Review Article

Lung cancer risk in never-smokers: An overview of environmental and genetic factors

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Abstract

Lung cancer is the leading cause of cancer-related mortality globally, accounting for 1.8 million deaths in 2020. While the vast majority are caused by tobacco smoking, 15%–25% of all lung cancer cases occur in lifelong never-smokers. The International Agency for Research on Cancer (IARC) has classified multiple agents with sufficient evidence for lung carcinogenesis in humans, which include tobacco smoking, as well as several environmental exposures such as radon, second-hand tobacco smoke, outdoor air pollution, household combustion of coal and several occupational hazards. However, the IARC evaluation had not been stratified based on smoking status, and notably lung cancer in never-smokers (LCINS) has different epidemiological, clinicopathologic and molecular characteristics from lung cancer in ever-smokers. Among several risk factors proposed for the development of LCINS, environmental factors have the most available evidence for their association with LCINS and their roles cannot be overemphasized. Additionally, while initial genetic studies largely focused on lung cancer as a whole, recent studies have also identified genetic risk factors for LCINS. This article presents an overview of several environmental factors associated with LCINS, and some of the emerging evidence for genetic factors associated with LCINS. An increased understanding of the risk factors associated with LCINS not only helps to evaluate a never-smoker's personal risk for lung cancer, but also has important public health implications for the prevention and early detection of the disease. Conclusive evidence on causal associations could inform longer-term policy reform in a range of areas including occupational health and safety, urban design, energy use and particle emissions, and the importance of considering the impacts of second-hand smoke in tobacco control policy.

Keywords: Lung cancer; never-smoker; risk factor; environmental factor; genetic factor

Submitted Aug 31, 2021. Accepted for publication Sep 17, 2021.
doi: 10.21147/j.issn.1000-9604.2021.05.02
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2021.05.02

Introduction

Lung cancer is the leading cause of cancer-related mortality in men and women in 93 and 25 individual countries respectively worldwide (1,2). It has been estimated that in 2020, lung cancer accounted for 1.8 million deaths worldwide, of which more than one-third occurred in China (1,3). Although smoking remains the leading risk factor for lung cancer, 15%–25% of all lung cancer cases globally occur in lifelong never-smokers (4-6), and it has been reported that this proportion is even higher in China, with 43.2% of lung cancer cases (483,040) occurring among never-smokers in 2005 (7). The International Agency for Research on Cancer (IARC) has classified multiple agents with sufficient evidence for lung carcinogenesis in humans as Group 1 carcinogens, including tobacco smoking, as well as several environmental exposures such as radon, second-hand tobacco smoke (SHS), outdoor air pollution, household combustion of coal and several occupational hazards (8-13). However, the IARC evaluation had not been stratified based on smoking status. Current evidence suggests that lung cancer in never-

smokers (LCINS) has different epidemiological, clinicopathologic and molecular characteristics from lung cancer in ever-smokers (4,14). When compared with lung cancer in ever-smokers, LCINS occurs more frequently among women, individuals of East Asian descent, and younger age groups, and is predominantly adenocarcinoma in histology subtype (4,14,15). Therefore, a separate evaluation of environmental risk factors for LCINS is warranted. Similarly, while initial genetic association studies largely focused on risk factors for lung cancer as a whole, more recent studies have also identified genetic risk factors for LCINS.

This article reviews epidemiological and mechanistic evidence for several environmental and genetic factors which are found to be associated with LCINS.

Radon

Radon, as a naturally occurring radioactive noble gas, is present throughout the Earth's crust with varying concentration in different parts of the world. It can readily diffuse through rocks and soil into any air space and accumulate in enclosed areas or unventilated environments. When radon is inhaled by humans, the decay products or radon progenies adhere to the airways of the lungs, where they are thought to continue to emit radioactive alpha particles which potentially induce lung carcinogenesis. Also, based on substantial epidemiological evidence showing a strong and consistent dose-response relationship between increased lung cancer risk and high-level occupational radon exposure amongst underground miners (16,17), radon has been identified as the second strongest risk factor for lung cancer after smoking and the leading risk factor for LCINS worldwide (18). It was classified as a Group 1 carcinogen by IARC in 1988 (8).

