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Review

Etiology of lung cancer: Evidence from epidemiologic studies ☆

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ABSTRACT

Lung cancer is one of the leading causes of cancer incidence and mortality worldwide. While smoking, radon, air pollution, as well as occupational exposure to asbestos, diesel fumes, arsenic, beryllium, cadmium, chromium, nickel, and silica are well-established risk factors, many lung cancer cases cannot be explained by these known risk factors. Over the last two decades the incidence of adenocarcinoma has risen, and it now surpasses squamous cell carcinoma as the most common histologic subtype. This increase warrants new efforts to identify additional risk factors for specific lung cancer subtypes as well as a comprehensive review of current evidence from epidemiologic studies to inform future studies. Given the myriad exposures individuals experience in real-world settings, it is essential to investigate mixture effects from complex exposures and gene-environment interactions in relation to lung cancer and its subtypes.

1. Introduction

Lung cancer remains the leading cause of cancer death and continues to be among the most commonly diagnosed cancers worldwide[1]. A recent analysis identified large regional and gender variations in the trends of age-adjusted incidence rates of lung cancer from 1978–2012 with 19 countries showing significantly decreasing trends among men and 26 countries exhibiting significantly increasing trends among women[2]. In China, the age-adjusted rate of lung cancer remained stable among men and increased among women from 2000 to 2010[3]. In addition to sex and geographical disparities, histologic subtypes of lung cancer also showed apparent difference in incidence trends. In the United States, three major subtypes including squamous cell carcinoma (SCC), large cell carcinoma (LCC), and small cell lung cancer (SCLC) showed initial increasing trends from 1973 to 1980s and then started to decrease; in contrast, adenocarcinoma surpassed SCC in 1985 as the most commonly diagnosed subtype of lung cancer, with rates further increasing from 2003 to 2015[4]. In China, investigators have reported the same shift in histologic subtype incidence, with adenocarcinoma becoming the most commonly-diagnosed lung cancer there as well[5]. A recent study pointed out that an increased use of low-dose computed tomography (LDCT) among non-smoking Asian women was associated with overdiagnosis of lung cancer[6]. LDCT can increase detection of adenocarcinoma[7], and would be expected to lead to an increase in adenocarcinoma out of proportion to other histologic subtypes.

Over the last decades, epidemiologists have taken significant steps to investigate the etiologic risk factors for lung cancer. While tobacco control programs have effectively reduced lung cancer incidence and mortality overall in many populations[1], the increasing incidence of adenocarcinoma and its spatial and gender variations underscore an urgent need to continue identifying the etiologic risk factors of lung cancer. In this review, we summarize the current evidence of lung cancer etiology from epidemiologic studies and discuss the challenges and opportunities for future epidemiologic studies of novel risk factors.

2. Smoking

Cigarette smoking is a well-documented risk factor for lung cancer[8]. A cigarette contains more than 70 carcinogens that have been evaluated by the International Agency for Research on Cancer (IARC) as human carcinogens, and the evidence of a causal relationship between lung cancer and cigarette smoking from epidemiologic studies has been

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summarized by IARC monographs[8,9]. The risk of lung cancer generally increases with increasing duration and intensity of cigarette smoking, with a greater risk in current smokers than in former smokers[9].

While earlier studies suggested a higher risk of lung cancer associated with cigarette smoking among women than men[10,11], recent evidence supports a comparable risk between men and women[12–14]. Evidence of racial and ethnic disparities is mixed[9], and variations in starting age of smoking, duration of smoking, cigarette filters, ingredients in tobacco products, and other lifestyle and environmental factors could explain some of the racial and ethnic differences in the association between smoking and lung cancer risk in other studies[9]. The Multiethnic Cohort Study in the USA found that while Japanese Americans had the lowest risk followed by Latinos, Whites and African Americans were among those who smoked no more than 20 cigarettes/day, and these racial and ethnic differences were no longer significant among those who smoked more than 30 cigarettes/day[15].

The strength of association between smoking and lung cancer varies by histologic subtypes, demonstrating a stronger association with SCC and SCLC and a weaker association with LCC and adenocarcinoma[16]. A meta-analysis of 8 cohort and 14 case-control studies conducted in Japan showed proportionally elevated risks of SCC and adenocarcinoma among active smokers in men (RR = 11.7 and 2.30 respectively) and women (RR = 11.3 and 1.37 respectively)[17].

Evidence linking non-cigarette tobacco products, such as cigars, pipes, and smokeless tobacco, to lung cancer risk has been less overwhelming[18]. Generally, studies support a positive association between cigars and pipes and lung cancer risk[19–22]. However, the association between lung cancer and smokeless tobacco products has been inconclusive[23–26]. One possible explanation for the inconsistent results is that smokeless tobacco consists of many different forms, such as chewing tobacco, Swedish snuff, etc., and the composition of different products varies[27]. Studies have also shown that smokers who additionally used non-cigarette tobacco had a higher risk of lung cancer than exclusive cigarette smokers[25,26].

Electronic cigarettes (e-cigarettes) have been on the market since 2007[18]. Even though e-cigarettes produce lower levels of toxic substances compared to traditional cigarettes, long-term exposure to low levels of carcinogens released by e-cigarettes, including ultrafine particulate matter, polycyclic aromatic hydrocarbons, formaldehyde nitrosamines, and heavy metals might also pose health impact[28–30]. In addition, e-cigarettes can lead to nicotine addiction[31]. Although there is a lack of human evidence on long-term exposure to e-cigarettes and lung cancer risk, animal evidence showed that mice exposed to e-cigarette smoke for 12 weeks developed lung adenocarcinoma[32], suggesting that future epidemiologic study of long-term exposure to e-cigarettes and lung cancer risk is warranted.

Exposure to secondhand tobacco smoke is associated with an increased risk of lung cancer[8,9]. The most compelling evidence is from studies on exposure to secondhand tobacco smoke from partners[9]. Studies of secondhand tobacco smoke exposure in the workplace generally showed an elevated risk among those with the highest level of exposure[8,9]. Limited evidence shows exposure to secondhand tobacco smoke during childhood associated with lung cancer risk[9].

In summary, cigarette smoking is strongly associated with an increased risk of lung cancer in an exposure-response manner, and the strength of the association varies by histologic subtypes. Association with secondhand tobacco smoke is challenged by exposure assessment, particularly exposure to secondhand smoke in the workplace and during childhood. Elucidating additional interactions between other lifestyle and environmental factors would provide insights to inform tobacco control prevention strategies.

3. Alcohol consumption

Alcohol has been identified as a Group c by IARC[9]. Although alcohol is causally associated with cancers of the head and neck, esophagus, colon, rectum, female breast, and liver, the relationship between alcohol and lung cancer remains inconclusive[9]. Several meta-[33,34] and pooled-analyses[35,36] suggested a J-shaped association between overall consumption of alcohol per day and lung cancer. A recent large prospective cohort study conducted in China reported a significant exposure-response relationship between alcohol consumption and lung cancer as well[37], which is consistent with two previous prospective studies conducted in China reporting elevated lung cancer mortality among heavy drinkers after adjusting for smoking[38,39]. This study also found a significant exposure-response relationship among both smokers and non-smokers[37]. However, earlier studies generally reported no association among non-smokers[40].

Several studies investigating alcoholic beverage type and risk of lung cancer found inconsistent results[35,36,41–51]. Both a meta- and a pooled-analysis suggested an inverse association with wine consumption at low to moderate levels and an increased risk of lung cancer from beer consumption at higher levels[34,35]. This meta-analysis also suggested an elevated risk associated with high consumption of liquor in men, but not in women[34].

Associations by histologic subtype are also inconclusive, with some studies reporting no association with any histologic subtype[52–54] and others showing significant associations for certain subtypes[44,55–59]. An elevated risk was generally reported for SCC[55], adenocarcinoma[44,58,59], or both[56,57].

In summary, the relationship between alcohol consumption and lung cancer is inconclusive, although a weak or moderate association has been reported by some studies. Controlling confounding from smoking is paramount when studying alcohol and lung cancer risk. Investigations by histologic subtype and by beverage type are also warranted in future large studies with sufficient statistical power and detailed information on both active and passive smoking.

4. Occupational exposures

A number of industries and occupations, including mining, construction, metalworking, and driving, have been linked to an increased risk of lung cancer[60]. Established occupational lung carcinogens, including asbestos, diesel fumes, arsenic, beryllium, cadmium, chromium, nickel, and silica, accounted for roughly 10% of lung cancer cases with large regional variations[61]. In China, an estimated 9.5% of lung cancer deaths were attributable to occupational exposure in 2005[62].

Epidemiologic studies using occupation or industry titles to investigate occupational exposure in relation to lung cancer risk were prone to exposure misclassification. Workers who were classified under a specific occupation or industry title could be exposed to multiple agents and vice-versa. Likewise, an occupational/industrial title could entail very different exposure levels of a specific agent. Using a job-exposure matrix to link information from both occupation and industry titles with specific exposure agents would minimize the exposure misclassification and increase statistical power. Recent reports from two large pooled case-control analyses used the job-exposure matrix to investigate the exposure-response relationship between occupational exposure to diesel exhaust or crystalline silica and lung cancer[63,64]. These studies found that exposure to diesel exhaust or crystalline silica was associated with lung cancer even at the lowest cumulative exposure level. As millions of workers are exposed to diesel exhaust and an increasing number of workers are exposed to crystalline silica while manufacturing stone countertops and sandblasting denim[65,66], these findings have significant public health implications and highlight the importance of occupational safety regulations and effective control programs to eliminate these exposures.

Night shift work leads to circadian rhythm disruption, which is associated with cancer initiation and progression, and has been classified as Group 2A human carcinogen by IARC[67]. The few studies that investigated shift work in relation to lung cancer risk reached inconsistent results[68–76], which could perhaps be explained by misclassification based

on shift work and its co-exposures to other lung carcinogens, as well as incomplete control of confounding factors such as smoking. Sleep duration may modify the association between shift work and lung cancer risk[70], although the relationship between sleep duration and lung cancer is also inconsistent[70,77–82].

