and smoking prevalence (25).

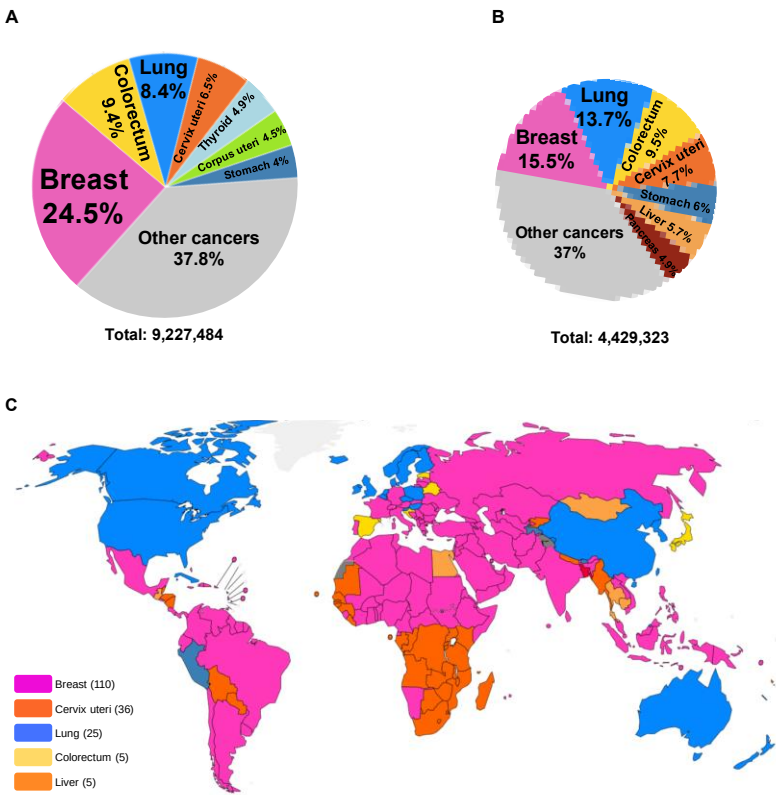

Figure 3. The proportions of top types of cancer in GLOBOCAN 2020. **(A)** shows the estimated percentage of new cancer cases in 2020, worldwide, females, all ages. (**B)** shows the estimated percentage of cancer deaths in 2020, worldwide, females, all ages. **(C)** Globally, the world map shows the top cancer per country, estimated number of deaths in 2020, only females, all ages. For mortality, female lung cancer as the top cancer in one country would be presented in blue color. Lung cancer was estimated as the leading cause of female cancer death in 36 countries showed in the world map. Data source: UNDP. World Health Organization. GLOBOCAN 2020.

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2.3. Lung cancer prevention

It is generally agreed that the CS associated lung cancers could be largely prevented by reducing smoking initiation and increasing smoking cessation. A population-based case-control study in France demonstrated that lung cancer risk increased linearly with intensity and duration of tobacco smoking while it decreased with time since cessation, to reach the risk in never-smokers after 20 years of abstinence (26). However, even after diagnosis, smoking cessation could also reduce the risk for lung cancer progression and mortality among the current smokers with early-stage lung cancer (27). Consistently, in a study of 1,134 NSCLC patients with smoking history, the length of smoking period was a significant prognostic indicator for those who underwent curative lung resection (28).

Most lung cancers are preventable by applying proven tobacco control interventions (1). The U.S. CDC launched Comprehensive Tobacco Control Programs in Best-practice, including effectively reducing active smoking, banning smoking in all indoor areas of workplaces and public places to prevent involuntary exposure to secondhand smoke, raising the retail price and taxes rate for tobacco products, restricting tobacco advertising and promotion, especially banning tobacco sales to young people, and enforcing plain packaging and graphic illustration of health warning on the tobacco products (1). In 2003, WHO established the Framework Convention on Tobacco Control to enable international coordinated efforts to curb the tobacco smoking epidemic, and 168 signatories have ratified the agreement after its adoption (29).

Alarmingly, tobacco use among youth is rapidly increasing in many lower-HDI countries. For young smokers, one strategy for tobacco control is printing effective warning images on cigarette products. Which could directly arouse the consciousness of smoking related health risks (Figure 4). Recently, an investigation of 353 Thailand undergraduates found that warning images illustrating patients' sufferings from smoking related cancer and body damages, could generate a significantly higher level of fear than other images in these adolescents. In addition, non-smokers were more sensitive to scary warning images (30).

In U.S., the comprehensive tobacco control programs in many states, such as California and New York, have markedly decreased smoking rates and accelerated the reduction in lung cancer occurrence (31, 32). Although the total number of cigarettes smoked worldwide is decreasing, Asia is still the largest tobacco consuming area, with China and India as the most populous countries in the earlier stage of tobacco epidemic (33). If smoking cessation and initiation prevention could be achieved by immediate actions, the lung cancer incidence and corresponding extraordinary burden experienced in developed countries could be largely attenuated.

The 5-year survival rate for patients with lung cancer in 2018 and 2020 were 18% and 19%, respectively (34, 35). However, the survival rate for lung cancer could be largely improved by early diagnosis. For the purpose of which, there is an increasing realization that most patients who are diagnosed with lung cancer as a result of annual CT lung screening (CTLS) could be cured, and heavy cigarette smokers without screening have a greater risk of lung cancer mortality (36). Consistently, a study with a minimum 10 years' follow-up, demonstrated that lung cancer mortality was significantly lower among those who underwent CTLS than among those without screening (37). Although there are uncertainties about over-diagnosis via CTLS, the meta-analysis suggested that the benefits of CTLS implementation outweigh potential harms, in subjects with CS history, ultimately supporting the systematic implementation of CTLS worldwide (38).