However, there are limitations to extrapolating the risk from occupational radon exposure among miners to residential radon exposure in the general population. To assess lung cancer risk attributable to residential radon exposure, large pooled collaborative studies (19-25) and several meta-analyses (26,27) have been conducted to compare the pooled risk estimates with extrapolations from the miner-based risk models (23). Notably, the residual confounding effect of smoking was a major limitation in these studies, as most assessed study populations of both ever-smokers and never-smokers. To establish a link between residential radon and lung cancer risk among never-smokers, we previously carried out a meta-analysis of 24 case-control studies which included 2,341 LCINS cases and 8,967 never-smoker controls, estimating an adjusted excess relative risk (RR) of 0.15 per 100 Bq/m^3 [95% confidence interval (95% CI), 0.06–0.25] (28). Our meta-analysis also found that among never-smokers in radon-prone areas, men were at higher risk of lung cancer than women, although the potential mechanisms underlying this difference remain obscure.

There have been some research into the process by which exposure to radon and the subsequent radiation effect leads to lung carcinogenesis among never-smokers. Past research has suggested that radon exposure might induce fusions of the "rearranged during transfection" (*RET*) gene, caused by an inversion on chromosome 10 (observed in 2/37 lung cancer patients exposed to radiation, compared to 1/240 not exposed, P=0.044) (29). Other research also found that residential radon exposure increased the tumor mutation burden in never-smokers with lung adenocarcinoma (median 4.94 mutations per 1 million base pairs in radon-high group, n=24, *vs*. 2.62 in radon-low group, n=17, P=0.01) (30). An exploratory analysis of DNA methylation has also found that radon exposure may be associated with some epigenetic changes (31). Studies with larger sample size are warranted to analyze the carcinogenic mechanisms of radon exposure among never-smokers.

SHS

SHS has been one of the most widely studied risk factors for LCINS since tobacco smoke was found to be the major cause of lung cancer (14) and is increasingly factored into tobacco control policy (32). SHS is the combination of the exposure to mainstream smoke exhaled by smokers and side-stream smoke produced directly by tobacco containing products (cigarettes, cigars, and pipes) between the smoking puffs (9). Like tobacco smoke, SHS is a complex mixture of numerous compounds with concentrations varying with time and environment. Both mainstream smoke and side-stream smoke contain a similar range of chemicals, but they differ in the relative proportions and amounts. Many of these chemicals belong to the classes known to be genotoxic and carcinogenic, including the IARC group 1, 2A and 2B carcinogens (9); and among them, polycyclic aromatic hydrocarbon (PAH) and nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone are likely to play major roles (33).

Several meta-analyses have provided important epidemiological evidence of the relationship between SHS

and LCINS. Taylor *et al*.'s meta-analysis of 55 studies evaluated lung cancer risk associated with SHS in never-smoking women exposed to smoking spouses in North America, Asia and Europe, and reported an overall pooled RR of 1.27 (95% CI, 1.17–1.37) (34). Another meta-analysis of 20 case-control studies among non-smoking adults in China found that the risk of lung cancer was significantly higher for those exposed to SHS: odds ratio (OR)=1.64 (95% CI, 1.34–2.01) (35). A recent meta-analysis of 28 case-control studies assessed the association between long-term exposures to SHS and lung cancer incidence in China, and reported that the pooled OR for exposure from parents (2.12; 95% CI, 1.63–2.76) was higher than that for exposure from a spouse (1.15; 95% CI 1.00–1.33) and from work (1.45; 95% CI, 1.31–1.62), suggesting higher lung cancer risk from childhood exposure than adulthood exposure (36). However, at least one meta-analysis reported that there was no evidence of an increased lung cancer risk for SHS exposure in childhood (summary RR=0.91; 95% CI, 0.80–1.05) (37).

