Narrative Review
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# Epidemiology and Prevention of Lung Cancer in Europe: A review of Burden, Disparities, and the Path to Equitable Early Detection

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**Abstract**

This review synthesizes current evidence on the global epidemiology and prevention of lung cancer, with a focused analysis of the Southeastern Europe region. Lung cancer remains the leading cause of cancer-related mortality worldwide, reflecting persistent exposure to modifiable risk factors and substantial inequities in early detection and treatment access. Data from GLOBOCAN, the Global Burden of Disease study, randomized controlled trials, and population-based registries were used to assess trends in incidence, mortality, and survival, and to examine the evolving distribution of histological subtypes and molecular profiles. While tobacco smoking remains the leading risk factor, a growing proportion of lung cancer, especially among never-smokers, is attributable to non-tobacco exposures, including ambient and household air pollution, occupational carcinogens, and residential radon. Despite advances in targeted therapies and immunotherapy, overall survival remains poor, largely due to late-stage diagnosis. Evidence from landmark trials demonstrates that low-dose computed tomography (LDCT) screening reduces lung cancer mortality primarily through stage migration, enabling detection at earlier, more treatable stages. Southeastern Europe continues to experience a high burden driven by tobacco exposure, limited screening implementation, and restricted access to molecular diagnostics. Inequities in screening eligibility, uptake, and access to advanced therapies worsen survival outcomes across socioeconomic and demographic groups. **Conclusions.** Effective lung cancer control requires a multi-level prevention strategy integrating strengthened tobacco control policies, risk-stratified LDCT screening, and equitable access to molecular testing and treatment. Future research priorities include understanding lung cancer in never-smokers, evaluating long-term risks of emerging exposures such as e-cigarettes, and utilizing multi-omics approaches to refine risk stratification and guide targeted therapy.

**Key Words:** Lung cancer ▪ Epidemiology ▪ Prevention ▪ Tobacco control ▪ Southeastern Europe.

## Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related mortality worldwide, accounting for 2.48 million new cases and 1.82 million deaths in 2023, 12.4% of all cancer diagnoses, and nearly one in five cancer deaths globally (1, 2). Despite meaningful advances in low-dose computed tomography (LDCT) screening, targeted therapy, and immune checkpoint inhibitor-based regimens, population-level five-year survival remains between 10% and 20% in most settings (3, 4). The persistently unfavorable prognosis is primarily attributable to the stage at the time of presentation, with approximately 70% of lung cancers being diagnosed at stage III or IV, when curative-intent treatment is seldom feasible (5, 6). Lung cancer comprises a biologically heterogeneous group of malignancies originating from the respiratory epithelium. It is broadly categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter accounting for more than 85% of cases (7). In

NSCLC, adenocarcinoma is currently recognized as the most prevalent subtype globally, accounting for approximately 50%, followed by squamous cell carcinoma at roughly 30-40% (8). The relative frequencies of these subtypes, as well as the prevalence of actionable somatic driver mutations within them, vary substantially by geographic region, sex, and smoking history. These differences have direct implications for treatment selection and the development of screening algorithms.

Lung cancer incidence and mortality are influenced by the historical trajectory of tobacco use in each population, separated from peak disease rates by a biological latency of two to four decades (9). As a result, rates are highest in countries where tobacco smoking peaked in the mid-to-late 20th century, particularly in North America and Europe. They are still rising in populations where the tobacco epidemic is more recent or ongoing (10, 11). The proportion of lung cancer among never-smokers is increasing, for whom tobacco-focused risk frameworks are inadequate. In these cases, factors such as ambient and household air pollution, residential radon, occupational carcinogens, and genetic susceptibility, particularly epidermal growth factor receptor (*EGFR*) gene-driven oncogenesis, play a proportionally larger role in causing the disease (10, 11).

The parallel shift in histological distribution, from squamous cell carcinoma dominance to adenocarcinoma predominance, has transformed the molecular landscape of the disease and the demands it places on diagnostic and therapeutic infrastructure. Adenocarcinoma more frequently harbors targetable driver mutations, making complete molecular profiling a prerequisite for optimal treatment, and screening algorithms built on tobacco-dominant cohort data may not adequately characterize risk in the contemporary never-smoker population (12).