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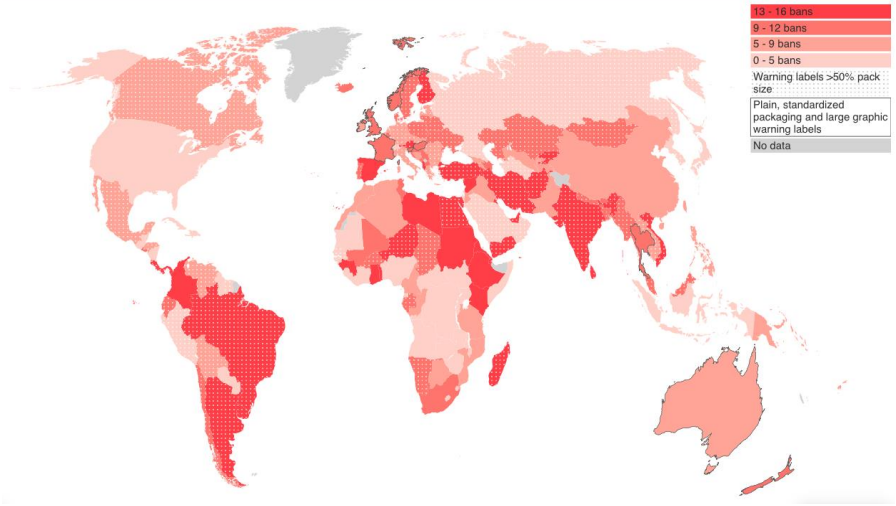

Figure 4. The world map shows the total number of bans on direct and indirect tobacco advertising, 2018. Data source: WHO GTCR 2019.

2.4. Challenges from new forms of cigarette

Recently, new forms of cigarette containing electric devices are raising concerns for potential public health risks. For instance, the heated tobacco products (HTP), have been developed as a less harmful alternative to traditional cigarettes. Although HTP products may impose a reduced risk of respiratory cancer compared to traditional smoking, the actual short-term and long-term impact of HTP on public health is still not fully undertood. It was found that HTP exposure such as I Quit Ordinary Smoking (IQOS) could alter mitochondrial functions and further lead to many adverse health consequences (39).

The prevalence of e-cigarettes has been increasing rapidly, particularly among the adolescents and non-smokers (40). However, the e-cigarette is greatly different from traditional cigarette, same irritant agents and carcinogens could also be found within (41). It was verified that electronic-cigarette smoke (ECS) is capable of inducing lung adenocarcinoma in mice, probably through causing DNA damage and inhibiting DNA repair (42). Similar pathological changes, as well as the mutagenic DNA adducts, were also evidenced in nicotine treated human lung cells (43).

Additionally, given the lag time of several decades extrapolated from tobacco smoking data, the long-term effect of these new forms of cigarette on public health should be concerning. Thus, comprehensive policies and regulations to assess, supervise, and monitor should be closely followed.

3. Mechanisms of CS associated lung cancer

The mechanism underlying the major CS carcinogens associated lung cancer are reviewed and illustrated (Figure 5).

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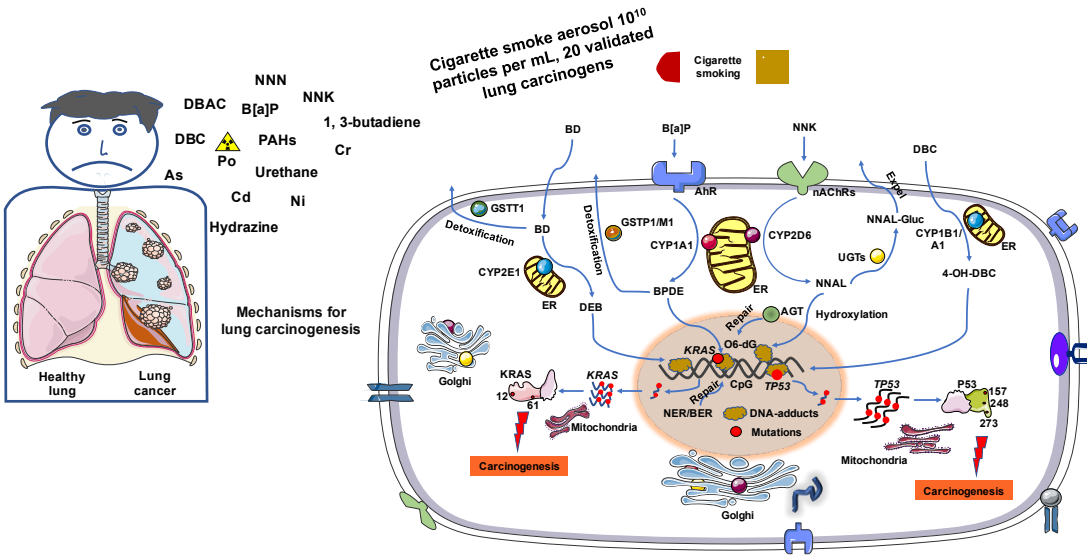

Figure 5. Mechanisms underlying cigarette smoking associated lung cancer. The above graph shows the representatives of major types of components in cigarette, and the mechanisms underlying cigarette smoking associated lung carcinogenesis were integratively illustrated on the cellular level.

3.1. Significant carcinogens in CS

The IARC reported that cigarette smoking could increase the lung cancer risks in all histological types, including adenocarcinoma, squamous-cell carcinoma, small-cell carcinoma, and large-cell carcinoma. In 1826, nicotine was isolated from tobacco for the first time and the investigation of mechanisms underlying cigarette smoking associated lung cancer began one century ago. Tobacco smoke contains a complex mixture of chemicals, with more than 70 validated carcinogens to humans (44). Twenty carcinogens have been demonstrated to convincingly cause lung cancer in laboratory animals (Table 1). Particularly, Nitrosamines (NNK and NNN), polycyclic aromatic hydrocarbons (benzo[*a*]pyrene) as significant carcinogens are believed to be two major aetiological factors for lung cancer.

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Table 1. Lung cancers were induced in experimental animals by the carcinogens presented in CS.

