CHAPTER 1

Risk factors: the known, the new, the feared

Edoardo Garbo, Silvia Novello

INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide and accounts for one in five cancer-related deaths.[1-3] In 2025 it is estimated to cause more than 1.8 million deaths globally, reflecting the continued burden despite advances in screening and therapy.[3] Although historically associated as a smoker's disease, a significant and growing proportion of cases occur in people who have never smoked, particularly women and persons from East Asia.[4] Understanding the spectrum of risk factors is critical for prevention, early detection and interventions. Traditional risk factors such as cigarette smoking, second-hand smoke and occupational exposures account for most lung cancers. However, emerging non-smoking related factors, such as immunological factors, microbiome dysbiosis and polygenic risk are increasingly recognized.[5] Finally, emerging threats—including e-cigarettes, cannabis, and indoor and outdoor pollution—represent tangible risks that must be addressed through future interventions. This chapter synthesizes current evidence on known, new and feared risk factors for lung cancer development (Figure 1.1).

THE MOST KNOWN: SMOKING

Epidemiologic trends and intervention strategies

Cigarette smoking remains the leading cause of lung cancer. According to the U.S. National Institute of Health (NIH), individuals are classified as smokers if they have smoked at least 100 cigarettes in their lifetime. The U.S. Centers for Disease Control and Prevention (CDC) estimate that 80-90% of lung cancer deaths in the United States are attributable to smoking.[2] Smokers are roughly 15-30 times more likely to develop or die

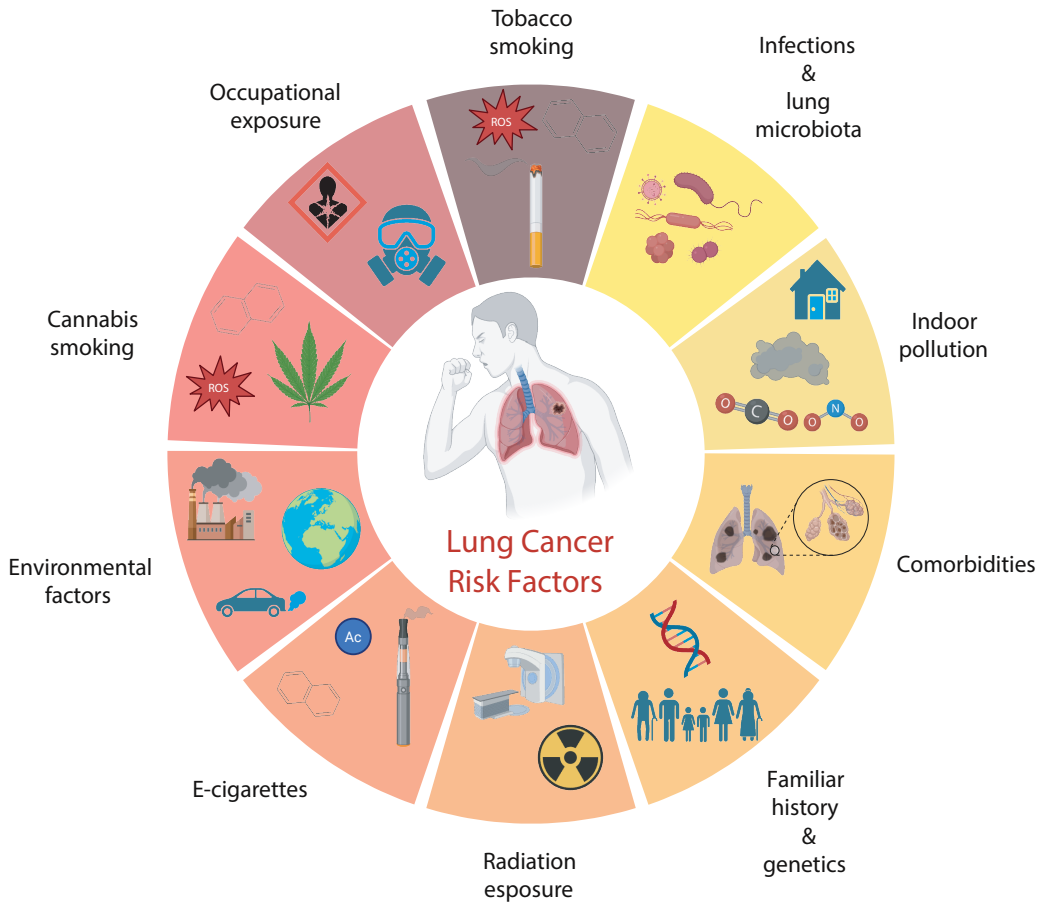

Figure 1.1. — Schematic overview of major lung cancer risk factors. Categories include tobacco smoking, indoor pollution, family history and genetic predisposition, radiation exposure, comorbidities, infections and lung microbiota, environmental factors, occupational exposures, and emerging risks such as e-cigarette use and cannabis.