This review provides a comprehensive synthesis of the global and regional epidemiology of lung cancer, with particular attention to Southeastern Europe, where incidence and mortality rates remain among the highest in the world. The review evaluates the evidence base for primary, secondary, and tertiary prevention strategies, drawing on temporal trend analyses of data from the Global Cancer Observatory (GLOBOCAN 2022) and the Global Burden of Disease (GBD 2023), and evidence from randomized controlled trials (RCTs), systematic reviews, and population-based registry data.

## Review Methodology

This manuscript was developed as a narrative review focused on the epidemiology, prevention, screening, and survival trends of lung cancer, with particular attention to trends in Europe, including Southeastern Europe. The review was structured around predefined thematic objectives, including global and regional incidence patterns, risk factors, screening strategies, molecular epidemiology, survival outcomes, and healthcare disparities. Evidence was synthesized from major epidemiological databases, randomized controlled trials, systematic reviews, international guidelines, and population-based registry studies relevant to lung cancer prevention and control.

## Epidemiology of Lung Cancer

### *Global Incidence and Mortality*

GLOBOCAN 2022 estimated 2,480,675 new lung cancer cases globally, making it the most commonly diagnosed cancer, with an age-standardized incidence rate (ASR) of 23.6 per 100,000 and 1,817,469 deaths at an age-standardized mortality rate (ASMR) of 16.8 per 100,000 (2). In absolute terms, Asia contributes the largest share of cases and deaths; however, a function of population size, age-standardized rates reveal a different hierarchy. North America records the highest ASR (31.9 per 100,000), followed by Europe (28.8), Asia (25.2), and Oceania (23.4 per 100,000), with ASRs in Latin America (12.1) and Africa (6.3 per 100,000) being substantially lower (2). Europe records the highest ASMR globally at 21.4 per 100,000, exceeding Asia (17.9) and North America (17.2 per 100,000) (2). Low reported rates in Sub-Saharan Africa reflect under-ascertainment due to limited diagnostic and registration capacity as much as a genuinely lower burden (9, 13). Stratification by Human Development Index (HDI) reveals a strong positive association between socioeconomic development and both incidence and mortality: ASRs reach 30.4 per 100,000 in high-HDI and 28.7 per 100,000 in very high-HDI countries, compared with 7.8 and 3.6 per 100,000 in medium- and low-HDI settings, respectively (2). Regional and HDI-stratified ASRs and ASMRs are summarized in Table 1.

This gradient reflects the cumulative timing of tobacco epidemics and greater diagnostic ascertainment in high-income settings rather than intrinsic biological predisposition (9, 14). Temporal patterns in the global distribution of lung cancer incidence are illustrated in Figure 1, which presents ASRs for both sexes in 1990 and 2023 based on GBD estimates (1). Consistent with the HDI gradient described above, higher incidence rates are concentrated in North America, Europe, and parts of East Asia. In comparison, substantially lower rates are observed across Sub-Saharan Africa. Over time, the overall geographic pattern remains broadly stable, though modest shifts are evident, reflecting evolving exposure to tobacco and other environmental risk factors and improvements in diagnostic capacity (9, 14). These findings reinforce the persistence of marked global inequalities in lung cancer burden.

Table 1. Age-standardized Incidence Rates (ASRs) and Age-standardized Mortality Rates (ASMRs) of Lung Cancer by Region and Human Development Index (HDI), Global Cancer Observatory 2022