Classifications	Carcinogens in CS	Lung tumorigenicity in rodents
Polycyclic aromatic hydrocarbons	Benzo[*a*]pyrene	Hamster(45)_1974; Hamster(46)_1978; Rat(47), (48)_1983; Mouse(49)_1995; Mouse(50)_1995;
	Benzo[*b*]fluoranthene	Rat(47)_1983; Mouse(49)_1995; Mouse(50)_1995; Mouse(51) _1996;
	Benzo[*j*]fluoranthene	Rat(47)_1983; Mouse(52)_1994;
	Benzo[*k*]fluoranthene	Rat(47)_1983;
	Dibenzo[*a,i*]pyrene	Hamster(53)_1974;
	Indeno[1,2,3-*cd*]pyrene	Rat(47)_1983;
	Dibenz[*a,h*]anthracene	Mouse(54)_1966; Rat(47)_1983; Mouse(49)_1995; Mouse(50) _1995;
	5-Methylchrysene	Mouse(49)_1995; Mouse(50)_1995;
	Cyclopenta[*c,d*]pyrene	Mouse(55)_1994; Mouse(49)_1995; Mouse(50)_1995;
Heterocyclics	Dibenz[*a,h*]acridine	Rat(48)_1983;
	7H-Dibenzo[*c,g*]carbazole	Hamster(56)_1977; Mouse(57)_1996;
N-Nitrosamines	N-Nitrosodiethylamine	Hamster(58)_1961; Mouse(59)_1992; Mouse(60)_2018;
	NNK	Mouse(61)_1978; Rat(62)_1987; Rat(63)_1997;
Other organics	1,3-Butadiene	Mouse(64)_1985; Mouse(65)_1989; Mouse(66)_1993;
	Urethane(Ethyl carbamate)	Rat(67)_1947; Mouse(68)_2007; Mouse(69)_2015;
Inorganics	Nickel	Rat(70)_1975; Mouse(71) _1984;
	Chromium	Rat(72-74)_1986; Rat(75)_2005;
	Cadmium	Rat(76)_1986; Mouse(77)_1994;
	Polonium-210	Rat(78)_1967; Hamster(45)_1974; Hamster(46)_1978;
	Arsenic	Rat(79)_1977; Human(80)_1980;
	Hydrazine	Mouse(81)_1965; Mouse(82)_1969; Mouse(83)_1976;

3.1.1. Polycyclic aromatic hydrocarbons

A variety of polycyclic aromatic hydrocarbons (PAH), including benzo[*a*]pyrene, benzo[*b,j,k*]fluoranthane, dibenzo[*a,i*]pyrene, indeno[1,2,3-*cd*]pyrene, dibenz[*a,h*]anthracene and 5-methylchrysene, could cause lung cancer *in vivo* (84). B[*a*]P was the first and the major carcinogenic precursors detected in CS (85). Millions of people are suffering lung cancer risks of being exposed to B[*a*]P via CS or consuming B[*a*]P-contaminated food. It was demonstrated in mice model that the carcinogenic capability of dibenz[a,h]anthracene and 5-methylchrysene with low percentage in CS tended to be stronger than B[*a*]P (50). However, the carcinogenic mechanisms underlying dibenz[*a,h*]anthracene may be different from other PAHs, for the frequent *Kras* mutations induced by PAHs were not shown in dibenz[*a,h*]anthracene (50). CS was found to enhance the metabolic activation of phenanthrene in humans, which is a representative of PAH (86).

3.1.2. Nitrosamines

4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK), N′-nitrosonornicotine (NNN), N′-nitrosoanatabine (NAT) and N′-nitrosoanabasine (NAB) belong to a group of

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chemicals called tobacco-specific nitrosamines (TSNA), which are found only in tobacco products. Epidemiologically, TSNA concentrations were shown to be higher in every day tobacco users than in intermittent users (87). The IARC has classified NNN and NNK as Group I carcinogen to humans. NNK, a potent carcinogen, can induce lung adenomas in female A/J mice (88), liver cancer and pancreatic cancer in male F344 rats (89). Activated Akt was evidenced in mice lung tumors induced by NNK, probably through the binding of nicotine or NNK with nicotine-acetylcholine receptors (nAChRs) (90). The CSC or NNK exposure was able to neoplatically transform BEAS-2B cells into invasive adenocarcinoma *in vitro*, which exhibited typical malignant features, such as increased invasiveness, resembling the progressive changes in human lung cancer (91). In mice, lung cancer could be induced by NNK in CS, and lung tumors with more malignant features appeared after combining with LPS (inflammation inducing) compared to NNK treatment alone (92). Interactions between specific chemicals in tobacco smoke were investigated; mice receiving both NNK and aldehydes had more adenomas than only NNK treated mice, which suggested that coexposure to inhaled aldehydes is capable to enhance the carcinogenic effects of NNK (93).

3.1.3. Heterocyclic organics

Heterocyclic organic compounds of lung carcinogenicity presented in tobacco smoke include Dibenz[*a*,*h*]acridine (DBAC) and 7H-dibenzo[*c*,*g*]carbazole (DBC)(48, 56, 57). In male CD rats treated with DBAC, the resulted genotoxicity was found in the form of DNA adducts using 32P-postlabeling analysis(94). DBC as a skin, liver, and lung carcinogen has both local and systemic effects in mice(95). The DBC-DNA adducts formed from DBC metabolites, including 4-OH-DBC, as the most potent are mostly catalyzed by lung CYP1B1 and CYP1A1(96). Stable DBC-DNA adducts were identified in mouse lung, including two newly discovered DBC-6-N7-Ade and DBC-6-N1-Ade, following a single i.p. of DBC(97). Consistently, seven DBC-DNA adducts were identified in the lung of A/J mice after DBC treatment via i.p. Additionally, K-ras mutations from the induced lung tumor predominantly occurred at codon 61(A-T transversion)(57).