In contrast to the evidence pointing to an association between SHS and lung cancer risk, several prospective cohort studies have found no association between SHS and LCINS (38-40). Also, in a recent meta-analysis of 41 studies of non-smoking women in Asia, Europe and North America, Ni *et al*. (2018) found a significant association between SHS and lung cancer in 34 case-control studies (pooled OR=1.35; 95% CI, 1.17–1.56), but the association did not reach statistical significance in the seven cohort studies (pooled RR=1.17; 95% CI, 0.94–1.44) (41). The discrepancy between the results of case-control and prospective cohort studies warrants reflection on the possibility of selection and recall biases in the previous case-control studies, and suggests that an update of the IARC evaluation may be informative. It is also important to note that all these studies are subject to exposure misclassification, with self-reported ascertainment of SHS exposure, under-reported exposure in the reference group, and potential confounding due to occupational or other environmental factors (9). Future studies using measurement of serum or urinary cotinine levels may help to identify SHS-attributable risk for lung cancer more accurately (42,43). Another emerging complementary approach is to identify exposure to SHS through the analysis of somatic "mutational signatures" observed within LCINS tumors (44,45). Nonetheless, before a conclusive role of SHS in lung cancer development is established, public health strategies should still highlight the importance of reducing SHS exposure in tobacco control policy and zero tolerance position of the World Health Organization (WHO).

As a higher incidence of epidermal growth factor receptor (*EGFR*) mutations has been observed in LCINS (up to 79%) compared with lung cancer in ever-smokers (10%–20%) (46,47), the relationship between SHS exposure and incidence of *EGFR* mutations in LCINS is another important area of interest for research. Lee *et al*. first reported that SHS exposure was inversely associated with the incidence of *EGFR* mutations in 179 incident cases of LCINS (48), and hypothesized that the mechanism of carcinogenesis in never-smokers exposed to SHS may be similar to that in active smokers, but different from the process involved in mutant-*EGFR*-dependent carcinogenesis (49). Therefore, SHS, like active smoking, could play a role as a negative predictive factor for *EGFR* mutations (50). However, there are also other conflicting findings. Liang *et al*. reported a direct association between SHS exposure duration and rate of *EGFR* mutation (51). Moreover, an extended multinational cohort including 498 LCINS cases found that increased SHS exposure was significantly associated with *EGFR* mutations in female never-smokers, but not in male subjects, suggesting a possible role for sex hormones in the development of lung cancer harbouring *EGFR* mutations (52). Both studies suggested that lung cancer harbouring *EGFR* mutations may be different between the SHS ever-exposed and never-exposed individuals, and it was hypothesized that among the SHS ever-exposed, a low but prolonged dose of tobacco carcinogens might be an inducing factor for *EGFR* mutations (53). In view of the relatively small sample sizes of these studies, caution should be taken when interpreting these results, and larger prospective studies are needed to verify the findings.

Air pollution

Air pollution is the contamination of air by harmful gases, dust and smoke, which are detrimental to human health and the planet as a whole. Air pollution represents a global environmental health problem, which is estimated to have contributed to 6.67 million deaths worldwide in 2019, with over 90% of the world's population living in places where air pollution levels exceed the WHO limits (54). The specific composition of outdoor or ambient air pollution varies across the globe. It depends on the specific climatic conditions and various sources of air pollutants, which arise

from many natural processes and anthropogenic activities, including household cooking and heating, biomass burning, transportation, power generation, and industrial processes (12). Among the most abundant and harmful pollutants are sulphur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3), as well as certain microscopic solid or liquid particles suspended in the air, referred to as particulate matter (PM) (55). A table summarizing the most common outdoor and indoor air pollutants of health concern can be found in Turner *et al*.'s overview article (56). According to the IARC classifications, Group 1 carcinogens for lung cancer in humans include indoor emissions from household combustion of coal, PM from outdoor air pollution, and diesel in engine exhaust, while household biomass fuel (e.g. wood, charcoal) was classified as a Group 2A agent (10,12,57). PM represents a complex and heterogenous mixture of inorganic, organic and biological compounds of various size and composition, including dust, dirt, droplets, soot, PAHs, aromatic amines, bacterial products (endotoxins), and fungi (58). It is classified based on aerodynamic diameter into coarse (2.5–10 μm, PM 10), fine (0.1–2.5 μm, PM 2.5) and ultrafine (0.1 μm, PM 1), and generally arises from different sources and various human activities. Smaller PM is more hazardous to health and PM 2.5 has been widely used by monitoring networks as an indicator of the level of anthropogenic pollutants in ambient or outdoor air pollution (59).