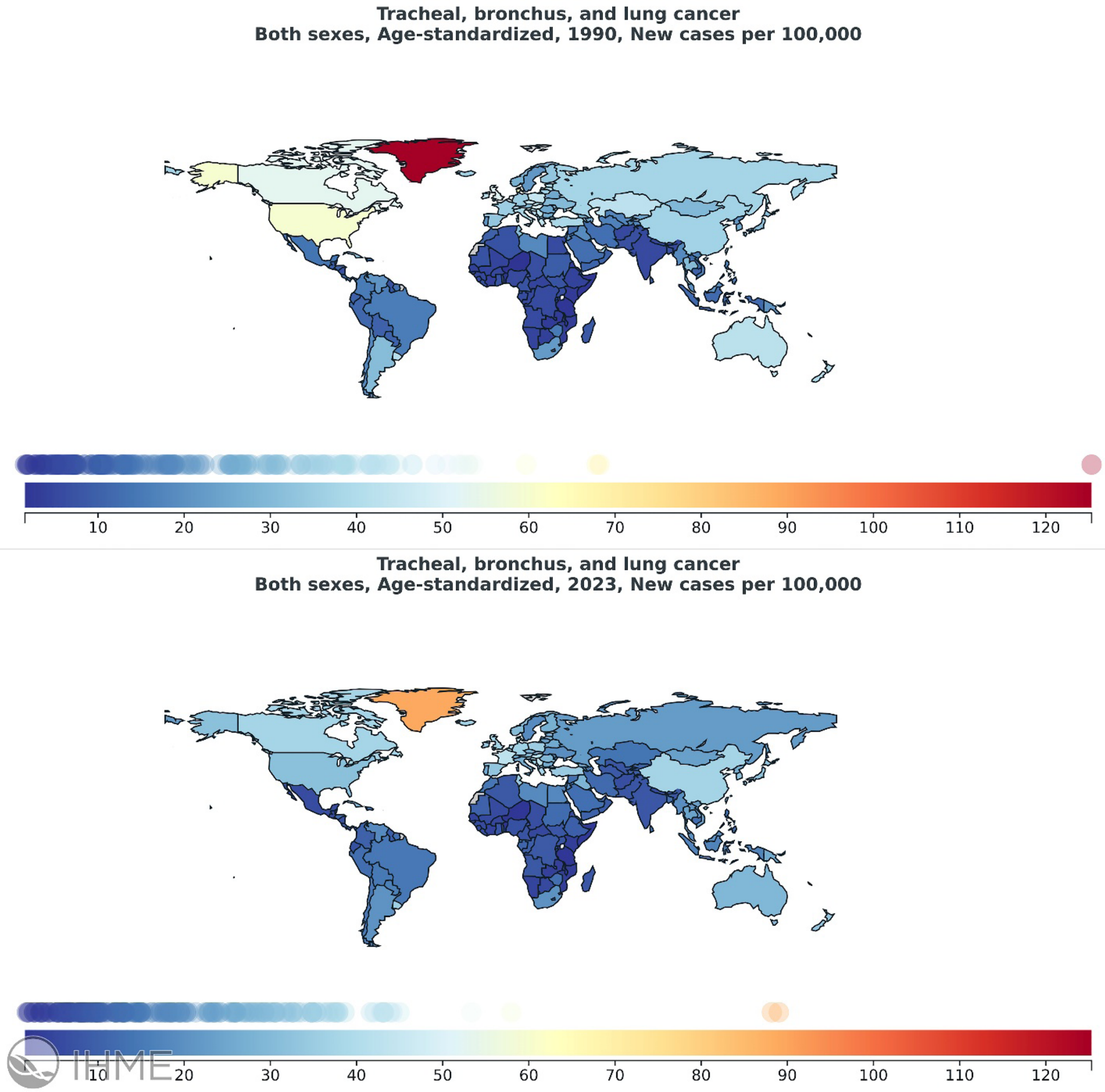
| Region | ASR (per 100,000) | ASMR (per 100,000) |
|---|---|---|
| Worldwide | 23.6 | 16.8 |
| Africa | 6.3 | 5.8 |
| Asia | 25.2 | 17.9 |
| Europe | 28.8 | 21.4 |
| Northern America | 31.9 | 17.2 |
| Latin America & Caribbean | 12.1 | 10.3 |
| Oceana | 23.4 | 16.0 |
| Very High HDI | 28.7 | 19.2 |
| High HDI | 30.4 | 21.2 |
| Medium HDI | 7.8 | 7.1 |
| Low HDI | 3.6 | 3.3 |