from lung cancer than never smokers.[2] The risk of lung cancer increases with cumulative smoking, measured as pack-years, and decreases after cessation but never returns to baseline. Dose–response meta-analyses show that heavy smokers (≥30 pack-years) have 20-fold higher risk than never smokers, whereas light smokers (1-5 pack-years) have ~5-fold risk.[6] Moreover, an updated analysis of the Framingham Heart Study shows that each additional 10 pack-years increased lung cancer risk depending on the individual's polygenic risk score, underscoring a potential interindividual susceptibility of cumulative smoke impact.[7]

Comprehensive tobacco control—including taxation, advertising bans, smoke-free legislation and public education—has reduced smoking prevalence and lung cancer mortality in many countries.[8, 9] For example, the age-adjusted lung cancer mortality rate in the United States decreased by ~40% from 1991 to 2021.[3] However, progress is uneven globally; high smoking rates persist in low- and middle-income countries (LMICs) and among disadvantaged populations, contributing to rising lung cancer incidence,[9, 10] highlighting the need for persistent global interventions. Over the past decades, smoking rates among women have risen and become increasingly similar to those of men, reflecting a narrowing gender gap in tobacco use.[11] This trend underscores the growing need for targeted prevention and cessation efforts.

Low-dose computed tomography (LDCT) screening of high-risk individuals—heavy smokers and former smokers aged 50-80 years—can detect early-stage lung cancers and reduce mortality by approximately 13%.[12] While the benefits are largely confined to high-risk groups, emerging evidence indicates a potential role in selected populations of never smokers.[12, 13] Despite the impact of such screening and tobacco control policies, the long latency of lung cancer means that risk persists for decades after cessation, and former smokers remain at higher risk than never smokers.[10, 14, 15]

Composition of tobacco smoke and mechanistic action of its carcinogens

Tobacco smoke contains more than 9,500 chemicals, including over 80 carcinogens such as polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), benzene, formaldehyde and heavy metals.[16-18] PAHs are metabolically activated to reactive intermediates that form bulky DNA adducts, leading predominantly to point DNA transversions, a hallmark in *TP53* and *KRAS* mutations observed in smoking-related lung cancers.[19] TSNAs, notably NNK and NNN, produce electrophiles that alkylate DNA, which promote base mispairing and mutagenesis.[20] Aldehydes induce DNA–protein crosslinks and impair repair processes, while metals like cadmium generate oxidative stress, indirectly damaging DNA.[21] Large-scale genomic analyses have defined a characteristic tobacco-associated mutational signature, dominated by C→A transversions in specific trinucleotide contexts, consistent with the persistence of bulky adducts due to inefficient nucleotide excision repair.[22, 23] This evidence established a clear causal connection between smoking and transformative genomic events leading to cancer development.

Differences in major lung cancer subtypes

Non-small cell lung cancer (NSCLC) represents about 85% of lung cancers and includes adenocarcinoma (~60%, LUAD), squamous cell carcinoma (~30%, LUSC), and large cell or other histology subtypes. Smoking is strongly associated with LUSC, which develops predominantly in smokers, whereas LUAD occurs in both smokers and never smokers.[24] Patients with smoking-associated NSCLC tend to have higher programmed death-ligand 1 (PD-L1) tumor proportion scores (TPS) compared with never smokers,[25] along with a distinct genomic profile. In smokers, driver mutations in *KRAS*[26] and *BRAF*[27] occur more

frequently than in never smokers, underscoring how tobacco exposure profoundly shapes the pathogenesis of different lung cancer subtypes.