3.1.4. Other carcinogenic organics

Of the many tobacco smoke constituents, 1,3-butadiene (BD) has a high cancer risk index due to its tumorigenic potency and its abundance in cigarette smoke(98, 99). The carcinogenicity of BD has been attributed to the formation of several epoxide metabolites, of which 1,2,3,4-diepoxybutane (DEB) is the most toxic and mutagenic(100). Recently, it is found that the status of GSTT1 genotype significantly influences BD metabolism and acute toxicity (101). Ethyl carbamate also known as urethane is presented in cigarette smoke (102), potent carcinogenicity of urethane to induce lung tumors was demonstrated in mouse and rat, and the process of lung carcinogenesis was partially promoted by the activation of NF-κB (68) (69). NF-κB as a critical effector of inflammatory responses is integral to lung tumorigenesis in urethane induced lung cancer mouse model (68).

3.1.5. Heavy metals

Tobacco products also contain carcinogenic metals in relative large quantities (85). It was shown that the abundance of heavy metal levels in smokers are significantly higher than that in non-smokers, including thallium (Ti), arsenic (As), manganese (Mn), and copper (Cu). Specifically, lead (Pb), cadmium (Cd), and cobalt (Co) are among the most important metals accumulated in smokers' blood (103). Upon nickel exposure, the nickel concentrations in lungs were significantly increased, and no apparent deposition was observed in other tested organs using a rat model (104). It was consistently demonstrated that nickel and cadmium could generate single-strand breaks in rat lung when administered alone (105). Interestingly in NFS mice, lung cancer was induced by cadmium only at a lower dose(77). Malignant and premalignant bronchial lesions in rats were induced in 9 months after a single strontium chromate treatment(75). The chromium-induced

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DNA damage and mutations observed in the lung of rodents has been correlated with the potential lung carcinogenicity in humans(106, 107). Arsenic in cigarettes was preliminarily reported in as early as 1896 (108). Arsenic exposure before pregnancy could increase the lung adenoma and bronchiolo-alveolar tumor incidence in the offspring (109).Since arsenic and B[*a*]P are lung cancer carcinogens both in CS and environment, it was speculated that arsenic and B[*a*]P combined-exposure have synergistic effect in the increased lung cancer risk observed in arsenic-exposed cigarette smokers (110).

3.2. The metabolic activation and detoxification of tobacco carcinogens

Cytochrome P450s and glutathione-S-transferases (GST) are two major type of enzymes for the metabolic activation and detoxification of the tobacco carcinogens (111, 112). Most carcinogens in cigarette smoke are metabolically activated by cytochrome P450. Subsequent formation of macromolecular adducts are responsible for carcinogenicity (111). Some low molecular weight chemicals such as ethylene oxide, formaldehyde, and acetaldehyde can reactively bind with DNA molecules. The CYP1A1, CYP2D6, and CYP2E1 in the cytochrome P450 gene family are significant enzymes for tobacco carcinogen metabolism. CYP2D6 can metabolically activate NNK (113). CYP2E1 actively metabolizes 1,2-butadiene, *N*-nitrosodimethylamine, and *N*-nitrosodiethylamine (114, 115). CS could induce the expression of CYP1A1 which is also known as aryl hydrocarbon hydroxylase (AHH). The catalysis of PAH (B[a]P) into carcinogenic metabolites is also processed by CYP1A1 (116). Further, more CYP1A1 activities promoted by B[*a*]P is partially attributed to the activation of AhR/Src/ERK axis (117). Consistently, It has been reported that a flavonoid pinocembrin (PCB) is to alleviate B[*a*]P toxicity via inhibiting DNA adduct formation by attenuating CYP1A1 expression through the suppression of the AhR/Src/ERK pathways (118). PAH detoxification is mainly catalyzed by GSTM1 and GSTP1(119). The detoxification of nitrosamines, such as NNK, is majorly govern by UGTs. First, NNK is metabolized into carcinogenic NNAL. Next, NNAL is glucuronidated and NNAL-Gluc is produced as the detoxified form by UGT. Recently, it was found that variations of the activity of specific UGTs may affect the efficiency of NNAL detoxification (120).

3.3. Genomic aberrances caused by carcinogens and DNA adducts

DNA adducts, formed through covalently binding carcinogen metabolites to human DNA, usually at guanine or adenine, are crucial to the lung carcinogenic process (85). The investigation of "DNA adducts" via a ^{32}P-DNA post-labeling approach was used to elucidate the association between CS carcinogens and lung cancer risk (121). PAHs like B[*a*]P are metabolically activated and converted to 7,8-diol-9,10-epoxides (BPDE), subsequently forming the BPDE-deoxyguanosine DNA adducts or protein adducts with albumin (122). NNAL is the predominant metabolite of NNK, which are hydroxylated to form the DNA adducts such as methyl adducts (7-methylguanine, O6-methylguanine), and pyridyloxobutyl adducts. The level of these DNA adducts are increased in lung cancer patients compared to in normal cases and are likely to cause lung tumors in rodents (123, 124). NNN could be metabolically activated to produce carcinogenic metabolites via 2'-hydroxylation and 5'-hydroxylation, which could directly alkylate DNA to form adducts (125, 126). 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB)-releasing DNA adducts derived from NNK and NNN, are significantly increased in smokers (127, 128). In addition, new DNA adducts from NNN are continuously being discovered (129, 130). Programmed cell death or apoptosis may occur in cells with DNA damage. However, DNA miscoding and genetic mutations would be produced. If these DNA adducts were not efficiently repaired. If a permanent mutation occurs in specific sites of an oncogene or a tumor suppressor gene, and multiple of these events may lead to aberrant genotypes and uncontrolled proliferation, ultimately, to lung cancer.