ASR: Age-standardized incidence rate per 100,000 population, standardized to the world standard population; ASMR: Age-standardized mortality rate per 100,000 population, standardized to the world standard population. Data obtained from the Global Cancer Observatory (GLOBOCAN) 2022, International Agency for Research on Cancer (IARC); Africa: Northern Africa, Middle Africa, Western Africa, Southern Africa, Eastern Africa; Asia: South Central Asia, Western Asia, South-Eastern Asia, Eastern Asia; Europe: Southern Europe, Western Europe, Eastern Europe, Northern Europe; Northern America: Canada, United States of America, Bermuda, Greenland, Saint Pierre and Miquelon; Latin America & Caribbean=South America, Caribbean, Central America; Oceana: Australia, New Zealand, Melanesia, Polynesia, Micronesia; HDI=Human Development Index. HDI categories are based on the United Nations Development Programme (UNDP) classification system; Very high-HDI settings predominantly include countries in North America, Western Europe, and high-income Asia-Pacific regions; high-HDI settings include parts of Eastern Europe, Latin America, and the Middle East; medium- and low-HDI settings include many countries in South Asia and Sub-Saharan Africa.

## Regional Patterns by HDI Tier

### *Europe*

In Europe, lung cancer is the third most commonly diagnosed malignancy and the leading cause of cancer death in men, and second in women (2). Eastern Europe reports an ASR of 27.6 per 100,000, and Southern Europe approximately 27.7 per 100,000, with countries such as Bosnia and Herzegovina, Serbia, Romania, and Bulgaria contributing substantially to this elevated regional burden (2). Lung cancer mortality trends are considerably less favorable in Central, Eastern, and Southern European countries than in Western counterparts, attributable to a later stage of the tobacco epidemic, persistently high current smoking prevalence, slower implementation of tobacco control measures, and more limited access to targeted therapies (15, 16). Between 2000 and 2017, lung cancer mortality actually increased in Bulgaria, Portugal, and Romania (17, 18). Five-year relative survival for NSCLC in Europe averages approximately 13–15%, ranging from 10% in Lithuania to 20% in Switzerland (19, 20). These survival disparities across European countries are distinct by differences in stage distribution at diagnosis, reflecting inequities in access to early detection pathways, molecular testing infrastructure, and guideline-concordant treatment (20, 21).




Age-standardized incidence rates (per 100,000) for tracheal, bronchus, and lung cancer, both sexes. Source: Global Burden of Disease (GBD) 2023, Institute for Health Metrics and Evaluation (GBD Compare tool) (1).

Figure 1. Global distribution of age-standardized lung cancer incidence rates, 1990 and 2023.

### *North America and High HDI Asia-Pacific*

In the United States (US), lung cancer accounts for approximately 22% of all cancer deaths annually, with male incidence and mortality declining since the early 1990s following sustained tobacco control; female rates are also now declining, though later and more gradually (22, 23). Notably, lung cancer incidence rates in women now exceed those in men in certain younger US birth cohorts born after 1960, a pattern not entirely explained by tobacco exposure trends (11). Japan and the Republic of Korea have high lung cancer rates broadly comparable to Western Europe; mortality has been declining in both countries, partly attributed to the comparatively high prevalence of *EGFR*-mutant NSCLC in East Asian populations and the corresponding response to targeted therapy (24).

### *Middle East and North Africa Region*

In the Middle East and North Africa (MENA) region, lung cancer represents an increasingly significant public health burden, although one characterized by far greater epidemiological heterogeneity than that observed across Europe (1, 25). In 2023, ASRs across the region span from 6.59 per 100,000 in Afghanistan to 34.85 per 100,000 in Tunisia, while ASMRs range from 7.18 to 33.39 per 100,000; a nearly six-fold disparity reflecting profound differences in tobacco exposure, demographic structure, and healthcare capacity across twenty-one countries (1, 25). Underpinning these figures is one of the most challenging tobacco landscapes globally. Smoking prevalence among males varies enormously across the region, from under 15% in Oman to nearly 47% in Jordan, while female smoking rates, though generally lower, reach as high as 34% in Lebanon against near-zero prevalence in Oman and Egypt, illustrating the profound cultural and policy-driven heterogeneity in tobacco exposure between and within countries (25).