There is substantial epidemiological evidence of the association between long-term exposure to ambient air pollution and lung cancer risk (56). In an analysis of 1,100 lung cancer deaths among 188,699 lifelong never-smokers in the large cohort Cancer Prevention Study-II of the American Cancer Society, each 10 μg/m^3 increase in PM 2.5 concentration was associated with a 15%–27% increase in lung cancer mortality (60). A meta-analysis of 18 studies (17 cohorts and one case-control) in 2014 reported a meta-RR of 1.18 (95% CI, 1.00–1.39) for lung cancer risk among never-smokers associated with a 10 μg/m^3 increase in exposure to PM 2.5 (61). A sub-group analysis in Huang *et al*.'s meta-analysis of 17 studies (16 cohorts and one case-control) found that the meta-estimates for lung cancer incidence and mortality associated with a 10 μg/m^3 increase in exposure to PM 2.5 for never-smokers were 1.10 (95% CI, 0.76–1.59) and 1.16 (95% CI, 1.02–1.33), respectively (62). A recent study in China with 16,483 lung cancer cases also found an increased risk of lung cancer associated with a 10 μg/m^3 increase in 3-year PM 2.5 exposure, reporting a RR of 1.12 (95% CI, 1.00–1.26) which adds to the currently limited evidence from studies conducted in low- and middle-income countries (63). Despite the assessment methods for PM exposure varying widely among these studies (61), they have reported consistent estimates for lung cancer risk or death associated with PM 2.5 exposure.

Measuring indoor or household air pollution (HAP) is complicated due to the interaction of multiple determinants related to the HAP source and the domestic environment (10). HAP is largely caused by incomplete combustion of household fuels for cooking and/or heating, with the most common fuels used in developing countries being biomass fuels (e.g. wood, charcoal) and coal, which are referred to as solid fuels (10). It was estimated that in 2019 about half of the world's population (3.8 billion people) was still exposed to HAP from solid fuel use (54), and that 3.8 million deaths were attributable to HAP in 2016 (64). Epidemiological evidence of the association of solid fuel use with lung cancer risk has primarily come from case-control studies (65-68), summarized in two IARC monographs evaluating the effects of HAP (10,11). However, there has been substantial heterogeneity across studies (65-68), with pooled ORs of lung cancer risk associated with solid fuel use ranging from 1.17 (95% CI, 1.01–1.37) to 2.31 (95% CI, 1.94–2.76). These case-control studies examined different types of coal or biomass fuels used by both ever- and never-smokers to assess the association between HAP and lung cancer risk, and were limited by their retrospective nature, selection and recall biases, and a potential residual confounding from smoking, all of which may have led to overestimated risks. Even the two cohort studies (69,70) cited in the IARC monographs (10,11) were retrospective studies which only included residents in Xuanwei, Yunnan, where lung cancer mortality rates are among the highest in China (71), and no direct evidence of an association between solid fuel use and lung cancer risk was provided. Therefore, large-scale prospective cohort studies are needed to examine the association between HAP and lung cancer risk.

As PM 2.5 has generally been used to designate the level of anthropogenic pollutants in ambient air pollution (59), studies have explored the mechanism underlying the relationship between PM 2.5 exposure and lung cancer. PM 2.5 exposure has been found to be associated with increased levels of DNA adducts, suggesting that exposure to air pollution may induce a range of effects at the cellular level, including inflammation, DNA damage, and genomic instability, which could potentially drive the carcinogenic

process (72,73). Also, PM 2.5 particles contain high concentrations of ubiquitous pollutants, PAHs, which are chemical compounds characterized by the presence of multiple aromatic rings containing only carbon and hydrogen. When activated, these compounds can bind covalently to DNA to form stable or depurinating adducts, and induce oxidative damage (74). Exposure to PAHs via various routes to the body has been shown to be associated with several cancers including lung cancer (75-77). The most studied PAH, benzo[a]pyrene (B[a]P), contributes more than 50% to the total carcinogenic potential, is often used as a marker of PAH exposure (78), and was classified as a Group 1 carcinogens by the IARC in 2010 (79).