Small cell lung cancer (SCLC) accounts for 10-15% of lung cancers and is almost exclusively linked to heavy tobacco exposure.[28] A fraction of SCLC cases (2.5-13%) occur in never smokers and for these patients a slightly better prognosis has been reported.[29] The strong relationship between smoking and SCLC reflects the cumulative carcinogenic effect on the bronchial epithelium, leading to a central airway origin, like what is observed in squamous cell histology.[28]

Smoking cessation, second-hand smoke and interaction with other risk factors

Smoking cessation reduces lung cancer risk but not immediately. Former smokers remain at elevated risk for decades; risk declines progressively but never reach that of never smokers.[6, 31] In fact, heavy former smokers remain at a substantially elevated risk compared with never smokers for decades, still reaching a nearly fourfold higher risk even after 25 years since quitting.[6] Persistent risk probably reflects irreversible DNA damage and epigenetic alterations induced by smoking, even after years since quitting.[32]

Second-hand smoke (SHS) is a significant risk factor, particularly for non-smokers. It has been reported that exposure to SHS increases lung cancer risk by 24%.[33] Specific determinants of SHS exposure include environmental settings, such as the home or workplace, and interpersonal factors, including a partner's smoking and exposure during childhood.[33] Policies prohibiting indoor smoking and promoting smoke-free environments have helped reduce exposure, but risks remain, particularly in households with smokers and in regions with limited regulation.[34] Moreover, clinical reporting of SHS in never-smokers can be unreliable, in fact recent studies of mutational signatures in never-smokers show that some reported histories may be inaccurate, as their tumors display patterns linked to smoking exposure.[35]

Smoking can act synergistically with other carcinogens to substantially increase lung cancer risk. For instance, occupational asbestos exposure is associated with a relative risk of about 3.6 in non-smokers, but when combined with smoking, the effect is additive or multiplicative, reaching RRs of ~14.4.[36] Similarly, combined exposure to radon and tobacco smoke produces more than additive risks.[37] Alcohol intake may also amplify smoking-related carcinogenesis via shared metabolic activation pathways and impaired DNA repair.[38, 39]

BEYOND SMOKING: THE KNOWN AND THE NEW

Lung cancer without smoking: unique characteristics and drivers

Lung cancer in never-smokers (LCINS) represents a distinct clinical and biological entity, accounting for an estimated 10-25% of lung cancer cases worldwide.[4] The burden is disproportionately higher in women and in certain geographic regions, particularly East Asia.[40] Unlike smoking-related lung cancer, adenocarcinoma is the predominant histology in

never-smokers, and it is often diagnosed at a more advanced stage, particularly in Western countries, due to the lack of early detection measures and tailored screening parameters.[41]

These tumors are frequently driven by oncogenic alterations with approved targeted therapies, most notably activating mutations in *EGFR*, as well as rearrangements involving *ALK*, *ROS1*, *RET*, and *NTRK*.[42] The prevalence of *EGFR* mutations in this population can exceed 50% in Asian cohorts, while *KRAS* mutations—common in smokers—are less frequent.[43] These distinct genomic profiles not only influence tumor biology but also have major therapeutic implications.[42]

Genetic predisposition and family history

Part of the reason for the epidemiological prominence of LCINS lies in inherited susceptibility. Individuals who have never smoked but have a family history of lung cancer face a higher risk, implicating germline genetic factors in disease predisposition.[44] Although genome-wide association studies (GWAS) have identified some common variants linked to lung cancer risk, these explain only a modest fraction of overall susceptibility.[4] Moreover, the findings are largely non-overlapping and have not converged on a consistent set of robust associations.[4] Whole-exome sequencing (WES) and whole-genome sequencing (WGS) studies have revealed a meaningful burden of pathogenic germline mutations, particularly in genes involved in DNA repair, though without a clear difference in prevalence between smokers and never-smokers.[4]

Familial lung cancer can be driven by inherited *EGFR* alterations, most notably the germline T790M mutation, which occurs in ~1% of NSCLC cases and is typically observed in never-smoking women with multiple primary lung lesions.[45] These tumors almost always harbor a second somatic *EGFR* activating mutation, and carriers frequently present with multiple ground-glass nodules, warranting CT-based surveillance. Less common germline *EGFR* variants include R776G/H, V769M, V834L, V843I, and the rare R831H.[45]

Beyond *EGFR*, rare but highly penetrant pathogenic variants have been reported in *ERBB2*, *BRCA2*, *CHEK2*, *MET*, and *YAP1*, often in female never-smokers with LUAD.[4, 45] Certain multi-organ hereditary cancer predisposition syndromes also feature LUAD as a principal malignancy, including Li–Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), and conditions associated with LKB1, *RB1*, or genes implicated in Bloom, Werner, and Birt–Hogg–Dubé syndromes.[4, 45] In Li–Fraumeni syndrome, *EGFR*-mutant NSCLC predominates, underscoring the interplay between germline tumor suppressor defects and oncogene-driven lung tumorigenesiss.[4, 45]

Although much of the heritable risk remains unexplained, environmental triggers such as radon, secondhand smoke, and air pollution likely interact with genetic susceptibility. It is becoming increasingly clear that germline predisposition contributes in important ways. Identifying pathogenic inherited mutations in never-smoker lung cancer may not only improve risk stratification but also open opportunities for more personalized early detection and prevention strategies.