Country-level trends reveal three distinct epidemiological patterns. A subset of nations, including Syria, Jordan, Palestine, Morocco, Algeria, Libya, and Sudan, have maintained relatively stable ASRs and ASMRs throughout the period from 1990 to 2023, suggesting neither meaningful progress nor acute deterioration (1). A second, more alarming group has recorded substantial increases in both incidence and mortality over the same period. Egypt exemplifies this trajectory, with ASRs rising more than threefold from 5.76 to 18.00 and ASMRs increasing in near-parallel from 5.75 to 18.17 (1). Lebanon presents the most pronounced escalation in the region, with ASRs surging from 11.80 to 30.71 and ASMRs rising commensurately from 12.06 to 28.63 per 100,000; a near-tripling of both metrics over three decades (1). Tunisia, conversely, reflects a chronically elevated rather than acutely worsening burden, with ASRs persisting at approximately 30–35 per 100,000 since 1990, consistent with a longstanding and deeply entrenched tobacco epidemic (1, 25).

In contrast, the Gulf Cooperation Council (GCC) states represent the most encouraging trajectory not only within MENA but arguably comparable to the strongest gains observed in Western Europe. Qatar and Kuwait recorded reductions in ASRs of approximately 50%, from around 18 per 100,000 in 1990 to 8–9 per 100,000 in 2023, with ASMRs declining in parallel from 18–19 to 7–9 per 100,000 (1). The United Arab Emirates achieved even more substantial reductions, with ASRs falling from 33.61 to 12.15 and ASMRs declining from 34.77 to 13.26, a reduction exceeding 60% in both measures (1). These gains likely reflect the convergence of progressive tobacco control legislation, shifting population demographics, and sustained investment in public health infrastructure across GCC health systems (26, 27).

## Emerging Economies and Low- and Middle-Income Countries (LMICs)

China bears the largest absolute lung cancer burden of any single country, with approximately 815,000 new cases in 2020, primarily driven by tobacco in men and by household biomass fuel combustion and outdoor air pollution in non-smoking women, a population with a high prevalence of *EGFR* mutations and adenocarcinoma histology (2, 28). India presents a characteristic profile, with a higher proportion of squamous cell carcinoma than in economically developed countries, partly attributable to widespread bidi smoking, and with lung cancer incidence rising in northeastern and urban regions (29, 30). In Latin America, lung cancer is the leading cause of cancer mortality, with incidence rates closely correlated with HDI and tobacco prevalence by country (31, 32). In low-HDI settings, low reported rates should be interpreted with caution, as limited diagnostic and registration infrastructure systematically underestimates true burden (2).

## Sex-Specific Temporal Trends

The GBD 2023 estimates document that global male ASR of lung cancer declined from 46.9 per 100,000 in 1990 to 35.9 per 100,000 in 2023, a reduction of approximately 23%, while female rates changed minimally over the same period (14.9 to 15.9 per 100,000; Figure 2A) (1). In Europe, the divergence is more pronounced, with male ASR falling from 74.3 to 47.0 per 100,000 (a decline of more than 36%), while female ASR rose from 12.4 to 17.8 per 100,000 (Figure 2B) (1). The United Kingdom (UK), the Netherlands, and Denmark, where female tobacco use peaked earlier, are exceptions, with female rates plateauing or declining (1, 33). The increase in female incidence across most of Central and Eastern Europe is a direct epidemiological consequence of sustained high female tobacco prevalence combined with the two-to-four-decade biological latency from peak smoking to peak cancer incidence (34). Overall adult smoking prevalence in Eastern Europe reaches approximately 28%, the highest of any European sub-region, and female-specific rates exceed 15% across all surveyed countries in the region (35). Moreover, female smoking prevalence in Eastern Europe is declining at a considerably slower rate than male prevalence, especially since tobacco control measures remain disproportionately concentrated among men (36). The consequences of this structural gap are now unambiguously confirmed: the WHO European Region achieved only a 12% reduction in female tobacco use prevalence between 2010 and 2025, against a global target of 30%, making it