Since PAHs are also emitted from cooking oils heated at high temperatures (80), there are growing concerns that exposure to cooking oil fumes could be a causative factor for LCINS, particularly among Asian women, who usually take on the task of domestic cooking (81). One of the major mutagenic compounds in cooking oil fumes, trans-trans-2,4-decadienal (t-t-2,4-DDE), has been shown to reduce the survival rate of human erythroleukemia cells and induce significant oxidative damage to DNA (82). Epidemiological studies conducted among Asian women in mainland China, Taiwan, China, and Singapore have reported that exposure to cooking oil fumes, especially in the absence of fume extractors, was significantly associated with an increased risk of LCINS (83-85). A recent meta-analysis of 23 studies (2 retrospective cohort studies and 21 case-control studies) (86) found that cooking oil fumes are associated with lung cancer risk among women regardless of smoking status, with a pooled OR of 1.98 (95% CI, 1.54–2.54) among non-smokers and 2.00 (95% CI, 1.46–2.74) among ever-smokers. It also suggested that stir frying was associated with an increased risk of lung cancer (pooled OR=1.89, 95% CI, 1.23–2.90). Additionally, different types of cooking oil have been studied, and an increased lung cancer risk has been reported with the use of rapeseed oil (compared with linseed oil) (84) and lard oil (compared with vegetable oil) (87). More research is warranted to investigate the carcinogenic effect of cooking oils.

Occupational hazards

Around 15% of lung cancer cases have been attributed to occupational exposures (88). It has been estimated that in 2000 eight occupational exposures (arsenic, asbestos, beryllium, cadmium, chromium, diesel fumes, nickel, and silica) were responsible for 10% (88,000) and 5% (14,300) of global lung cancer deaths in men and women, respectively (89,90). These agents were all classified as Group 1 carcinogens for lung cancer by the IARC (91). A table listing all carcinogenic agents related to occupational exposure with sufficient or limited evidence in humans is reproduced from Spyratos *et al.*'s article (92) (*Table 1*). Although there is considerable epidemiological evidence for the association between these occupational exposures and lung cancer, it could be difficult to identify their carcinogenic role due to the probable confounding effect of smoking among most of these occupational groups, and similar studies among never-smokers are very limited (93,94).

Occupational exposures to asbestos has been known to be of concern for lung carcinogenesis since the 1930s (95,96), and exposure is associated with five-fold higher risk of lung cancer (97). As a result, there have been extensive studies of the associated epidemiological, clinical, biological and medico-legal aspects. Asbestos is a generic term referring to six naturally occurring silicate minerals that can be generally grouped into the serpentine and amphibole class. All minerals are made up of long and thin fibrous crystals, and each fibre contains many microscopic "fibrils" that can be released into the atmosphere and easily inhaled by humans (98). Long-term inhalation of asbestos fibres can lead to various diseases including asbestosis. It also increases risk for asbestos-related lung cancer and mesothelioma, and the risk is dependent on both fibre type and level of exposure. Asbestos exposure is the only known cause of mesothelioma, but asbestos exposure causes six times more cases of lung cancer than mesothelioma (99,100).

Arsenic is a metallic element which is highly toxic in its inorganic form, and arsenic exposure affects more than 150 million people worldwide (98). It is found naturally throughout the environment in the air, water and soil, and long-term exposure to arsenic is known to cause cancer (101). Based on epidemiological evidence from ecological, case-control and cohort studies since the 1950s, lung cancer has been observed to be associated with arsenic intoxicated patients (102) via exposure to inhaled arsenic or ingestion of arsenic in drinking-water (98). According to a study in the United States (U.S.), arsenic exposure may have a significantly greater effect on lung cancer incidence than previously expected and may contribute to over 5,000 lung cancer cases (after adjusting for smoking and income) in the U.S. per year (103).