Non-occupational lung cancer risk factors may play a synergistic or antagonistic role with occupational factors. Studies have reported joint effects of smoking and occupational exposures, including diesel exhausts, crystalline silicas, and exposure circumstances as welders, bricklayers, and painters, in lung cancer risk[63,64,83–85]. Future large studies are needed to integrate both occupational and non-occupational risk factors to understand their interactions and mixed effect on lung cancer. Finally, the "healthy worker effect" should be considered when interpreting study results that compare the incidence or mortality of occupational settings to those of the general population, in which the true associations are likely to be underestimated.

5. Radon

Radon has been classified as a Group 1 human carcinogen by IARC based on sufficient evidence from epidemiologic studies reporting a strong exposure-response relationship between occupational exposure to radon and its decay products and risk of lung cancer[86]. It is the leading cause of lung cancer in nonsmokers[86]. Subsequent studies investigating exposure to residential radon and risk of lung cancer have generally supported an adverse association[87–90], although epidemiologic studies have encountered methodologic challenges to exposure assessment of residential radon concentration, which can be affected by the type and age of the house, renovation materials, ventilation capacity of indoor air, temperature, humidity, atmospheric pressure, and season[91].

Studies investigating the association by histologic subtypes have generally supported an adverse association across all histologic subtypes as summarized by a meta-analysis[92].

6. Air pollution

Outdoor air pollution and particulate matter (PM) in outdoor air pollution were classified as Group 1 human carcinogens by IARC in 2013 based on sufficient evidence from human and experimental animal studies, as well as mechanistic evidence[93]. Several large-scale cohort studies with data on confounding variables (i.e., cigarette smoking) provided strong evidence of a positive link between ambient air pollution and lung cancer incidence and mortality[94–96]. A meta-analysis reported a statistically significant increased risk of lung cancer incidence in each 10 μg/m^3 increase in $PM_{2.5}$ (RR = 1.09, 95% CI: 1.04, 1.14)[97]. A recently updated meta-analysis including 20 cohort studies reported an even greater risk of lung cancer associated with $PM_{2.5}$[98]. Although there was no significant heterogeneity in findings across studies where either fixed site monitoring or model-based approaches for exposure assessment were used, most of these studies were conducted in North America and Europe, where ambient exposure is lower; to date, very few studies have been conducted in Asia and other parts of the world with higher known exposure levels[99–103]. Several recent large epidemiologic studies also support an adverse effect of $PM_{2.5}$ and PM_{10} on lung cancer risk[104–107], although two studies showed no clear association with PM due to lack of controlling for cigarette smoking[108] and short follow-up time[109].

In addition to PM, studies on nitrogen dioxide (NO_2), a marker of traffic-related air pollution, suggested an increased risk of lung cancer associated with increasing exposure to NO_2. These studies were summarized in two meta-analyses[110,111]. Several recent large epidemiologic studies provided inconsistent results, with some studies supporting an increased risk of lung cancer associated with exposure to NO_2[104,112], and others showing no association[106,109,113]. A recent study among postmenopausal never-smoker women reported an increased risk of lung cancer among those residing <50 m from primary highways, suggesting that other traffic-related indicators including ultrafine particles, particle-bound polycyclic aromatic hydrocarbons (PPAHs) and volatile organic compounds (VOCs) might contribute to an increased risk of lung cancer[113]. The few studies that investigated O_3 and lung cancer risk yielded inconsistent results[104,106,114].

Household burning of coal and biomass fuel (primarily wood) has been classified as Group 1 and Group 2A human carcinogens for lung cancer, respectively[115]. Combustion of solid fuels is also a major contributor to indoor and outdoor air pollution, particularly in "developing countries" including China[116]. Epidemiologic studies conducted in China[117,118], North America, and Europe[115] gave compelling evidence to support the relationship between coal combustion and risk of lung cancer. An updated review of epidemiologic studies reported a summarized OR of 1.17 (95% CI: 1.01, 1.37) for lung cancer associated with biomass for cooking and/or heating, and a higher risk among women in "developing countries" compared with "developed countries", which was consistent with higher exposure among the former[119]. Exposure levels of indoor air pollution from combustion of solid fuels for cooking and heating are largely influenced by the type and quality of fuels, the type and condition of stoves, the type of ventilation and housing, the specific tasks and skill of the stove operator, and weather conditions[115]. Better exposure assessment is warranted to elucidate exposure-response relationship between solid fuels and lung cancer risk.

A limited number of studies have investigated air pollution and risk of lung cancer by histologic subtypes. A meta-analysis reported a stronger association of adenocarcinoma with $PM_{2.5}$ (RR = 1.40, 95% CI: 1.07, 1.83 per 10 $\mu g/m^3$) based on three studies, and with PM_{10} (RR = 1.29, 95% CI: 1.02, 1.63 per 10 $\mu g/m^3$) based on two studies[97]. Some - but not all - subsequent studies supported a stronger association between $PM_{2.5}$[120,121], PM_{10}[122], and adenocarcinoma[123]. Further studies of the relationship between air pollution and lung cancer histologic subtypes are needed.

Evidence of the link between different components of PM and risk of lung cancer is also limited[97,124]. A study using $PM_{2.5}$ oxidative burden, the product of $PM_{2.5}$ mass, and oxidative potential, which is the ability of regional filter extracts to deplete antioxidants glutathione or ascorbate in a synthetic respiratory tract lining fluid, reported a significantly increased risk of lung cancer mortality associated with glutathione-related, but not ascorbate-related, $PM_{2.5}$ oxidative burden[125]. Several other studies reported a similar adverse association between various $PM_{2.5}$ components and lung cancer risk[126–128]. Several PM components including nickel, chromium, cadmium, and silica dust, as well as diesel engine exhaust have been classified as lung cancer carcinogens by IARC based on sufficient evidence in humans[129,130].

Very few studies have examined the combined effects of air pollution, cigarette smoking, and other lifestyle factors. The American Cancer Society Cancer Prevention Study II (ACS CPS-II) suggested a greater risk of lung cancer mortality among those with $PM_{2.5}$ and cigarette smoking exposures than what was expected from the sum of their individual effects[131]. European cohort studies found no interaction between ambient $PM_{2.5}$ or PM_{10} concentrations and fruit consumption in relation to lung cancer risk[95]. Studying the interactions of various lifestyle factors with air pollution in lung cancer risk has important public health implications. Future longitudinal studies with detailed information on confounding factors and modifiable lifestyle factors are needed.

7. Dietary factors

Epidemiologic studies investigating the relationship between dietary intake and lung cancer risk have reported mixed results. The variety of food frequency questionnaires used in these studies makes comparison challenging. Meta-analyses suggested a moderately reduced risk of lung cancer associated with greater intake of fruits and vegetables[132,133], soy-products[134], and fish[135], as well as a moderately increased risk associated with high intakes of red and processed meat[136,137]. However, studies of supplementary nutrients including vitamin A, vitamin C, vitamin E, carotenoid, folate, selenium, and multivitamins provided no

evidence of their protective effect against lung cancer[138,139]. Two interventional studies indicated that beta-carotene supplements increased the risk of lung cancer among smokers[140–142].

In addition to specific food items and nutrients, recent studies have also investigated dietary patterns in relation to lung cancer risk. Although definitions of dietary patterns differed between studies, healthy dietary patterns, generally defined as a diet rich in fruits, vegetables, fish, white meat, and soy products, have been linked to a reduced risk of lung cancer according to some studies reporting statistically significant results[143–146] and others showing non-significant results[147–149]. On the other hand, studies suggested an increased risk associated with a Western diet high in red meat and low in fruits and vegetables[147,148,150,151].

In summary, the relationship between dietary intake and risk of lung cancer is inconclusive. The complexity of food items, variety of cooking methods, and variations in eating patterns over time make dietary exposure assessment extremely challenging. Future large prospective studies with longitudinally collected information on dietary intake are needed to elucidate the role of diet and its interactions with other lifestyle and environmental factors in relation to lung cancer risk.

8. Physical activity

Physical activity has proven benefits for prevention of many chronic diseases including certain cancers[152]. Epidemiologic studies investigating physical activity and risk of lung cancer, however, have reached inconclusive results. Studies generally supported an inverse association between leisure time physical activity and risk of lung cancer and its histologic subtypes, and found an inverse association mainly among smokers or men[153–156]. The few studies that investigated household physical activity and risk of lung cancer reported no association[157,158]. In contrast, the majority of studies investigating occupational physical activity and lung cancer risk found no significant association[157,159–164], except three studies reported a significantly increased risk associated with occupational physical activity[165–167] and that one study showed a reduced risk[168]. A recent meta-analysis suggested an elevated risk of lung cancer associated with high-level occupational physical activity compared with low-level occupational physical activity or sedentary occupation among men, but not among women[169].

The observed variations in the association between lung cancer and physical activity by different types of physical activity, by smoking status, and by gender highlight the importance of future research. Residual confounding due to lack of detailed information on smoking intensity and other environmental and lifestyle factors could be a potential concern. Reverse causation should also be considered. For example, a long history of unhealthy lifestyle (i.e., smoking) may cause subclinical cancer or respiratory conditions, which may in turn impede the ability or desire to exercise even years before the lung cancer becomes overt. Therefore, the disease process may be the cause of reduction in physical activity. On the other hand, degrading health might motivate the individuals to change unhealthy lifestyles and become more physically active. It is also essential to understand concurrent co-exposures when assessing occupational physical activity and to elucidate interactions between physical activity and other environmental and lifestyle factors in lung cancer risk.

9. Psychological factors

Few studies have explored psychological factors in relation to lung cancer risk, and the results have been inconclusive. Work stress is not significantly associated with increased risk of lung cancer[170]. Early life stress measured as a parental death during childhood is associated with increased risk of lung cancer[171]. An early meta-analysis reported positive association between stress-related psychological factors and lung cancer risk[172]. A recent meta-analysis of cohort studies showed an increased risk of lung cancer associated with anxiety and depression with significant study heterogeneity[173]. Depression has been linked to reduced immune function and increased inflammation, potentially leading to cancer development and progression[174,175]. Individuals with anxiety or depression are also likely to smoke, drink, and be physically inactive and obese[176]. It is essential to control these important lifestyle factors when studying the relationship between depression and anxiety and lung cancer risk.