Occupational exposures

Occupational exposure to carcinogenic agents remains a significant contributor to lung cancer risk, as already well known in literature.[46] Recently a pooled analysis from the International Agency for Research on Cancer (IARC/WHO), has evaluated the combined effects of asbestos, respirable crystalline silica, PAH, hexavalent chromium, and nickel.[47] Asbestos exposure, long recognized as a potent lung carcinogen, is prevalent among certain occupational groups, with risk magnified when combined with other exposures.[47] In never-smokers, the relative risk from asbestos alone is substantially elevated.[47] Non-occupational exposure, such as living near asbestos mines or processing facilities, also confers excess risk, though at lower levels than direct occupational contact.[47]

Silica and diesel exhaust are similarly important hazards.[46, 47] Prolonged inhalation of respirable crystalline silica, common in industries such as mining and construction, induces chronic inflammation and fibrotic lung disease, both strongly linked to lung carcinogenesis.[46] Silicosis increases lung cancer risk in a dose-dependent manner, and coexisting pneumoconioses such as asbestosis further amplify this risk. Diesel exhaust, a mixture rich in PAHs and other mutagenic compounds, is estimated to account for a measurable proportion of lung cancers in industrialized countries.[46, 47] Epidemiological evidence supports that combined exposure to smoking and diesel or silica has more than additive effects on lung cancer risk.[47]

Other occupational carcinogens, including beryllium, nickel, chromium-VI, arsenic, cadmium, and vinyl chloride, have also been implicated.[48, 49] Most evidence derives from worker cohorts with high exposure intensity, where combined exposures often occur.[48, 49] Findings from the IARC's SYNERGY study indicate that co-exposure to certain metals and other agents, such as asbestos/nickel or chromium-VI/silica, can modestly modify risk, with variations by histological subtype—squamous cell carcinoma often showing the strongest associations.[47] Even if the added effect is small, co-exposures usually carry a higher risk than single exposures.

General environmental factors

Radon is a colorless, odorless radioactive gas generated by the decay of uranium in soil and rocks, capable of accumulating in poorly ventilated indoor environments. It is the second leading cause of lung cancer after smoking and the primary cause among never-smokers, contributing to an estimated 3-20% of lung cancer deaths worldwide and up to 30% in never-smokers.[50] In Europe, it has been shown to increase by 16% the cancer risk of lung cancer for every 100 Bq m^{-3} increase in indoor radon,[51] with similar findings in North America[52] and in never-smokers.[53] Radon is associated with increased risk for adenocarcinoma, when not associated to other confounders such as smoking.[50] It has a synergistic effect with tobacco smoke on lung carcinogenesis: more than 85% of radon-related lung cancer deaths occur in smokers, whose relative risk is 10-20 times higher than in never-smokers.[50] Moreover, its potential impact on the molecular landscape of NSCLC in

never smokers is now being systematically investigated in the BIORADON study, which aims to correlate indoor radon exposure with key oncogenic drivers.[54]

Ambient air pollution, particularly fine particulate matter ($PM_{2·5}$), is a well-established risk factor for lung cancer.[55] $PM_{2·5}$ consists of airborne particles ≤2.5 µm in diameter, generated from sources such as vehicle exhaust, industrial emissions, residential heating, and biomass combustion.[55, 56] Its small size enables deep penetration into the respiratory tract, where it induces oxidative stress, DNA damage, chronic inflammation, and epigenetic changes that contribute to carcinogenesis.[55, 56] The carcinogenic potential of $PM_{2·5}$ has been recognized by the IARC, which classifies outdoor air pollution and particulate matter as Group 1 human carcinogens. Pooled cohort analyses and meta-analyses indicate a linear dose–response relationship without an apparent safe threshold.[57] Data suggest also an increased risk even at concentrations below current WHO air quality guidelines (5 µg m^{-3} annual mean).[58] Nitrogen dioxide (NO_2), a marker of traffic-related pollution, has also been linked to lung cancer, though associations weaken after adjusting for $PM_{2·5}$ levels.[55, 56] It has been recently shown how $PM_{2·5}$ exposure may promote malignant progression of pre-existing lung lesions, particularly in individuals with somatic *EGFR* mutations, through inflammatory reprogramming of the lung microenvironment.[59] A recent study has also been shown that $PM_{2·5}$ exposure is linked to a specific mutational signature in LCINS (SBS16-like patterns), and that these mutations may precede malignant transformation by creating a permissive microenvironment.[35]