Diesel fumes from motor engine exhaust, another

Table 1 Carcinogenic agents related to occupational exposure with sufficient (left column) or limited (right column) evidence in humans (92)*

Sufficient evidence	Limited evidence
1. Aluminum production	1. Acid mists, strong inorganic
2. Arsenic and inorganic arsenic compounds 3. Asbestos (all forms) 4. Beryllium and beryllium compounds	2. Art glass, glass containers and pressed ware (manufacture of)
5. Bis (chloromethyl) ether; chloromethyl methyl ether (technical grade) 6. Cadmium and cadmium compounds	3. Biomass fuel (primarily wood), indoor emissions from household combustion of
7. Chromium (VI) compounds 8. Coal, indoor emissions from household combustion 9. Coal gasification	4. Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing
10. Coal-tar pitch 11. Coke production 12. Engine exhaust, diesel 13. Hematite mining (underground)	5. Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work
14. Iron and steel founding	6. Carbon electrode manufacture
15. MOPP (vincristine-prednisone-nitrogen mustard procarbazine mixture) 16. Nickel compounds	7. alpha-Chlorinated toluenes and benzoyl chloride (combined exposures)
17. Painting 18. Plutonium	8. Cobalt metal with tungsten carbide
19. Radon-222 and its decay products	9. Creosotes
20. Rubber production industry	10. Frying, emissions from high temperature
21. Silica dust, crystalline 22. Soot 23. Sulfur mustard	11. Insecticides, non-arsenical (occupational exposures in spraying and application)
24. Tobacco smoke, second-hand	12. Printing processes
25. Tobacco smoking 26. X-radiation, gamma-radiation	13. 2,3,7,8-Tetrachlorodibenzopara-dioxin
	14. Welding fumes

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important source of PAHs (104), are also one of the most prevalent occupational lung carcinogens worldwide, especially in developed countries (105). Their ubiquitous nature also renders diesel fumes a public health risk for the general population. Diesel fumes were reclassified by the IARC from Group 2A (probable human carcinogen) to Group 1 (definite human carcinogen) in 2012 (106), based on re-analysis of data from the Diesel Exhaust in Miners study: a cohort mortality study and a nested case-control study (107,108). Although a critical review has pointed out several methodological flaws of the re-analysis and claimed that a causal link between diesel exhaust and lung cancer risk was not definite (109), aggregated evidence from experimental, epidemiologic, and mechanistic research provides strong evidence that diesel exhaust causes lung cancer in humans (106,110).

Other occupational exposures which are Group 1 carcinogens for lung cancer include exposure to PAHs as reported by millions of workers in industries like aluminium production, coal gasification and coke production (75,111), exposure to some environmental heavy metals such as arsenic, beryllium, chromium and nickel (91) in industries like wood preservation, ceramic production, stainless steel production and glass work, respectively (112), and exposure to crystalline silica, which can occur for millers, ceramic workers, glassmakers and granite workers (113). Although there is sufficient evidence for the carcinogenicity of these exposures in humans according to the IARC (13), the exact mechanism of pathogenesis leading to lung cancer has not been fully understood. Other occupations which have been associated with lung cancer include bartenders (likely due to SHS exposure), carpenters, bricklayers, painters, electricians, roofers (112) and hairdressers (114).

Familial aggregation

Since Tokuhata and Lilienfeld provided the first

epidemiologic evidence for familial aggregation of lung cancer in 1963 (115), several subsequent studies have reported increased familial risk for lung cancer. Inherited susceptibility was found to contribute to increased familial risk (116-119). It is, however, extremely complex to disentangle the specific contribution of genetic predisposition from the shared environmental exposures within family members, with smoking being the most important shared risk factor.