10. Family history

Family history of lung cancer has been linked to an increased risk of lung cancer in the majority of published studies with an estimated twofold association[177–180]. The strength of the association varied by geographic regions and certain sociodemographic factors as reviewed in a recent systematic review and meta-analysis, with a stronger association generally reported among Asians, younger individuals, ever smokers, and individuals with multiple affected relatives (Table 1)[177]. Currently no strong evidence indicates significant difference in the association by histologic subtypes[178,181]. Although heritable genetic susceptibility could explain some of the association between family history and lung cancer risk[182,183], shared environmental and lifestyle risk factors as well as gene-environment interactions are also important contributors to the relationship[177].

11. Genetic factors

A number of genetic susceptibility loci have been identified by genome-wide association studies (GWAS) for lung cancer overall and for specific histologic subtypes over the past decade. Among European populations, 19q13, 15q25, 15q21.1, 10q23.33, 8p21.1, 6q27, 6p21, 5p15, 5q14.2, 4p15.2, 3p26, and 1p31.1 were significantly associated with lung cancer[184–195], whereas 22q12.1, 13q13.1, 12q13.33, 9p21.3, 6p21, 4p15.2, and 2q32.1 were associated with SCC[196–198], 20q13.33, 18q12.1, 11q23.3, 10q24.3, 8p12, 5p15, and 3q28 were associated with adenocarcinoma[185,191,196–199]. Among Asian populations, studies have identified 20q13.2, 20q11.21, 17q24.3, 13q12.12, 12q12.2, 10p14, 6p21.33, 6p22.2, 5q32, 5q31.1, 5p15, 3q28, and 1p36.32 for lung cancer[200–204], 3q29 for non-small cell lung cancer [205], 12q23.1 for SCC [206], and 5p15, 3q28, and 6p21 for adenocarcinoma[204] (Table 1). Studies, mainly on Asian non-smoking women, have identified 17q24.3, 13q31.3, 12q13.13, 10q25.2, 6q22.2, 6p21, 5p15, 3q28, and 2p16.3 for lung cancer[207–210], and 18p11 for non-small cell lung cancer[211] among non-smokers. These identified loci are mainly located in the regions related to smoking behavior, nicotine addiction, DNA repair, and immune response[186,188,193], suggesting potential directions for future etiologic studies. The effect size of most genetic associations reported in the literature was modest with an OR of ~1.3[182], although higher effect size has been reported in familial lung cancers[187]. Considering small effect size of single genetic locus, Shen et al. constructed polygenic risk scores (PRS) and showed that individuals with high PRS (the highest 10%) had 96% higher risk of lung cancer than the lowest 10% (HR = 1.96, 95% CI: 1.53, 2.51), suggesting that PRS could be potentially used to identify high-risk populations for lung cancer[212].

A growing body of literature has investigated gene-environment interactions and lung cancer risk. Studies using GWAS data to explore gene-environment interactions in lung cancer risk have identified loci on 15q22.32 and 14q22.1 that interact with smoking[213], loci on 6p21.32 and 3q28 with household air pollution[214], and loci on 22q13.31, 11q13, 7q32.1, and 2q34 with asbestos[215,216]. A number of interactions have been reported by a study exploring interactions with occupational exposure to 70 agents[217]. Although gene-environment interactions are likely to play an essential role in individual susceptibility to lung cancer[218,219], studies investigating gene-environment interactions are still in an exploratory stage due to the limitations of available study populations with sufficient statistical power and data on exposures.

Table 1
Associations between genetic factors, family history and the risk of lung cancer and its subtypes.

	Loci[a]	Family history[b] HR (95% CI)
Lung cancer		
Western	19q13, 15q25, 15q21.1, 10q23.33, 8p21.1, 6q27, 6p21, 5p15, 5q14.2, 4p15.2, 3p26, and 1p31.1	1.73 (1.58–1.89)
Asia	20q13.2, 20q11.21, 17q24.3, 13q12.12, 12q12.2, 10p14, 6p21.33, 6p22.2, 5q32, 5q31.1, 5p15, 3q28, and 1p36.32	2.14 (1.83–2.50)
Squamous cell carcinoma		
Western	22q12.1, 13q13.1, 12q13.33, 9p21.3, 6p21, 4p15.2, and 2q32.1	1.55 (1.29–1.85)
Asia	12q23.1	0.65 (0.09–4.68)
Adenocarcinoma		
Western	20q13.33, 18q12.1, 11q23.3, 10q24.3, 8p12, 5p15, and 3q28	1.70 (1.49–1.94)
Asia	5p15, 3q28, and 6p21	1.86 (1.34–1.94)
Non-small cell lung cancer		
Western	–	1.72 (1.54–1.92)
Asia	3q29	1.76 (1.44–2.16)

[a] Western refers to European population.
[b] Pooled summary estimates (95% CI) from Ang L et al[177].

12. Other factors

Several other factors have also been studied in relation to lung cancer risk, but to a lesser extent. Studies linking obesity to lung cancer risk reached inconsistent results. Two meta-analyses of prospective cohort studies showed that waist circumference, a simple yet sensitive indicator of obesity, is positively associated with lung cancer risk regardless of smoking status[220,221]. Compared with the normal category, the highest category of body mass index was inversely associated with lung cancer risk, but the inverse association disappeared for never smokers or SCC after stratifying by smoking status or histological subtype, respectively[221]. A study covering 42% of the United States population reported an increased risk of lung cancer associated with low social economic status (SES)[222]. The observed association is likely to be explained by confounding factors. Smoking is more prevalent among populations with low SES, which is associated with poor access to healthy food, hygiene, health insurance, and professional healthcare[223]. Another study from the United States found a significant negative correlation between lung cancer incidence rates in men and median income at state level, however, the significant correlation disappeared after controlling for smoking, age, and race[224].

A growing body of evidence supports that sex hormones might play a role in the development of lung cancer[225]. Epidemiologic studies investigated menstrual and reproductive factors, hormonal contraception, and hormone replacement therapy (HRT) in relation to female lung cancer risk, and the results were inconsistent. A recent meta-analysis employing a combined indicator reported that exposure to higher levels of endogenous and exogenous sex steroid hormones was associated with a reduced risk of lung cancer among non-smoking women[226]. The higher levels of endogenous sex steroid hormone exposure were defined as younger ages at menarche, older ages at menopause, longer reproductive windows (only for postmenopausal women), longer menstrual cycle, pregnancy history, first pregnancy at younger ages, and multiple pregnancies. The higher levels of exogenous sex steroid hormone exposure were defined as use of oral contraception, use of HRT, and isoflavone intake from food[226]. One population-based prospective study among Caucasian men investigated androgens and found higher testosterone levels associated with increased risk of lung cancer[227].

Infectious agents can activate inflammatory cells and inflammatory signaling pathways that facilitate the development of an inflammatory environment and subsequently promote lung carcinogenesis[228]. Mechanistic evidence supports that both bacterial (e.g., *Chlamydophila pneumonia, Mycobacterium tuberculosis, Helicobacter pylori*) and viral (e.g., human immunodeficiency virus, human papilloma virus, Epstein–Barr virus, cytomegalovirus, and influenza virus) infections may increase the risk of lung cancer, but epidemiologic studies have been limited[228]. A recent meta-analysis showed that previous lung diseases, such as asthma, chronic bronchitis, emphysema, pneumonia, tuberculosis, and chronic obstructive pulmonary disease, were associated with increased risk of lung cancer and its subtypes, and the association was stronger among older individuals and Asian populations[229]. On the contrary, a history of hay fever was associated with lower risk of lung cancer[229].

13. Risk factors for non-smokers

Lung cancer among non-smokers has been considered as a different disease[230]. Approximately 15–25% of lung cancers occur in non-smokers, and the proportion varies significantly among different populations with a much higher proportion for women than men worldwide, particularly in South Asia[230]. A majority of lung cancer in non-smokers are adenocarcinomas[231]. It is essential to evaluate the risk factors for lung cancer among non-smokers. Epidemiologic studies among non-smokers have generally supported an increased risk of lung cancer associated with exposure to second-hand smoke[232,233], radon[234], $PM_{2.5}$[97], cooking oil fumes[235], and family history[177]. Limited studies have investigated occupational hazards and lung cancer risk among non-smokers[236,237].

14. Conclusions

As a result of previous studies, smoking, radon, air pollution, and occupational exposure to asbestos, diesel fumes, arsenic, beryllium, cadmium, chromium, nickel, and silica are well-established risk factors for lung cancer. Alcohol consumption, physical activity, obesity, dietary factors, social and psychological considerations, infectious agents, hormones, as well as complex genetic predispositions and interactions have also been suggested as contributing factors for lung cancer, although the roles of these factors are inconclusive.

Residual confounding from smoking and collinearity/multicollinearity due to co-exposures to correlated risk factors has been a major challenge for studying lung cancer risk factors, particularly those with moderate and low associations with lung cancer. Statistical approaches such as adjusting confounding factors to a finer degree, conducting stratified analyses, and performing mixture analyses are available solutions. In addition, given the complex exposure of humans in the real world, it is pivotal to understand the complex exposure patterns among populations and investigate the mixture effects from complex exposures and gene-environment interactions. To achieve this goal, detailed information from large and diverse populations is needed to provide sufficient statistical power to investigate multiple exposures and their mixture effects on lung cancer risk.