DNA adducts resulting from PAHs and NNK can directly cause genetic mutations in significant oncogenes and tumor suppressor genes, especially the frequent mutations of G-T and G-A in *KRAS* and *TP53* (131-133). *TP53* mutations with an excess of G-T

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transversions have been observed in smoking-associated lung cancers. These G-T transversion hotspots are the sites preferring the formation of PAH adducts and also the position of endogenously methylated CpG dinucleotides (133). BPDE preferentially forms DNA adducts and induces G-T transversion in codon 157, 248, and 273, which are three mutational hot spots in *TP53* (134). In 550 lung tumor samples with *TP53* mutations, 33% of which were classified as G-T transversions, and 26% were G-A transitions, especially at the CpG sites of the deamination of 5-methylcytosine, where the cytosine methylation further enhances guanine alkylation by a variety of carcinogens (135). Collectively, these data suggested that the BPDE-DNA adducts could directly cause mutations in *TP53* (136). G-A transitions induced by the DNA adduct O6-POB-dG in *TP53*, derived from NNK or NNN, could be repaired by O^6-methylguanine–DNA alkyltransferase (AGT) (137).

Mutations in codon12 of *KRAS* are prevalent in lung adenocarcinomas and are more common in smokers than in never smokers, indicating that this mutation pattern may be causatively associated with carcinogens in CS (138, 139). Consistently, the same mutation pattern of *Kras* was induced by treating mice with PAHs (140). Particularly, the GGT-GAT mutation predominant in Kras codon12 was shown to be caused by NNK metabolite-DNA adducts (O^6-methylguanine) (141). CDKN2A, as a tumor-suppressor gene, was hypermethylated in the promoter area was found in 23% lung cancer cases (142). Consistently, the hypermethylated promoter region of Cdkn2a was identified in almost all of the adenocarcinomas induced by NNK, and even detected in precancerous lesions. These genetic lesions were also recapitulated in human SCCs, indicating the causal associations between the silenced Cdkn2a and the carcinogenicity of NNK(143). The mutational inactivation in FHIT identified in lung tumors were found to be associated with the duration of CS (144). These data suggested that carcinogens in CS could induce genetic and epigenetic alterations in tumor-suppressor genes, and make them incapable of efficiently suppressing lung carcinogenesis.

However, these DNA adducts resulting from cigarette smoke could be repaired by host repair mechanisms, such as base excision repair (BER) for oxidized bases and DNA alkylation, and nucleotide excision repair (NER) for PAH resulted DNA lesions (145, 146) . In addition to the NER pathway for O^6–alkylguanines DNA adducts derived from PAH, NNK, N-nitrosodimethylamine, and N-nitrosodiethylamine, the alkyl groups could also be removed from the O^6-deoxyguanosine by AGT, restored to deoxyguanosine (147, 148).

Moreover, recent studies showed that CS carcinogens not only cause point mutations but also lead to genome instabilities. A large genome-wide study of NSCLC demonstrated that more copy number alterations (CNAs) occurred on different genomic scales in heavy smokers other than in light or non-smokers. The higher level of CNAs may have resulted from CS caused genome instability, which was demonstrated in CSC treated human bronchial epithelial cell (149).

3.4. CS biomarkers for evaluation of lung cancer risks

The DNA adducts, protein adducts, and urinary metabolites produced in the metabolic processing of tobacco carcinogens provide biomarkers for evaluation of lung cancer risks from cigarette smoking. These metabolic products also reflect the carcinogen uptake, metabolic activation and detoxification in people exposed to cigarette smoke (85, 150). For example, the level of DNA-adduct in white blood cells was sensitive in predicting the risks of lung cancer for smokers (151). Cotinine, t,t-Muconic acid, 1-hydroxypyrene, and NNAL and NNAL-Glucuronides (NNAL-Gluc, detoxified metabolite of NNK) are common urinary carcinogen biomarkers for nicotine, benzene, PAH, and NNK, respectively, which are measured for evaluation of environmental tobacco smoke (ETS) exposure (150).

Given the fact that only partial smokers would finally develop lung cancer, which may attributable to the substantial differences in the metabolic response to tobacco carcinogens, with differed capability of catalyze carcinogens into DNA adducts, so these biomarkers could potentially be used for discriminating smokers who can efficiently activate or detoxify tobacco carcinogens. For instance, the ratio of NNAL-Gluc to NNAL was

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significantly higher in white smokers than in black smokers, which partially explains the higher lung cancer incidences in black smokers (152). Interestingly, in the normal lung tissue from 63 lung cancer patients, the levels of DNA adducts in females were higher than that in males after adjusted for smoking doses, indicating that women are likely at higher risks for CS associated lung cancer (153).

The Golestan Cohort Study showed that current male smokers with lung cancer had higher average levels of total nicotine equivalents (TNE-2), NNAL, and 3-FLU. On the other hand, lung cancer risk increased with concentrations of TNE-2 and NNN (154). Consistently, the urinary NNAL level was found to be associated with the risk of lung cancer in general population and independent from CS, indicating the experience of potential ETS exposure (155). Collectively, these data indicated that smokers or involuntary smokers, capable of activating NNK or NNN and forming DNA adducts, are likely at higher lung cancer risks.

3.5. Oxidative damage caused by CS

The oxidative damage (OD) induced by CS may be attributed to the reactive oxygen species (ROS, such as nitric oxide, NO) in the gas phase (156), and free radicals (such as the quinones) in particulate matter (157-159). Peroxynitrite, generated from nitric oxide and superoxide anion, causes the DNA single-strand breaks (160). ROS also causes increased DNA adducts such as 8-oxodeoxyguanosine (161). In lung cancer cell lines, CS induces oxidative stress and mitochondrial damage, which further increases glycolytic flux, downregulates FOXO3a, and facilitate EMT and cell migration (162). Additionally, the CS caused OD increases circulating F2-isoprostanes via arachidonic acid peroxidation, which could be improved by supplementation of ascorbic acid (163). In human bronchial epithelial cells, the OD and inflammatory responses induced by CSE could be alleviated by eucalyptol and curcumin (164). CSC could activate the Ca^{2+}/PKC signaling *in vitro* and increase the metastatic nodules in the lung of mice, which could be alleviated via inhibition of Ca^{2+}/PKC or decreasing ROS production (165). Extensive hypoxia resulted from CS can trigger endoplasmic reticulum stress (ERS). Subsequently, the unfolded protein response (UPR) caused by ERS would activate cell death pathways and promote lung carcinogenesis (166).