In the same study, another notable mutational signature was identified (SBS22a), which is known to be associated with aristolochic acid exposure.[35] This signature was found almost exclusively in patients from Taiwan and represents the first genomic evidence linking this environmental carcinogen to lung cancer.[35] Aristolochic acid has previously been implicated mainly in urothelial, liver, and kidney cancers, making its presence in lung cancers a potentially important new etiological insight.[61]

Radiation exposure

Exposure to ionizing radiation is a well-established risk factor for lung cancer. This includes both therapeutic and diagnostic radiation, as well as occupational exposures.[62] A recent projection estimated that CT imaging conducted in 2023 in the U.S. could lead to approximately 103,000 future radiation-induced cancers, including about 22,400 lung cancers, if current imaging trends persist. While the benefits of CT in lung cancer screening and diagnosis—particularly among high-risk populations—generally outweigh the risks, judicious use of imaging remains critical.[63] Adherence to ALARA ("As Low As Reasonably Achievable") principles is recommended in clinical practice. Furthermore, interventional physicians, radiologic technologists, and cancer survivors exposed to thoracic radiation may have elevated long-term lung cancer risk. In fact, a small but measurable increase in lung cancer incidence after adjuvant radiotherapy for breast cancer, particularly after 10–15 years of follow-up was observed.[64, 65]

Lung cancer and the relationship with comorbidities

Chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are not only common comorbidities in patients with lung cancer but also independent risk factors for its development.[66, 67] Epidemiologic studies consistently show that COPD approximately doubles the risk of lung cancer, even after adjusting for smoking history.[66] Shared pathogenic mechanisms include chronic airway inflammation, oxidative stress, and impaired mucociliary clearance, which promote genomic instability and malignant transformation. Importantly, lung cancer in patients with COPD is frequently diagnosed at an advanced stage, partly due to overlapping respiratory symptoms that delay detection.[66] IPF is a progressive interstitial lung disease associated with aberrant wound-healing responses and fibrotic remodeling. Patients with IPF have a markedly elevated risk of developing lung cancer—up to 5-7 times higher than the general population—with adenocarcinoma and squamous cell carcinoma being the most common histologies.[67]

Beyond clinically diagnosed interstitial lung diseases, imaging-detected interstitial lung abnormalities (ILAs)—subclinical CT findings characterized by increased lung density, reticulation, or ground-glass opacities—are increasingly recognized as relevant risk markers,[68] and similar elevated risks have been observed in pneumoconioses such as silicosis and asbestosis, which are strongly associated with lung carcinogenesis through chronic inflammation and fibrotic remodeling.[69]

Infections and microbiota

The role of infectious agents and the lung microbiota in lung carcinogenesis is increasingly recognized, though causality remains difficult to establish due to potential confounding by smoking, comorbidities, and environmental exposures. Chronic infections have been implicated in increased lung cancer risk. Mycobacterium tuberculosis has been associated with a 1.5–2-fold higher risk, potentially via chronic inflammation, fibrosis, and scarring that promote malignant transformation.[70] Human immunodeficiency virus (HIV) infection is associated with an increased incidence of lung cancer, independent of smoking history.[71] Cohort analyses adjusting for key confounders have shown hazard ratios in the range of 1.6-3.6, suggesting that chronic immune activation, immunosuppression, and higher prevalence of co-exposures may contribute to this risk.[71] Other viral infections, such as Epstein–Barr virus (EBV), have been detected in lung cancer tissues in some studies, with this being particularly linked to pulmonary lymphoepithelioma-like carcinoma.[72] However, most associations rely on retrospective or case–control data with incomplete adjustment for confounders such as smoking and air pollution, and the possibility of reverse causality cannot be excluded.

Also, lung microbiota could play a role in the development of lung cancer.[73] The lungs, once thought to be sterile, harbor a resident microbiome that may influence cancer risk through chronic inflammation, immune modulation, and metabolic interactions. Several studies, including those analyzing CT-guided lung biopsies, show increased