An emerging novel approach blending cancer primary prevention service and research through a digital platform may provide a cost-effective solution to the challenges in cancer prevention, including lung cancer. Chinese National Cancer Center recently developed the Smart Health Management Digital Platform for Primary Cancer Prevention

(SmartHMDP-PCP), which can provide a tool to build personal exposure profiles for risk assessment, individualized cancer prevention recommendations, and alerts of cutting-edge scientific findings on management of behavioral, environmental, and psychosocial risk factors[238]. De-identified exposure profiles of consented individuals will be compiled into the unique epidemiologic databases that are customizable for analytics[238]. Implementation studies are needed to understand the effectiveness of SmartHMDP-PCP in lung cancer prevention.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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Author contributions

All authors contributed to writing and revising the manuscript.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660.
2. Zhang Y, Luo G, Etxeberria J, et al. Global patterns and trends in lung cancer incidence: a population-based study. *J Thorac Oncol*. 2021;16(6):933–944. doi:10.1016/j.jtho. 2021.01.1626.
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115–132. doi:10.3322/caac.21338.
4. Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag Res*. 2019;11:943–953. doi:10.2147/CMAR.S187317.
5. Zou XN, Lin DM, Wan X, et al. Histological subtypes of lung cancer in Chinese males from 2000 to 2012. *Biomed Environ Sci*. 2014;27(1):3–9. doi:10.3967/bes2014.010.
6. Gao W, Wen CP, Wu A, et al. Association of computed tomographic screening promotion with lung cancer overdiagnosis among Asian women. *JAMA Intern Med*. 2022;182(3):283–290. doi:10.1001/jamainternmed.2021.7769.
7. Hsu HT, Tang EK, Wu MT, et al. Modified lung-RADS improves performance of screening LDCT in a population with high prevalence of non-smoking-related lung cancer. *Acad Radiol*. 2018;25(10):1240–1251. doi:10.1016/j.acra.2018.01.012.
8. IARC Working Group on the Evaluation of Carcinogenic Risks to HumansTobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum*. 2004;83:1–1438.
9. IARC Working Group on the Evaluation of Carcinogenic Risks to HumansPersonal habits and indoor combustions. Volume 100 E. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum*. 2012;100(Pt E):1–538.
10. Risch HA, Howe GR, Jain M, et al. Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. *Am J Epidemiol*. 1993;138(5):281–293. doi:10.1093/oxfordjournals.aje.a116857.
11. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst*. 1996;88(3–4):183–192. doi:10.1093/jnci/88.3-4.183.
12. Flanders WD, Lally CA, Zhu BP, et al. Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption: results from Cancer Prevention Study II. *Cancer Res*. 2003;63(19):6556–6562.
13. Freedman ND, Leitzmann MF, Hollenbeck AR, et al. Cigarette smoking and subsequent risk of lung cancer in men and women: analysis of a prospective cohort study. *Lancet Oncol*. 2008;9(7):649–656. doi:10.1016/S1470-2045(08)70154-2.
14. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer*. 2008;122(1):155–164. doi:10.1002/ijc.23033.
15. Haiman CA, Stram DO, Wilkens LR, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med*. 2006;354(4):333–342. doi:10.1056/NEJMoa033250.
16. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer*. 2001;31(2–3):139–148. doi:10.1016/s0169-5002(00)00181-1.
17. Wakai K, Inoue M, Mizoue T, et al. Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol*. 2006;36(5):309–324. doi:10.1093/jjco/hyl025.
18. Schivo M, Avdalovic MV, Murin S. Non-cigarette tobacco and the lung. *Clin Rev Allergy Immunol*. 2014;46(1):34–53. doi:10.1007/s12016-013-8372-0.
19. Wynder EL, Mabuchi K. Lung cancer among cigar and pipe smokers. *Prev Med*. 1972;1(4):529–542. doi:10.1016/0091-7435(72)90035-7.
20. Akl EA, Gaddam S, Gunukula SK, et al. The effects of waterpipe tobacco smoking on health outcomes: a systematic review. *Int J Epidemiol*. 2010;39(3):834–857. doi:10.1093/ije/dyq002.
21. Boffetta P, Pershagen G, Jöckel KH, et al. Cigar and pipe smoking and lung cancer risk: a multicenter study from Europe. *J Natl Cancer Inst*. 1999;91(8):697–701. doi:10.1093/jnci/91.8.697.
22. Iribarren C, Tekawa IS, Sidney S, et al. Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. *N Engl J Med*. 1999;340(23):1773–1780. doi:10.1056/nejm199906103402301.
23. Boffetta P, Aagnes B, Weiderpass E, et al. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer*. 2005;114(6):992–995. doi:10.1002/ijc.20811.
24. Luo J, Ye W, Zendehdel K, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet*. 2007;369(9578):2015–2020. doi:10.1016/s0140-6736(07)60678-3.
25. Andreotti G, Freedman ND, Silverman DT, et al. Tobacco use and cancer risk in the agricultural health study. *Cancer Epidemiol Biomarkers Prev*. 2017;26(5):769–778. doi:10.1158/1055-9965.Epi-16-0748.
26. Accortt NA, Waterbor JW, Beall C, et al. Cancer incidence among a cohort of smokeless tobacco users (United States). *Cancer Causes Control*. 2005;16(9):1107–1115. doi:10.1007/s10552-005-0247-0.
27. Boffetta P, Hecht S, Gray N, et al. Smokeless tobacco and cancer. *Lancet Oncol*. 2008;9(7):667–675. doi:10.1016/s1470-2045(08)70173-6.
28. Bracken-Clarke D, Kapoor D, Baird AM, et al. Vaping and lung cancer - a review of current data and recommendations. *Lung Cancer*. 2021;153:11–20. doi:10.1016/j.lungcan.2020. 12.030.
29. Orr MS. Electronic cigarettes in the USA: a summary of available toxicology data and suggestions for the future. *Tob Control*. 2014;23(2):22 SupplSuppl 2ii18-. doi:10.1136/tobaccocontrol-2013-051474.
30. Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. *Nicotine Tob Res*. 2014;16(10):1319–1326. doi:10.1093/ntr/ntu078.
31. Dinardo P, Rome ES. Vaping: the new wave of nicotine addiction. *Cleve Clin J Med*. 2019;86(12):789–798. doi:10.3949/ccjm.86a.19118.
32. Tang MS, Wu XR, Lee HW, et al. Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. *Proc Natl Acad Sci U S A*. 2019;116(43):21727–21731. doi:10.1073/pnas.1911321116.
33. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112(3):580–593. doi:10.1038/bjc. 2014.579.
34. Chao C. Associations between beer, wine, and liquor consumption and lung cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2007;16(11):2436–2447. doi:10.1158/1055-9965.EPI-07-0386.
35. Brenner DR, Fehringer G, Zhang ZF, et al. Alcohol consumption and lung cancer risk: a pooled analysis from the international lung cancer consortium and the SYNERGY study. *Cancer Epidemiol*. 2019;58:25–32. doi:10.1016/j.canep.2018.10.006.
36. Freudenheim JL, Ritz J, Smith-Warner SA, et al. Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr*. 2005;82(3):657–667. doi:10.1093/ajcn.82.3.657.
37. Im PK, Millwood IY, Kartsonaki C, et al. Alcohol drinking and risks of total and site-specific cancers in China: a 10-year prospective study of 0.5 million adults. *Int J Cancer*. 2021;149(3):522–534. doi:10.1002/ijc.33538.
38. Shen C, Schooling CM, Chan WM, et al. Alcohol intake and death from cancer in a prospective Chinese elderly cohort study in Hong Kong. *J Epidemiol Community Health*. 2013;67(10):813–820. doi:10.1136/jech-2013-202684.
39. Yang L, Zhou M, Sherliker P, et al. Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up. *Int J Epidemiol*. 2012;41(4):1101–1113. doi:10.1093/ije/dys075.
40. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. *Ann Oncol*. 2011;22(12):2631–2639. doi:10.1093/annonc/mdr027.
41. Bandera EV, Freudenheim JL, Graham S, et al. Alcohol consumption and lung cancer in white males. *Cancer Causes Control*. 1992;3(4):361–369. doi:10.1007/BF00146890.
42. Benedetti A, Parent ME, Siemiatycki J. Consumption of alcoholic beverages and risk of lung cancer: results from two case-control studies in Montreal, Canada. *Cancer Causes Control*. 2006;17(4):469–480. doi:10.1007/s10552-005-0496-y.
43. Chow WH, Schuman LM, McLaughlin JK, et al. A cohort study of tobacco use, diet, occupation, and lung cancer mortality. *Cancer Causes Control*. 1992;3(3):247–254. doi:10.1007/BF00124258.
44. De Stefani E, Correa P, Deneo-Pellegrini H, et al. Alcohol intake and risk of adenocarcinoma of the lung. A case-control study in Uruguay. *Lung Cancer*. 2002;38(1):9–14. doi:10.1016/s0169-5002(02)00153-8.
45. De Stefani E, Correa P, Fierro L, et al. The effect of alcohol on the risk of lung cancer in Uruguay. *Cancer Epidemiol Biomarkers Prev*. 1993;2(1):21–26.
46. Hu J, Mao Y, Dryer D, et al. Canadian cancer registries epidemiology research G. Risk factors for lung cancer among Canadian women who have never smoked. *Cancer Detect Prev*. 2002;26(2):129–138. doi:10.1016/s0361-090x(02)00038-7.
47. Kubik AK, Zatloukal P, Tomasek L, et al. Dietary habits and lung cancer risk among non-smoking women. *Eur J Cancer Prev*. 2004;13(6):471–480. doi:10.1097/00008469-200412000 -00002.
48. Mettlin C. Milk drinking, other beverage habits, and lung cancer risk. *Int J Cancer*. 1989;43(4):608–612. doi:10.1002/ijc.2910430412.
49. Pollack ES, Nomura AM, Heilbrun LK, et al. Prospective study of alcohol consumption and cancer. *N Engl J Med*. 1984;310(10):617–621. doi:10.1056/NEJM198403083101003.