3.6. CS associated inflammation and immunosuppression in lung cancer

The activated NF-κB pathway and increased expression of inflammatory factors occur in response to CS. Therefore, pulmonary inflammatory responses can be induced via AhR activation by CS ligands. However, smoke-induced inflammation can be attenuated by endogenous AhR ligand (167). NF-κB, a critical effector of inflammatory responses, is integral to lung tumorigenesis in the urethane induced lung cancer mouse model (68). DAPK2, as a tumor suppressor gene, can be methylated at N6-adenosine via CS activated NF-κB pathway, which significantly associated with poor prognosis in NSCLC patients, especially in smokers (168). In airway epithelium and lung cancer cells, CS activated MARCKS promotes the expression of pro-inflammatory cytokines, EMT, and stem-like properties. Additionally, CS activated NF-kB signaling pathways can be suppressed via the inhibition of MARCKS phosphorylation (169). Increased levels of IL-17 were accompanied with DNA damage response (DDR) in human lung tissues and in mice after CS exposure, indicating that IL-17 mediated inflammation may promote CS-induced genomic instability. Moreover, IL-17 application can increase DDR and chromosome breakage in human bronchial epithelium cells, which was diminished in IL-17 KO mice after CS exposure (170).

CS causes an influx of inflammatory cells, including Langerhans cells, into the lung tissue and induces extensive pathological changes, such as emphysema and fibrosis. Additionally, this situation can be deteriorated upon increased infiltration of Langerhans cells (171). In mice, alveolar damages were observed, including alveoli enlargement, collagen deposition, mucus production, and higher AIM2 expression in dendric cells and

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macrophages recruited in lung after CS exposure (172). A recent study reported that ACE2 was significantly overexpressed in the bronchial and alveolar epithelial cells in smokers, independent of age or gender, indicating that CS related ACE2 overexpression may assist the SARS-CoV-2 infection, and smoking cessation may potentially attenuate the risk of COVID-19 transmission (173). An *in vitro* air-liquid-interface (ALI) human airway tissue model was successfully developed to assess the effects of CS on the function and phenotype of airway epithelial cells in smokers, including xenobiotic metabolism, oxidative stress, and inflammatory responses (174).

The immunological activities of CD8+ T cells against tumor cells could be attenuated by nicotine in CS (175). Furthermore, the density of tumor associated neutrophils increased with lung cancer progression, particularly in NSCLC smokers (176). In mice lung cancer induced by B[a]P, extensive immunosuppressive changes and more cancer stem like cells were observed, including increased expression of TGF beta, CTLA-4, PD-L1, FOXP3 and decreased IL-12, together with increased CD166+ cells and decreased CD83+, CD8+ cells (177). Additionally, a recent study found that B[*a*]P could induce PD-L1 expression on lung epithelial cells both *in vitro* and *in vivo*, which is mediated by AhR, the B[*a*]P receptor. Furthermore, AhR inhibitors can synergize with anti-PD-L1 antibody, showing potent anti-tumor effect (178). In NSCLC patients treated with nivolumab and pembrolizumab(anti-PD-1 antibody), longer PFS did not favor never smoking patients, probably due to the low level of mutation heterogeneity (179). Moreover, the response rate of pembrolizumab was nearly two times higher in current or former smokers than in never smokers with NSCLC (180). These findings partially explain why lung cancer patients with a history of smoking respond better to pembrolizumab than non-smoker.

3.7. miRNA in CS associated lung cancer

It was discovered that the levels of miR-532-5p, miR-25-3p, and miR-133a-3p were significantly higher in adenocarcinoma patients than in healthy participants. The miR-133a-3p was independently associated with CS, which was also associated with pulmonary inflammation (181). The immunosuppressive effect of miRNA was observed after CS exposure; upregulated miR-629-5p partially contributed to the exhaustion of CD8+ T cells after nicotine exposure (175). Additionally, the anti-tumor effects of certain miRNAs could be impaired by CS. For example, miR-584-5p, capable of suppressing cancer migration and invasion, was methylated and downregulated after CS application in human bronchial epithelial cells (182).

3.8. Microbiota in smokers

The microbe and lung respiratory host cells form a sophisticated and balanced ecosystem, which can negatively be impacted by CS. In a study of 103 bronchoalveolar lavage fluid samples from lung cancer, the local microbiota was sequenced. The results indicated that lung cancer microbiota possessed higher diversity in squamous cell carcinoma than in adenocarcinoma and was enriched with Proteobacteria (183). The change of microbial diversity was also illustrated in a general population study of 529 Australian adults, which found that CS was associated with diversity loss of the airway bacterial communities, negative effects on abundant taxa, profound alterations to network structure and expansion of Streptococcus spp (184). Particularly for lung squamous cell carcinoma, increased abundance of unique bacterial consortium, such as Acidovorax, was evidenced in CS associated tumors (185). These marked abnormal imbalanced relationships between microbiome and host side in smokers may contribute to lung carcinogenesis.

3.9. Radon

In the general population, environmental exposure to radon is recognized as the second leading cause for lung carcinogenesis. Recently, in a model proposed by the International Commission on Radiological Protection, the radon exposure was found to have a positive correlation with the excess of lung cancer cases (186). From the perspective of CS

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status, radon is the leading risk factor for lung cancer in never-smokers (LCINS), especially in radon-prone areas. In these cases, men were at higher risk of lung cancer than women (187). However, an investigation on the interaction between radon and CS indicated that smoking may act as a promoter of radon-initiated cells, and exposure to radon followed by smoking produced a significantly more-than-multiplicative effect (188). CS associated lung carcinogenesis is partly attributed to the cumulative alpha-radiation dose at bronchial bifurcations from indoor radon progeny and radionuclide attached smoke particles produced by tobacco combustion (189). Fractionation in burning cigarettes gives rise to the association of radon progeny with micron particles in mainstream CS, which are selectively deposited in "hot spots" at bifurcations, enriched radon progeny undergo substantial radioactive decay at bifurcations before clearance. Moreover, progressive chemical and radiation damage to the bifurcation epithelium gives rise to prolonged retention of insoluble ^{210}Pb-enriched radioactive smoke particles. It was estimated that a carcinogenic alpha-radiation dose of 80-100 rads is delivered to approximately equal to 10^7 cells of most smokers who die of lung cancer (190).