In Matakidou *et al*.'s meta-analysis that included 11 case-control studies of never-smokers (116), a family history of lung cancer in one or more affected relatives was associated with an increased risk of LCINS (RR=1.51; 95% CI, 1.11–2.06). Lissowska *et al.*'s meta-analysis of 20 European studies (18 case-control and 2 cohort studies that provided estimates for a subgroup analysis of non-smokers) also showed that a family history of lung cancer was associated with increased lung cancer risk (OR=1.40; 95% CI, 1.17–1.68) (118). In a pooled analysis of 24 case-control studies from the International Lung Cancer Consortium with 3,301 LCINS cases, it was found that lung cancer risk among never-smokers was associated with a familial history of lung cancer in a sibling (OR=1.44; 95% CI, 1.07–1.93) but not with a history of lung cancer in a parent (117). In another recent meta-analysis that included 23 studies (including Asian/Western and cohort as well as case-control studies), the pooled summary estimate for familial risk of lung cancer in a subgroup analysis of never-smokers was 1.72 (95% CI, 1.39–2.14), and the estimate was greater in Asian studies (2.62; 95% CI, 2.25–3.06) as compared with Western studies (1.24; 95% CI, 1.05–1.47) (120). These large-scale analyses, which included some studies that overlapped, demonstrated a similar risk estimate (about 1.5-fold) of lung cancer among never-smokers with a family history of the disease, and the risk was generally higher for Asians and for those with an affected sibling than other first-degree relatives. While genomic research on lung cancer is developing and the role of genetic factors in lung carcinogenesis remains to be fully defined, family history assessment is still valuable and might additionally provide indirect information on shared environmental risk exposures.

Genetic factors

Genetic susceptibility plays an important role in lung cancer risk for both ever-smokers and never-smokers (121). With the advent of new genomics technologies, research on lung cancer has been expanding rapidly, with particular focus on two different areas: identifying inherited genetic variants that are associated with lung cancer risk, and investigating molecular tumour characteristics to elucidate carcinogenic mechanisms and/or predict response to treatment. Multiple studies have focused on never-smokers to gain insights into primary lung carcinogenesis rather than smoking-driven carcinogenesis (122), and potentially advance future development of personalised screening, diagnosis and treatment approaches for LCINS (123).

In the past decade, analyses based on large-scale multistage genome-wide association studies (GWAS) have used robust approaches to systematically test for association between lung cancer risk and hundreds of thousands of inherited genetic variants (often called "single-nucleotide polymorphisms" or SNPs). To date, these studies have identified 45 genetic regions ("susceptibility loci") associated with lung cancer in different ethnic populations, and several of these loci were associated with LCINS (123). The first lung cancer GWAS were published in 2008, when three independent studies (124-126) consistently found strong associations of lung cancer with a genetic region (15q25) that contained three nicotinic acetylcholine receptor subunits (*CHRNA5*, *CHRNA3*, and *CHRNB4*), and was also found to be associated with tobacco consumption. A subsequent GWAS reported two other loci (5p15 and 6p21) associated with lung cancer risk, which were found to have no association with smoking behavior (127). In 2010, the first GWAS on LCINS found an association with the 13q31.3 region (128). Since then, several other loci associated with LCINS have been identified (with evidence for multiple independent risk variants in some regions) (123,129,130), including some loci that were also found to be associated in the original lung cancer GWAS (131-136). Several LCINS GWAS were carried out in Asian populations, so the underlying risk variants may also have different frequencies in populations with other ancestry (123,137).

Notably, the genetic associations detected to date only confer modest increases in LCINS risk (with per-allele OR of at most 1.30) (136). As for other cancers, so-called "polygenic risk scores" (PRS) can be constructed to combine risk information across many genetic regions to capture inherited lung cancer predisposition more fully. Dai *et al*. identified 19 susceptibility loci significantly associated with non-small cell lung cancer (NSCLC) risk (six of them were newly identified in the study) and used

them as well as other known susceptibility loci to construct a PRS (138). Among 95,408 participants of the China Kadoorie Biobank cohort, the PRS was significantly associated with lung cancer incidence, with an adjusted hazard ratio of 1.96 (95% CI, 1.53–2.51) for individuals with the 10% highest compared to those with the 10% lowest PRS. Another study constructed a different PRS and evaluated it in the United Kingdom Biobank data (n=335,931), estimating an OR of 2.39 (95% CI, 1.92–3.00) for individuals with the 10% highest compared to those with the 10% lowest PRS (139). Both studies provide evidence that GWAS-derived PRS might support risk stratification and help identify groups at high risk of lung cancer. However, given the strong risk conferred by smoking, non-smokers with the 5% highest PRS still only had comparable risk to light smokers with the 5% lowest PRS, and much lower risk than heavy smokers (138).