50. Prescott E, Gronbaek M, Becker U, et al. Alcohol intake and the risk of lung cancer: influence of type of alcoholic beverage. *Am J Epidemiol*. 1999;149(5):463–470. doi:10.1093/oxfordjournals.aje.a009834.
51. Ruano-Ravina A, Figueiras A, Barros-Dios JM. Type of wine and risk of lung cancer: a case-control study in Spain. *Thorax*. 2004;59(11):981–985. doi:10.1136/thx.2003.018861.
52. Rohrmann S, Linseisen J, Boshuizen HC, et al. Ethanol intake and risk of lung cancer in the European prospective investigation into cancer and nutrition (EPIC). *Am J Epidemiol*. 2006;164(11):1103–1114. doi:10.1093/aje/kwj326.
53. Shimazu T, Inoue M, Sasazuki S, et al. Alcohol and risk of lung cancer among Japanese men: data from a large-scale population-based cohort study, the JPHC study. *Cancer Causes Control*. 2008;19(10):1095–1102. doi:10.1007/s10552-008-9173-2.
54. Li Y, Yang H, Cao J. Association between alcohol consumption and cancers in the Chinese population–a systematic review and meta-analysis. *PLoS ONE*. 2011;6(4):e18776. doi:10.1371/journal.pone.0018776.
55. Bandera EV, Freudenheim JL, Marshall JR, et al. Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). *Cancer Causes Control*. 1997;8(6):828–840. doi:10.1023/a:1018456127018.
56. Dosemeci M, Gokmen I, Unsal M, et al. Tobacco, alcohol use, and risks of laryngeal and lung cancer by subsite and histologic type in Turkey. *Cancer Causes Control*. 1997;8(5):729–737. doi:10.1023/a:1018479304728.
57. Koo LC. Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. *Nutr Cancer*. 1988;11(3):155–172. doi:10.1080/01635588809513983.
58. Troche JR, Mayne ST, Freedman ND, et al. The association between alcohol consumption and lung carcinoma by histological subtype. *Am J Epidemiol*. 2016;183(2):110–121. doi:10.1093/aje/kwv170.
59. Woodson K, Albanes D, Tangrea JA, et al. Association between alcohol and lung cancer in the alpha-tocopherol, beta-carotene cancer prevention study in Finland. *Cancer Causes Control*. 1999;10(3):219–226. doi:10.1023/a:1008911624785.
60. Malhotra J, Boffetta P. Epidemiology of occupational lung cancer. In: Anttila S, Boffetta P, eds. *Occupational Cancers*; 2020:287–294.
61. Veglia F, Vineis P, Overvad K, et al. Occupational exposures, environmental tobacco smoke, and lung cancer. *Epidemiology*. 2007;18(6):769–775. doi:10.1097/ede.0b013e318142c8a1.
62. Wang JB, Fan YG, Jiang Y, et al. Attributable causes of lung cancer incidence and mortality in China. *Thorac Cancer*. 2011;2(4):156–163. doi:10.1111/j.1759-7714.2011.00067.x.
63. Ge C, Peters S, Olsson A, et al. Diesel engine exhaust exposure, smoking, and lung cancer subtype risks. a pooled exposure-response analysis of 14 case-control studies. *Am J Respir Crit Care Med*. 2020;202(3):402–411. doi:10.1164/rccm.201911-2101OC.
64. Ge C, Peters S, Olsson A, et al. Respirable crystalline silica exposure, smoking, and lung cancer subtype risks. A pooled analysis of case-control studies. *Am J Respir Crit Care Med*. 2020;202(3):412–421. doi:10.1164/rccm.201910-1926OC.
65. The Lancet Respiratory MedicineThe world is failing on silicosis. *Lancet Respir Med*. 2019;7:283.
66. Christiani DC. Occupational exposures and lung cancer. *Am J Respir Crit Care Med*. 2020;202(3):317–319. doi:10.1164/rccm.202004-1404ED.
67. IARC Monographs Vol 124 groupCarcinogenicity of night shift work. *Lancet Oncol*. 2019;20(8):1058–1059. doi:10.1016/S1470-2045(19)30455-3.
68. Arafa A, Eshak ES, Iso H, et al. Night work, rotating shift work, and the risk of cancer in japanese men and women: the JACC study. *J Epidemiol*. 2021;31(12):585–592. doi:10.2188/jea.JE20200208.
69. Kwon P, Lundin J, Li W, et al. Night shift work and lung cancer risk among female textile workers in Shanghai, China. *J Occup Environ Hyg*. 2015;12(5):334–341. doi:10.1080/15459624.2014.993472.
70. McNeil J, Heer E, Willemsen RF, et al. The effects of shift work and sleep duration on cancer incidence in Alberta's Tomorrow Project cohort. *Cancer Epidemiol*. 2020;67:101729. doi:10.1016/j.canep.2020.101729.
71. Parent ME, El-Zein M, Rousseau MC, et al. Night work and the risk of cancer among men. *Am J Epidemiol*. 2012;176(9):751–759. doi:10.1093/aje/kws318.
72. Schernhammer ES, Feskanich D, Liang G, et al. Rotating night-shift work and lung cancer risk among female nurses in the United States. *Am J Epidemiol*. 2013;178(9):1434–1441. doi:10.1093/aje/kwt155.
73. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health*. 2007;33(5):336–343. doi:10.5271/sjweh.1150.
74. Yong M, Blettner M, Emrich K, et al. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. *Scand J Work Environ Health*. 2014;40(5):502–510. doi:10.5271/sjweh.3438.
75. Pukkala E, Helminen M, Haldorsen T, et al. Cancer incidence among Nordic airline cabin crew. *Int J Cancer*. 2012;131(12):2886–2897. doi:10.1002/ijc.27551.
76. Pukkala E, Martinsen JI, Weiderpass E, et al. Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. *Occup Environ Med*. 2014;71(6):398–404. doi:10.1136/oemed-2013-101803.
77. Gu F, Xiao Q, Chu LW, et al. Sleep duration and cancer in the NIH-AARP diet and health study cohort. *PLoS ONE*. 2016;11(9):e0161561. doi:10.1371/journal.pone.0161561.
78. Hurley S, Goldberg D, Bernstein L, et al. Sleep duration and cancer risk in women. *Cancer Causes Control*. 2015;26(7):1037–1045. doi:10.1007/s10552-015-0579-3.
79. Khawaja O, Petrone AB, Aleem S, et al. Sleep duration and risk of lung cancer in the physicians' health study. *Zhongguo Fei Ai Za Zhi*. 2014;17(9):649–655. doi:10.3779/j.issn.1009-3419.2014.09.02.
80. Luojus MK, Lehto SM, Tolmunen T, et al. Sleep duration and incidence of lung cancer in ageing men. *BMC Public Health*. 2014;14:295. doi:10.1186/1471-2458-14-295.
81. Wang J, Tang H, Duan Y, et al. Association between sleep traits and lung cancer: a mendelian randomization study. *J Immunol Res*. 2021;2021:1893882. doi:10.1155/2021/1893882.
82. Xie J, Zhu M, Ji M, et al. Relationships between sleep traits and lung cancer risk: a prospective cohort study in UK Biobank. *Sleep*. 2021;44(9):zsab089. doi:10.1093/sleep/zsab089.
83. Kendzia B, Behrens T, Jöckel KH, et al. Welding and lung cancer in a pooled analysis of case-control studies. *Am J Epidemiol*. 2013;178(10):1513–1525. doi:10.1093/aje/kwt201.
84. Consonni D, De Matteis S, Pesatori AC, et al. Lung cancer risk among bricklayers in a pooled analysis of case-control studies. *Int J Cancer*. 2015;136(2):360–371. doi:10.1002/ijc.28986.
85. Guha N, Bouaoun L, Kromhout H, et al. Lung cancer risk in painters: results from the SYNERGY pooled case-control study consortium. *Occup Environ Med*. 2021;78(4):269–278. doi:10.1136/oemed-2020-106770.
86. Man-made mineral fibres. *IARC Monographs Eval Carcinogenic Risks Humans*. 1988;43:39–171.
87. Darby S, Hill D, Auvinen A, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ*. 2005;330(7485):223. doi:10.1136/bmj.38308.477650.63.
88. Krewski D, Lubin JH, Zielinski JM, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology*. 2005;16(2):137–145. doi:10.1097/01.ede.0000152522.80261.e3.
89. Lubin JH, Wang ZY, Boice Jr JD, et al. Risk of lung cancer and residential radon in China: pooled results of two studies. *Int J Cancer*. 2004;109(1):132–137. doi:10.1002/ijc.11683.
90. Malinovsky G, Yarmoshenko I, Vasilyev A. Meta-analysis of case-control studies on the relationship between lung cancer and indoor radon exposure. *Radiat Environ Biophys*. 2019;58(1):39–47. doi:10.1007/s00411-018-0770-5.
91. Tchorz-Trzeciakiewicz DE, Klos M. Factors affecting atmospheric radon concentration, human health. *Sci Total Environ*. 2017;584-585:911–920. doi:10.1016/j.scitotenv.2017.01.137.
92. Li C, Wang C, Yu J, et al. Residential radon and histological types of lung cancer: a meta-analysis of case–control studies. *Int J Environ Res Public Health*. 2020;17(4):1457. doi:10.3390/ijerph17041457.
93. Outdoor air pollution. *IARC Monogr Eval Carcinog Risks Hum*. 2016;109:9–444.
94. Krewski D, Jerrett M, Burnett RT, et al. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst*. 2009(140):5–114 discussion 115-36.
95. Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol*. 2013;14(9):813–822. doi:10.1016/S1470-2045(13) 70279-1.
96. Turner MC, Krewski D, Pope 3rd CA, et al. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. *Am J Respir Crit Care Med*. 2011;184(12):1374–1381. doi:10.1164/rccm.201106-1011OC.
97. Hamra GB, Guha N, Cohen A, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. *Environ Health Perspect*. 2014;122(9):906–911. doi:10.1289/ehp.1408092.
98. Pope 3rd CA, Coleman N, Pond ZA, et al. Fine particulate air pollution and human mortality: 25+ years of cohort studies. *Environ Res*. 2020;183:108924. doi:10.1016/j.envres. 2019.108924.
99. Cao J, Yang C, Li J, et al. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. *J Hazard Mater*. 2011;186(2–3):1594–1600. doi:10.1016/j.jhazmat.2010.12.036.
100. Katanoda K, Sobue T, Satoh H, et al. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. *J Epidemiol*. 2011;21(2):132–143. doi:10.2188/jea.je20100098.
101. Peng Z, Liu C, Xu B, et al. Long-term exposure to ambient air pollution and mortality in a Chinese tuberculosis cohort. *Sci Total Environ*. 2017;580:1483–1488. doi:10.1016/j.scitotenv. 2016.12.128.
102. Wong CM, Tsang H, Lai HK, et al. Cancer mortality risks from long-term exposure to ambient fine particle. *Cancer Epidemiol Biomarkers Prev*. 2016;25(5):839–845. doi:10.1158/1055-9965.EPI-15-0626.
103. Yin P, Brauer M, Cohen A, et al. Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of chinese men. *Environ Health Perspect*. 2017;125(11):117002. doi:10.1289/EHP1673.
104. Bai L, Shin S, Burnett RT, et al. Exposure to ambient air pollution and the incidence of lung cancer and breast cancer in the ontario population health and environment cohort. *Int J Cancer*. 2020;146(9):2450–2459. doi:10.1002/ijc.32575.
105. Coleman NC, Burnett RT, Higbee JD, et al. Cancer mortality risk, fine particulate air pollution, and smoking in a large, representative cohort of US adults. *Cancer Causes Control*. 2020;31(8):767–776. doi:10.1007/s10552-020-01317-w.
106. Hvidtfeldt UA, Geels C, Sorensen M, et al. Long-term residential exposure to PM2.5 constituents and mortality in a Danish cohort. *Environ Int*. 2019;133(Pt B):105268. doi:10.1016/j.envint.2019.105268.
107. Pun VC, Kazemiparkouhi F, Manjourides J, et al. Long-term PM2.5 exposure and respiratory, cancer, and cardiovascular mortality in older US adults. *Am J Epidemiol*. 2017;186(8):961–969. doi:10.1093/aje/kwx166.
108. Wang B, Eum KD, Kazemiparkouhi F, et al. The impact of long-term PM2.5 exposure on specific causes of death: exposure-response curves and effect modification among 53 million U.S. Medicare beneficiaries. *Environ Health*. 2020;19(1):20. doi:10.1186/s12940-020-00575-0.