4. Indoor air pollution, outdoor air pollution

4.1. Indoor air pollution

Indoor air pollution resulting from poor heating ventilation facilities equipped for heating and cooking are main risk factors for Chinese household women. In 2012, lung cancer rates in Chinese women were approximately 20.4 cases per 100,000 (10). In 2018, the incidence of lung cancer in Chinese women increased to 22.8 per 100,000, which is equal to or even higher than the rates among women in some European countries, whereas the smoking prevalence is of substantial differences between the two regions (11). One explanation accounting for this is that the high incidence of lung cancer in Chinese women possibly reflects severe exposure to indoor air pollution directly emitted from the combustion of biomass fuels via unventilated coal-fueled stoves and from cooking oil fumes (19, 191-193). These household pollutants caused by coal burning and biomass fuels have been classified as Group 1 and Group 2A carcinogen for lung cancer by IARC.

4.2. Outdoor air pollution

4.2.1. Particulate matter (PM) in air pollutions

A majority of air pollution is caused by emissions from industry, power generation, transportation, and domestic burning. Together, these sources increase the air particulate matter (PM), which has been shown to have a causal link with lung cancer incidence and mortality (7). In 2013, IARC classified PM and other outdoor air pollutants as Group 1 carcinogens for lung cancer (6). The PM pollution can be evaluated and measured in mass concentration as ug/m^3. 10 ug/m^3 is the world health-based air-quality guideline from WHO, while the global population-weighted mean annual average $PM_{2.5}$ was 46 ug/m^3 in 2017, almost 5 times higher than the safe value. In India, $PM_{2.5}$ reached as high as 91 ug/m^3 in 2017. Particles with diameter more than 10 um would largely be retained at the respiratory barriers in the nose and throat. The $PM_{2.5\text{-}10}$ are coarse fraction particles, which are capable of travelling only short distance and then precipitate to the earth. Astonishingly, because of the small size, large amount, and higher surface area-to-mass ratio (194), $PM_{2.5}$ can travel as far as several thousand kilometers and remain suspended in the air for weeks (195). These properties of $PM_{2.5}$ particles and ultrafine particles (UFPs) greatly increase exposure for humans, and penetrate deeper into the lung tissue (196). After the inhalation of air pollutants, these retained particles can produce long-term effects of inflammation and oxidative stress on both the local and systemic levels (197).

4.2.2. PM associated with lung cancer

Recently, ambient environment pollution has been determined to cause lung cancer (198). In an analysis of 80, 285 participants, $PM_{2.5}$ was shown to have a significant adverse association with total lung cancer incidence (199). The ambient $PM_{2.5}$, PM_{10} and NO_2 were

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associated with poorer lung cancer survival, particularly in 352,053 lung cancer patients of early stage (200). Moreover, in the ACS CPS-II study, long-term $PM_{2.5}$ exposure was demonstrated to be associated with increased lung cancer mortality in never-smokers, with the exclusion of the potential confounder of cigarette smoking (201). More than half of the lung cancer deaths attributable to ambient fine particles were projected to have been in China and other East Asian countries (8), which include the most polluted regions (Figure 6). Generally, there were combined effects among lung disease history, environmental exposures, and family history toward susceptibility to lung cancer in Chinese non-smokers. Non-smokers who had a family history of lung cancer were at higher risk of lung cancer than non-smokers who did not have lung disease history. Non-smokers with family cancer history may obtain benefits from active treatment of lung disease and removal of environmental exposures (202).