Some studies have also investigated gene-environment interaction effects, which is challenging as it requires well-characterised environmental exposures and large sample sizes to ensure sufficient power (123). Studies have found suggestive evidence for interactions between multiple genetic regions and asbestos exposure (140), or with solid fuel burning for heating and cooking in never-smoking women from Asia (141). Exploratory analyses in other studies have also generated additional hypotheses, but have been limited by low statistical power and lack of independent validation. Consequently, very large cohort studies with accurately measured information for environmental exposures are needed to establish robust evidence in this area.

Genomic studies of lung cancer tumors to characterise their molecular features have found differences between LCINS tumors and lung cancer tumors from smokers, generally with a smaller number of mutations in LCINS and differences in the dominant mutation spectrum (predominantly C:G → T:A mutations for LCINS, but predominantly C:G → A:T mutations for lung cancer in smokers) (47,142). Lung carcinogenesis is a complex multistage process involving irreversible genetic changes that alter cellular processes such as proliferation and differentiation, and progressively leading to invasion and metastasis (143). Mutations in so-called "driver genes" can enable the unchecked proliferation, and some driver gene mutations are found more often in LCINS. In particular, mutations in *EGFR* and Kirsten rat sarcoma virus (*KRAS*), as well as anaplastic lymphoma kinase (*ALK*) rearrangements are the three major recurrent oncogenic alterations found in LCINS tumors, with *EGFR* mutations being the most frequently encountered in LCINS (144). *EGFR* gene mutations in NSCLC were first reported in 2004, when it was also found that tumors with *EGFR* mutations are highly sensitive to EGFR tyrosine kinase inhibitors (TKI) (145,146). Subsequently, clinical studies also confirmed that *EGFR* mutations are associated with better clinical response to targeted therapy with EGFR-TKI (146,147). *EGFR* mutations are overall more common in LCINS than lung cancer in smokers, in adenocarcinoma than other histology types, in women than men, and in people with East Asian ancestry (148). *TP53* is another key driver gene with mutations present in 10%–48% of LCINS cases, although the risk of these mutations also increases with tobacco consumption (149). Moreover, molecular profiling of lung cancer tumors has also given rise to many clinical trials of other targeted treatments (150). Ongoing and future research for the identification of mutational signatures to predict clinical responses and/or more widespread molecular and genomic profiling of LCINS tumors is pivotal to the understanding of LCINS carcinogenesis and corresponding risk factors.

Conclusions

We have provided epidemiological and mechanistic evidence for some major environmental risk factors for LCINS. We have also discussed the new development in lung cancer genomics with a focus on never-smokers. This fast-expanding area aims to explore and comprehend the complex and sophisticated roles of environmental and genetic factors in lung cancer development among never-smokers. Future research with large sample sizes and refined exposure assessments is warranted to better understand the role of these factors. This understanding will not only help to evaluate a never-smoker's personal risk for lung cancer, but also has important implications for public health, as it could inform longer-term policy reform in a range of areas including occupational health and safety, urban design, energy use and particle emissions. Meanwhile, it will provide a basis for well-informed recommendations for prevention, as well as potentially establishing practical and feasible criteria for lung cancer screening programmes.

Acknowledgements

Elvin Cheng thanks support from the 2019 Cancer Council

NSW PhD Research Scholarship program. The funding agency played no role in the planning or writing of this review.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Cheng ES, Weber M, Steinberg J, Yu XQ. Lung cancer risk in never-smokers: An overview of environmental and genetic factors. Chin J Cancer Res 2021;33(5):548-562. doi: 10.21147/j.issn.1000-9604.2021.05.02