109. Klompmaker JO, Hoek G, Bloemsma LD, et al. Surrounding green, air pollution, traffic noise exposure and non-accidental and cause-specific mortality. *Environ Int*. 2020;134:105341. doi:10.1016/j.envint.2019.105341.
110. Atkinson RW, Butland BK, Anderson HR, et al. Long-term concentrations of nitrogen dioxide and mortality: a meta-analysis of cohort studies. *Epidemiology*. 2018;29(4):460–472. doi:10.1097/ede.0000000000000847.
111. Hamra GB, Laden F, Cohen AJ, et al. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. *Environ Health Perspect*. 2015;123(11):1107–1112. doi:10.1289/ehp.1408882.
112. Eum KD, Kazemiparkouhi F, Wang B, et al. Long-term NO2 exposures and cause-specific mortality in American older adults. *Environ Int*. 2019;124:10–15. doi:10.1016/j.envint. 2018.12.060.
113. Gowda SN, DeRoos AJ, Hunt RP, et al. Ambient air pollution and lung cancer risk among never-smokers in the Women's health initiative. *Environ Epidemiol*. 2019;3(6):e076. doi:10.1097/ee9.0000000000000076.
114. Kazemiparkouhi F, Eum KD, Wang B, et al. Long-term ozone exposures and cause-specific mortality in a US Medicare cohort. *J Expo Sci Environ Epidemiol*. 2020;30(4):650–658. doi:10.1038/s41370-019-0135-4.
115. IARC Working Group on the Evaluation of Carcinogenic Risks to HumansHousehold use of solid fuels and high-temperature frying. *IARC Monogr Eval Carcinog Risks Hum*. 2010;95:1–430.
116. GBD MAPS Working Group. *Burden of Disease Attributable to Coal-Burning and Other Major Sources of Air Pollution in China. Special Report 20*. Health Effects Institute; 2016.
117. Gao YT. Risk factors for lung cancer among nonsmokers with emphasis on lifestyle factors. *Lung Cancer*. 1996;14(1):S39–S45 Suppl. doi:10.1016/s0169-5002(96)90209-3.
118. Zhao Y, Wang S, Aunan K, et al. Air pollution and lung cancer risks in China–a meta-analysis. *Sci Total Environ*. 2006;366(2–3):500–513. doi:10.1016/j.scitotenv.2005.10.010.
119. Bruce N, Dherani M, Liu R, et al. Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. *Thorax*. 2015;70(5):433–441. doi:10.1136/thoraxjnl-2014-206625.
120. Gharibvand L, Lawrence Beeson W, Shavlik D, et al. The association between ambient fine particulate matter and incident adenocarcinoma subtype of lung cancer. *Environ Health*. 2017;16(1):71. doi:10.1186/s12940-017-0268-7.
121. Tomczak A, Miller AB, Weichenthal SA, et al. Long-term exposure to fine particulate matter air pollution and the risk of lung cancer among participants of the Canadian National Breast Screening Study. *Int J Cancer*. 2016;139(9):1958–1966. doi:10.1002/ijc.30255.
122. Moon DH, Kwon SO, Kim SY, et al. Air pollution and incidence of lung cancer by histological type in Korean adults: a Korean national health insurance service health examinee cohort study. *Int J Environ Res Public Health*. 2020;17(3):915. doi:10.3390/ijerph 17030915.
123. Consonni D, Carugno M, De Matteis S, et al. Outdoor particulate matter (PM10) exposure and lung cancer risk in the EAGLE study. *PLoS ONE*. 2018;13(9):e0203539. doi:10.1371/journal.pone.0203539.
124. . *Using 21st Century Science to Improve Risk-Related Evaluations*; 2017.
125. Weichenthal S, Crouse DL, Pinault L, et al. Oxidative burden of fine particulate air pollution and risk of cause-specific mortality in the Canadian census health and environment cohort (CanCHEC). *Environ Res*. 2016;146:92–99. doi:10.1016/j.envres.2015.12.013.
126. Cakmak S, Hebbern C, Pinault L, et al. Associations between long-term PM2.5 and ozone exposure and mortality in the Canadian census health and environment cohort (CANCHEC), by spatial synoptic classification zone. *Environ Int*. 2018;111:200–211. doi:10.1016/j.envint.2017.11.030.
127. Raaschou-Nielsen O, Beelen R, Wang M, et al. Particulate matter air pollution components and risk for lung cancer. *Environ Int*. 2016;87:66–73. doi:10.1016/j.envint.2015. 11.007.
128. Turner MC, Jerrett M, Pope 3rd CA, et al. Long-term ozone exposure and mortality in a large prospective study. *Am J Respir Crit Care Med*. 2016;193(10):1134–1142. doi:10.1164/rccm.201508-1633OC.
129. IARC Working Group on the Evaluation of Carcinogenic Risks to HumansDiesel and Gasoline Engine Exhausts and Some Nitroarenes. IARC monographs on the evaluation of carcinogenic riskd to humans. *IARC Monogr Evaluat Carcinogenic Risks Humans*. 2014;105:9–699.
130. Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst*. 2011;103(24):1827–1839. doi:10.1093/jnci/djr483.
131. Turner MC, Cohen A, Jerrett M, et al. Interactions between cigarette smoking and fine particulate matter in the risk of lung cancer mortality in cancer prevention study II. *Am J Epidemiol*. 2014;180(12):1145–1149. doi:10.1093/aje/kwu275.
132. Wang C, Yang T, Guo XF, et al. The associations of fruit and vegetable intake with lung cancer risk in participants with different smoking status: a meta-analysis of prospective cohort studies. *Nutrients*. 2019;11(8):1791. doi:10.3390/nu11081791.
133. Wang Y, Li F, Wang Z, et al. Fruit and vegetable consumption and risk of lung cancer: a dose-response meta-analysis of prospective cohort studies. *Lung cancer*. 2015;88(2):124–130. doi:10.1016/j.lungcan.2015.02.015.
134. Yang WS, Va P, Wong MY, et al. Soy intake is associated with lower lung cancer risk: results from a meta-analysis of epidemiologic studies. *Am J Clin Nutr*. 2011;94(6):1575–1583. doi:10.3945/ajcn.111.020966.
135. Song J, Su H, Wang BL, et al. Fish consumption and lung cancer risk: systematic review and meta-analysis. *Nutr Cancer*. 2014;66(4):539–549. doi:10.1080/01635581.2014.894102.
136. Farvid MS, Sidahmed E, Spence ND, et al. Consumption of red meat and processed meat and cancer incidence: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol*. 2021;36(9):937–951. doi:10.1007/s10654-021-00741-9.
137. Xue XJ, Gao Q, Qiao JH, et al. Red and processed meat consumption and the risk of lung cancer: a dose-response meta-analysis of 33 published studies. *Int J Clin Exp Med*. 2014;7(6):1542–1553.
138. Cho E, Hunter DJ, Spiegelman D, et al. Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: a pooled analysis of 8 prospective studies. *Int J Cancer*. 2006;118(4):970–978. doi:10.1002/ijc.21441.
139. Gallicchio L, Boyd K, Matanoski G, et al. Carotenoids and the risk of developing lung cancer: a systematic review. *Am J Clin Nutr*. 2008;88(2):372–383. doi:10.1093/ajcn/88.2.372.
140. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study GroupThe effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330(15):1029–1035. doi:10.1056/NEJM199404143301501.
141. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst*. 1996;88(21):1550–1559. doi:10.1093/jnci/88.21.1550.
142. Middha P, Weinstein SJ, Mannisto S, et al. β-carotene supplementation and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: the role of tar and nicotine. *Nicotine Tob Res*. 2019;21(8):1045–1050. doi:10.1093/ntr/nty115.
143. Anic GM, Park Y, Subar AF, et al. Index-based dietary patterns and risk of lung cancer in the NIH-AARP diet and health study. *Eur J Clin Nutr*. 2016;70(1):123–129. doi:10.1038/ejcn.2015.122.
144. Gnagnarella P, Maisonneuve P, Bellomi M, et al. Nutrient intake and nutrient patterns and risk of lung cancer among heavy smokers: results from the COSMOS screening study with annual low-dose CT. *Eur J Epidemiol*. 2013;28(6):503–511. doi:10.1007/s10654-013-9803-1.
145. Gorlova OY, Weng SF, Hernandez L, et al. Dietary patterns affect lung cancer risk in never smokers. *Nutr Cancer*. 2011;63(6):842–849. doi:10.1080/01635581.2011.589958.
146. Mai V, Kant AK, Flood A, et al. Diet quality and subsequent cancer incidence and mortality in a prospective cohort of women. *Int J Epidemiol*. 2005;34(1):54–60. doi:10.1093/ije/dyh388.
147. Balder HF, Goldbohm RA, van den Brandt PA. Dietary patterns associated with male lung cancer risk in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev*. 2005;14(2):483–490. doi:10.1158/1055-9965.EPI-04-0353.
148. De Stefani E, Deneo-Pellegrini H, Boffetta P, et al. Dietary patterns and risk of cancer: a factor analysis in Uruguay. *Int J Cancer*. 2009;124(6):1391–1397. doi:10.1002/ijc.24035.
149. Tsai YY, McGlynn KA, Hu Y, et al. Genetic susceptibility and dietary patterns in lung cancer. *Lung Cancer*. 2003;41(3):269–281. doi:10.1016/s0169-5002(03)00238-1.
150. Gnagnarella P, Maisonneuve P, Bellomi M, et al. Red meat, Mediterranean diet and lung cancer risk among heavy smokers in the COSMOS screening study. *Ann Oncol*. 2013;24(10):2606–2611. doi:10.1093/annonc/mdt302.
151. De Stefani E, Boffetta P, Ronco AL, et al. Nutrient patterns and risk of lung cancer: a factor analysis in Uruguayan men. *Lung Cancer*. 2008;61(3):283–291. doi:10.1016/j.lungcan. 2008.01.004.
152. Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. *Mol Oncol*. 2021;15(3):790–800. doi:10.1002/1878-0261.12772.
153. Liu Y, Li Y, Bai YP, Fan XX. Association between physical activity and lower risk of lung cancer: a meta-analysis of cohort studies. *Front Oncol*. 2019;9:5. doi:10.3389/fonc. 2019.00005.
154. Brenner DR, Yannitsos DH, Farris MS, et al. Leisure-time physical activity and lung cancer risk: a systematic review and meta-analysis. *Lung cancer*. 2016;95:17–27. doi:10.1016/j.lungcan.2016.01.021.
155. Rezende LFM, Sá TH, Markozannes G, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. *Br J Sports Med*. 2018;52(13):826–833. doi:10.1136/bjsports-2017-098391.
156. Schmid D, Ricci C, Behrens G, et al. Does smoking influence the physical activity and lung cancer relation? A systematic review and meta-analysis. *Eur J Epidemiol*. 2016;31(12):1173–1190. doi:10.1007/s10654-016-0186-y.
157. Bak H, Christensen J, Thomsen BL, et al. Physical activity and risk for lung cancer in a Danish cohort. *Int J Cancer*. 2005;116(3):439–444. doi:10.1002/ijc.21085.
158. Steindorf K, Friedenreich C, Linseisen J, et al. Physical activity and lung cancer risk in the European prospective investigation into cancer and nutrition cohort. *Int J Cancer*. 2006;119(10):2389–2397. doi:10.1002/ijc.22125.
159. Colbert LH, Hartman TJ, Tangrea JA, et al. Physical activity and lung cancer risk in male smokers. *Int J Cancer*. 2002;98(5):770–773. doi:10.1002/ijc.10156.
160. Dosemeci M, Hayes RB, Vetter R, et al. Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. *Cancer Causes Control*. 1993;4(4):313–321. doi:10.1007/bf00051333.
161. Lee IM, Sesso HD, Paffenbarger Jr RS. Physical activity and risk of lung cancer. *Int J Epidemiol*. 1999;28(4):620–625. doi:10.1093/ije/28.4.620.
162. Parent ME, Rousseau MC, El-Zein M, et al. Occupational and recreational physical activity during adult life and the risk of cancer among men. *Cancer Epidemiol*. 2011;35(2):151–159. doi:10.1016/j.canep.2010.09.004.
163. Severson RK, Nomura AM, Grove JS, et al. A prospective analysis of physical activity and cancer. *Am J Epidemiol*. 1989;130(3):522–529. doi:10.1093/oxfordjournals.aje.a115366.
164. Thune I, Lund E. The influence of physical activity on lung-cancer risk: a prospective study of 81,516 men and women. *Int J Cancer*. 1997;70(1):57–62. doi:10.1002/(sici)1097-0215(19970106)70:1<57::aid-ijc9>3.0.co;2-5.
165. Brownson RC, Chang JC, Davis JR, et al. Physical activity on the job and cancer in Missouri. *Am J Public Health*. 1991;81(5):639–642. doi:10.2105/ajph.81.5.639.