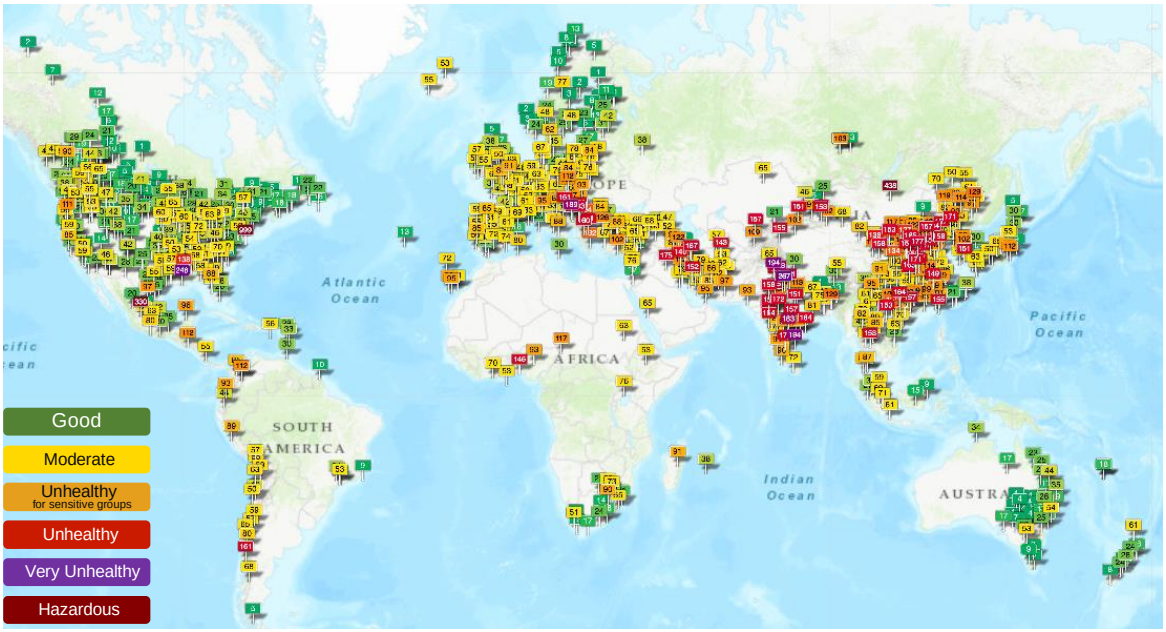

Figure 6. The world's real-time air pollution distribution in term of $PM_{2.5}$ levels on Oct 20, 2021. The air quality index (AQI) is classified into six levels to represent the severity of air pollution, including Good (AQI 0-50), Moderate (AQI 51-100), Unhealthy for Sensitive Groups (AQI 101-150), Unhealthy (AQI 151-200), Very Unhealthy (AQI 201-300) and Hazardous (AQI 300+). The caution statement for "Hazardous" is that everyone should avoid all outdoor exertion. The AQI scale used for indexing the real-time pollution in the map is based on the latest US EPA standard, using the Instant Cast reporting formula.

PM pollution was reported to be associated with many types of lung cancer. The heightened risk of adenocarcinoma over the last four decades is considered as reflecting changes in cigarettes and the delivery of carcinogens. A meta-analysis carried out in North America and Europe reported that $PM_{2.5}$ and PM_{10} were both found to have a strong adverse association with lung adenocarcinoma. Particularly, the risk for lung cancer incidence or mortality rate increased 8% and 9% per each 10ug/m^3 increase in $PM_{2.5}$ and PM_{10} concentration, respectively (198, 203). In the participants who reported spending more than one hour per day outdoors, an adverse association of exposure to outdoor pollutions with adenocarcinoma was implicated (204). A significant adverse association of $PM_{2.5}$ with small cell carcinoma was reported in the Canadian Breast Screening Study with 89,234 women participants (205). Adverse association of ambient PM_{10} concentration and squamous cell lung carcinoma incidence were concluded after analyzing 4,219 participants (206). Contradictorily, a non-significant association of PM_{10} concentrations with lung cancer was reported in a large-scale study of 6.5 million participants conducted in Korea, whereas an adverse association of PM_{10} with lung adenocarcinoma in male smokers was identified in this study (207).

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4.2.3. Specific carcinogens in PM

Studies also indicated the associations between lung cancer and the exact carcinogens in $PM_{2.5}$ pollutions. The association of $PM_{2.5}$ pollutants emitted from coal combustion with lung cancer mortality was found, especially Se and S (208). Glutathione-related rather than the ascorbate-related $PM_{2.5}$ was found to be significantly associated with lung cancer mortality (209). In the ESCAPE study of 245, 782 participants, relative risks of lung cancer increase with the elemental components in $PM_{2.5}$ and PM_{10}, such as S and Ni (210). Combustion of fossil fuels, such as coal, account for around 25% of total As and Hg emissions (211, 212), which have close association with several types of cancer including lung cancer. The IARC reported that the PM constituents such as the diesel engine exhaust, nickel, Chromium, Cd and silica dust are potential carcinogens for lung cancer (213). PAHs (214), dioxins (215), sulfur-derivatives (216), and 3-nitrobenzanthrone (217) commonly found in air pollutions are well-defined mutagens and carcinogens. Mutagenic PAHs can interact and bind DNA molecules (218), and the following repair process of these DNA adducts could potentially introduce mutations in the affected DNA sequences (219).

4.2.4. Genetic aberrances associated with PM

Substantial findings have illustrated that the number of mutations in air pollution associated lung cancer were three times higher than those in lung cancer patients from regions with cleaner air (220). Alarmingly, genomic mutations resulting from air borne carcinogens are inheritable. An in vivo mouse study found that higher level of germline mutations could be inherited after being exposed to industrial air pollutants (221). Additionally, ambient air pollution can cause epigenetic alterations, such as the aberrant status of DNA methylation (222-225), which could result in *TP53* silencing and chromosome instability (226, 227). *TP53* is a significant tumor suppressor gene, its abnormal mutation expression status are closely related with lung carcinogenesis (228). Low-dose $PM_{2.5}$ is sufficient to induce epigenetic silencing of *TP53* in human alveolar epithelial cells (229). Human epithelial cells exposed to $PM_{2.5}$ are more susceptible to hypomethylation, which can result in upregulation of cancer-related signaling pathways (230). $PM_{2.5}$ can also promote autophagy and malignancy of lung cells via ROS (231), including transformation of mouse fibroblasts occurs after exposure to ROS (232). Collectively, ROS can stimulate the malignant phenotypes of tumor cells to, such as proliferation, invasiveness, angiogenesis, metastasis, and resistance to apoptosis (233).

4.2.5. Synergistic effect of CS and PM

It is estimated that tobacco smoking contributed to 63.2% of lung cancer deaths, whereas 14.1% of the total lung cancer mortalities was attributable to ambient $PM_{2.5}$ pollutions (14). CS and ambient air pollution are two ubiquitous factors extensively overlapped for a large population. Additionally, evidence has shown that a potential synergistic effect of exposure to CS and ambient air pollution exposure was greater than the sum of the effects from either exposure alone (234). Together, these factors tremendously increase the burden of lung cancer in the areas with high prevalence of cigarette smoking and heavy air pollutions, such as China and India, the most populous Asian countries. However, as the declining trend of lung cancer incidence occurred in many developed countries after the CS epidemic, the air pollution associated lung cancer could also be largely avoided if the etiology factors were effectively eliminated.

5. Conclusion

Genomic aberrations including germline inherited and carcinogen induced, play an important role in tumor initiation, progression, and metastasis. Although CS is the main risk factor for lung cancer, the exposure to potential risk factors of lung cancer is ubiquitous, including exposure to a variety of carcinogens from environment, such as pollutants from second-hand smoke, domestic radon, and fuel combustion. Additionally, complex mechanisms underlie carcinogen associated lung carcinogenesis. However, lung cancer is

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one of the most preventable type of cancer that could potentially be largely avoided, if comprehensive policies and measures are taken to control and eliminate lung cancer risk factors.

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