166. He F, Chen LM, Xiong WM, et al. A case-control study of the association between self-reported occupational and recreational physical activity and lung cancer. *Medicine (Baltimore)*. 2017;96(36):e7923. doi:10.1097/md.0000000000007923.
167. Ho V, Parent ME, Pintos J, et al. Physical activity and lung cancer risk in men and women. *Cancer Causes Control*. 2017;28(4):309–318. doi:10.1007/s10552-017-0872-4.
168. Kaneko R, Zaitsu M, Sato Y, et al. Risk of cancer and longest-held occupations in Japanese workers: a multicenter hospital-based case-control study. *Cancer Med*. 2019;8(13):6139–6150. doi:10.1002/cam4.2499.
169. Rana B, Hu L, Harper A, et al. Occupational physical activity and lung cancer risk: a systematic review and meta-analysis. *Sports Med*. 2020;50(9):1637–1651. doi:10.1007/s40279-020-01312-w.
170. Heikkila K, Nyberg ST, Theorell T, et al. Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116,000 European men and women. *BMJ*. 2013;346:f165. doi:10.1136/bmj.f165.
171. Kennedy B, Valdimarsdóttir U, Sundström K, et al. Loss of a parent and the risk of cancer in early life: a nationwide cohort study. *Cancer Causes Control*. 2014;25(4):499–506. doi:10.1007/s10552-014-0352-z.
172. Chida Y, Hamer M, Wardle J, et al. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol*. 2008;5(8):466–475. doi:10.1038/ncponc1134.
173. Wang YH, Li JQ, Shi JF, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. *Mol Psychiatry*. 2020;25(7):1487–1499. doi:10.1038/s41380-019-0595-x.
174. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171–186. doi:10.1097/PSY. 0b013e3181907c1b.
175. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatry*. 2003;54(3):269–282. doi:10.1016/s0006-3223(03)00566-3.
176. Strine TW, Mokdad AH, Dube SR, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry*. 2008;30(2):127–137. doi:10.1016/j.genhosppsych.2007.12.008.
177. Ang L, Chan CPY, Yau WP, et al. Association between family history of lung cancer and lung cancer risk: a systematic review and meta-analysis. *Lung Cancer*. 2020;148:129–137. doi:10.1016/j.lungcan.2020.08.012.
178. Cote ML, Liu M, Bonassi S, et al. Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis from the International Lung Cancer Consortium. *Eur J Cancer*. 2012;48(13):1957–1968. doi:10.1016/j.ejca.2012.01.038.
179. Gu J, Hua F, Zhong D, et al. Systematic review of the relationship between family history of lung cancer and lung cancer risk. *Zhongguo Fei Ai Za Zhi*. 2010;13(3):224–229. doi:10.3779/j.issn.1009-3419.2010.03.07.
180. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer*. 2005;93(7):825–833. doi:10.1038/sj.bjc.6602769.
181. Lissowska J, Foretova L, Dabek J, et al. Family history and lung cancer risk: international multicentre case-control study in Eastern and Central Europe and meta-analyses. *Cancer Causes Control*. 2010;21(7):1091–1104. doi:10.1007/s10552-010-9537-2.
182. Bosse Y, Amos CI. A decade of GWAS results in lung cancer. *Cancer Epidemiol Biomarkers Prev*. 2018;27(4):363–379. doi:10.1158/1055-9965.EPI-16-0794.
183. Musolf AM, Simpson CL, de Andrade M, et al. Parametric linkage analysis identifies five novel genome-wide significant loci for familial lung cancer. *Hum Hered*. 2016;82(1–2):64–74. doi:10.1159/000479028.
184. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet*. 2008;40(5):616–622. doi:10.1038/ng.109.
185. Broderick P, Wang Y, Vijayakrishnan J, et al. Deciphering the impact of common genetic variation on lung cancer risk: a genome-wide association study. *Cancer Res*. 2009;69(16):6633–6641. doi:10.1158/0008-5472.CAN-09-0680.
186. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature*. 2008;452(7187):633–637. doi:10.1038/nature06885.
187. Liu P, Vikis HG, Wang D, et al. Familial aggregation of common sequence variants on 15q24-25.1 in lung cancer. *J Natl Cancer Inst*. 2008;100(18):1326–1330. doi:10.1093/jnci/djn268.
188. McKay JD, Hung RJ, Gaborieau V, et al. Lung cancer susceptibility locus at 5p15.33. *Nat Genet*. 2008;40(12):1404–1406. doi:10.1038/ng.254.
189. Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature*. 2008;452(7187):638–642. doi:10.1038/nature06846.
190. Wang Y, Broderick P, Webb E, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nat Genet*. 2008;40(12):1407–1409. doi:10.1038/ng.273.
191. McKay JD, Hung RJ, Han Y, et al. Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nat Genet*. 2017;49(7):1126–1132. doi:10.1038/ng.3892.
192. Wang Y, McKay JD, Rafnar T, et al. Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer. *Nat Genet*. 2014;46(7):736–741. doi:10.1038/ng.3002.
193. Wang M, Liu H, Liu Z, et al. Genetic variant in DNA repair gene GTF2H4 is associated with lung cancer risk: a large-scale analysis of six published GWAS datasets in the TRICL consortium. *Carcinogenesis*. 2016;37(9):888–896. doi:10.1093/carcin/bgw070.
194. Li Y, Huang J, Amos CI. Genetic association analysis of complex diseases incorporating intermediate phenotype information. *PLoS ONE*. 2012;7(10):e46612. doi:10.1371/journal.pone. 0046612.
195. Poirier JG, Brennan P, McKay JD, et al. Informed genome-wide association analysis with family history as a secondary phenotype identifies novel loci of lung cancer. *Genet Epidemiol*. 2015;39(3):197–206. doi:10.1002/gepi.21882.
196. Landi MT, Chatterjee N, Yu K, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. *Am J Hum Genet*. 2009;85(5):679–691. doi:10.1016/j.ajhg.2009.09.012.
197. Timofeeva MN, Hung RJ, Rafnar T, et al. Influence of common genetic variation on lung cancer risk: meta-analysis of 14 900 cases and 29 485 controls. *Hum Mol Genet*. 2012;21(22):4980–4995. doi:10.1093/hmg/dds334.
198. Brenner DR, Amos CI, Brhane Y, et al. Identification of lung cancer histology-specific variants applying Bayesian framework variant prioritization approaches within the TRICL and ILCCO consortia. *Carcinogenesis*. 2015;36(11):1314–1326. doi:10.1093/carcin/bgv128.
199. Brennan P, McKay J, Moore L, et al. Uncommon CHEK2 mis-sense variant and reduced risk of tobacco-related cancers: case control study. *Hum Mol Genet*. 2007;16(15):1794–1801. doi:10.1093/hmg/ddm127.
200. Dong J, Hu Z, Wu C, et al. Association analyses identify multiple new lung cancer susceptibility loci and their interactions with smoking in the Chinese population. *Nat Genet*. 2012;44(8):895–899. doi:10.1038/ng.2351.
201. Hu Z, Wu C, Shi Y, et al. A genome-wide association study identifies two new lung cancer susceptibility loci at 13q12.12 and 22q12.2 in Han Chinese. *Nat Genet*. 2011;43(8):792–796. doi:10.1038/ng.875.
202. Jin G, Zhu M, Yin R, et al. Low-frequency coding variants at 6p21.33 and 20q11.21 are associated with lung cancer risk in Chinese populations. *Am J Hum Genet*. 2015;96(5):832–840. doi:10.1016/j.ajhg.2015.03.009.
203. Miki D, Kubo M, Takahashi A, et al. Variation in TP63 is associated with lung adenocarcinoma susceptibility in Japanese and Korean populations. *Nat Genet*. 2010;42(10):893–896. doi:10.1038/ng.667.
204. Shiraishi K, Kunitoh H, Daigo Y, et al. A genome-wide association study identifies two new susceptibility loci for lung adenocarcinoma in the Japanese population. *Nat Genet*. 2012;44(8):900–903. doi:10.1038/ng.2353.
205. Yoon KA, Park JH, Han J, et al. A genome-wide association study reveals susceptibility variants for non-small cell lung cancer in the Korean population. *Hum Mol Genet*. 2010;19(24):4948–4954. doi:10.1093/hmg/ddq421.
206. Dong J, Jin G, Wu C, et al. Genome-wide association study identifies a novel susceptibility locus at 12q23.1 for lung squamous cell carcinoma in Han Chinese. *PLoS Genet*. 2013;9(1):e1003190. doi:10.1371/journal.pgen.1003190.
207. Lan Q, Hsiung CA, Matsuo K, et al. Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. *Nat Genet*. 2012;44(12):1330–1335. doi:10.1038/ng.2456.
208. Li Y, Sheu CC, Ye Y, et al. Genetic variants and risk of lung cancer in never smokers: a genome-wide association study. *Lancet Oncol*. 2010;11(4):321–330. doi:10.1016/s1470-2045(10) 70042-5.
209. Wang Z, Seow WJ, Shiraishi K, et al. Meta-analysis of genome-wide association studies identifies multiple lung cancer susceptibility loci in never-smoking Asian women. *Hum Mol Genet*. 2016;25(3):620–629. doi:10.1093/hmg/ddv494.
210. Kim JH, Park K, Yim SH, et al. Genome-wide association study of lung cancer in Korean non-smoking women. *J Korean Med Sci*. 2013;28(6):840–847. doi:10.3346/jkms.2013.28.6.840.
211. Ahn MJ, Won HH, Lee J, et al. The 18p11.22 locus is associated with never smoker non-small cell lung cancer susceptibility in Korean populations. *Hum Genet*. 2012;131(3):365–372. doi:10.1007/s00439-011-1080-z.
212. Dai J, Lv J, Zhu M, et al. Identification of risk loci and a polygenic risk score for lung cancer: a large-scale prospective cohort study in Chinese populations. *Lancet Respir Med*. 2019;7(10):881–891. doi:10.1016/S2213-2600(19)30144-4.
213. Zhang R, Chu M, Zhao Y, et al. A genome-wide gene-environment interaction analysis for tobacco smoke and lung cancer susceptibility. *Carcinogenesis*. 2014;35(7):1528–1535. doi:10.1093/carcin/bgu076.
214. Hosgood 3rd HD, Song M, Hsiung CA, et al. Interactions between household air pollution and GWAS-identified lung cancer susceptibility markers in the Female Lung Cancer Consortium in Asia (FLCCA). *Hum Genet*. 2015;134(3):333–341. doi:10.1007/s00439-014-1528-z.
215. Liu CY, Stucker I, Chen C, et al. Genome-wide gene-asbestos exposure interaction association study identifies a common susceptibility variant on 22q13.31 associated with lung cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2015;24(10):1564–1573. doi:10.1158/1055-9965.EPI-15-0021.
216. Wei S, Wang LE, McHugh MK, et al. Genome-wide gene-environment interaction analysis for asbestos exposure in lung cancer susceptibility. *Carcinogenesis*. 2012;33(8):1531–1537. doi:10.1093/carcin/bgs188.
217. Malhotra J, Sartori S, Brennan P, et al. Effect of occupational exposures on lung cancer susceptibility: a study of gene-environment interaction analysis. *Cancer Epidemiol Biomarkers Prev*. 2015;24(3):570–579. doi:10.1158/1055-9965.EPI-14-1143-T.
218. Hoeijmakers JH. DNA damage, aging, and cancer. *N Engl J Med*. 2009;361(15):1475–1485. doi:10.1056/NEJMra0804615.
219. Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability-an evolving hallmark of cancer. *Nat Rev Mol Cell Biol*. 2010;11(3):220–228. doi:10.1038/nrm2858.
220. Hidayat K, Du X, Chen G, et al. Abdominal obesity and lung cancer risk: systematic review and meta-analysis of prospective studies. *Nutrients*. 2016;8(12):810. doi:10.3390/nu8120810.
221. Gao J, Lin X, He Y, et al. The comparison of different obesity indexes and the risk of lung cancer: a meta-analysis of prospective cohort studies. *Nutr Cancer*. 2019;71(6):908–921. doi:10.1080/01635581.2019.1595037.
222. Boscoe FP, Johnson CJ, Sherman RL, et al. The relationship between area poverty rate and site-specific cancer incidence in the United States. *Cancer*. 2014;120(14):2191–2198. doi:10.1002/cncr.28632.

223. Casetta B, Videla AJ, Bardach A, et al. Association between cigarette smoking prevalence and income level: a systematic review and meta-analysis. *Nicotine Tob Res*. 2017;19(12):1401–1407. doi:10.1093/ntr/ntw266.
224. Lehrer S, Green S, Rosenzweig KE. Poverty and lung cancer incidence. *Cancer*. 2014;120(24):4007–4008. doi:10.1002/cncr.28960.
225. Fuentes N, Silva Rodriguez M, Silveyra P. Role of sex hormones in lung cancer. *Exp Biol Med (Maywood)*. 2021;246(19):2098–2110. doi:10.1177/15353702211019697.
226. Zeng H, Yang Z, Li J, et al. Associations between female lung cancer risk and sex steroid hormones: a systematic review and meta-analysis of the worldwide epidemiological evidence on endogenous and exogenous sex steroid hormones. *BMC Cancer*. 2021;21(1):690. doi:10.1186/s12885-021-08437-9.
227. Hyde Z, Flicker L, McCaul KA, et al. Associations between testosterone levels and incident prostate, lung, and colorectal cancer. A population-based study. *Cancer Epidemiol Biomarkers Prev*. 2012;21(8):1319–1329. doi:10.1158/1055-9965.Epi-12-0129.
228. Budisan L, Zanoaga O, Braicu C. Links between infections, lung cancer, and the immune system. *Int J Mol Sci*. 2021;22(17):9394. doi:10.3390/ijms22179394.
229. Ang L, Ghosh P, Seow WJ. Association between previous lung diseases and lung cancer risk: a systematic review and meta-analysis. *Carcinogenesis*. 2021;42(12):1461–1474. doi:10.1093/carcin/bgab082.
230. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers–a different disease. *Nat Rev Cancer*. 2007;7(10):778–790. doi:10.1038/nrc2190.
231. Couraud S, Zalcman G, Milleron B, et al. Lung cancer in never smokers–A review. *Eur J Cancer*. 2012;48:1299–1311. doi:10.1016/j.ejca.2012.03.007.
232. Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. *Int J Epidemiol*. 2007;36:1048–1059. doi:10.1093/ije/dym158.
233. Li M, Liu X, Zhang L. The relationship of indoor coal use and environmental tobacco smoke exposure with lung cancer in China: a meta-analysis. *J Cancer Res Ther*. 2018;14(Supplement):S7–S13. doi:10.4103/0973-1482.168965.
234. Cheng ES, Egger S, Hughes S, et al. Systematic review and meta-analysis of residential radon and lung cancer in never-smokers. *Eur Respir Rev*. 2021;30:200230. doi:10.1183/16000617.0230-2020.
235. Ko YC, Cheng LS, Lee CH, et al. Chinese food cooking and lung cancer in women nonsmokers. *Am J Epidemiol*. 2000;151:140–147. doi:10.1093/oxfordjournals.aje.a010181.
236. Brownson RC, Alavanja MC, Chang JC. Occupational risk factors for lung cancer among nonsmoking women: a case-control study in Missouri (United States). *Cancer Causes Control*. 1993;4:449–454. doi:10.1007/bf00050864.
237. Zeka A, Mannetje A, Zaridze D, et al. Lung cancer and occupation in nonsmokers: a multicenter case-control study in Europe. *Epidemiology*. 2006;17:615–623. doi:10.1097/01.ede.0000239582.92495.b5.
238. Huang H, Sun PY, Zou KY, et al. Current situation and prospect of primary prevention of malignant tumor in China. *Zhonghua Zhong Liu Za Zhi*. 2022;44(9):942–949. doi:10.3760/cma.j.cn112152-20220209-00083.