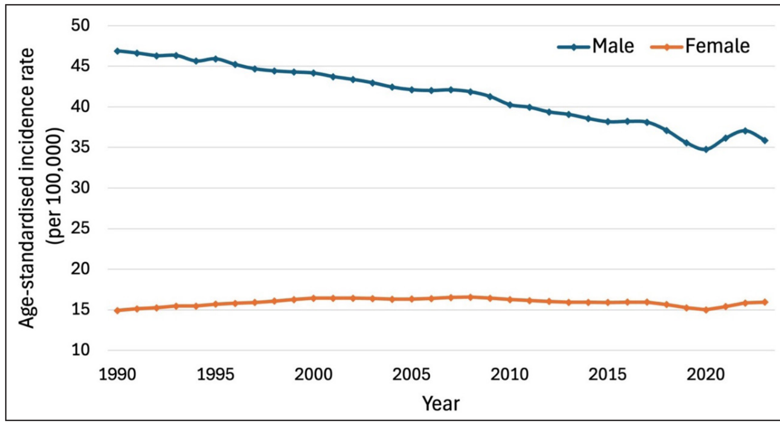



Figure 2A.

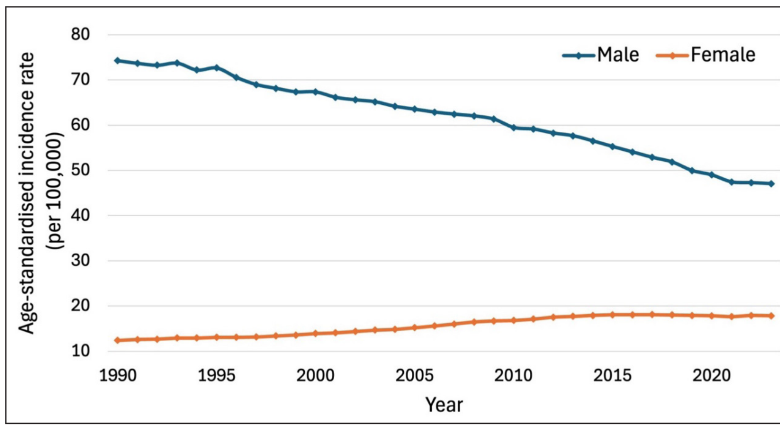



Figure 2B.

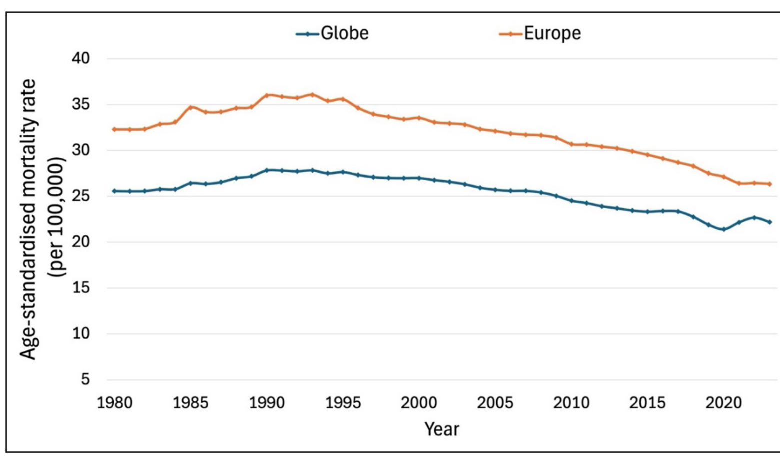



Figure 2C.

Source: Global Burden of Disease (GBD) 2023, Institute for Health Metrics and Evaluation (1).

Figure 2. Temporal trends in age-standardized incidence and mortality rates; Figure 2A. Global age-standardized lung cancer incidence rates (per 100,000 population) by sex (male and female), 1990–2023; Figure 2B. European age-standardized lung cancer incidence rates (per 100,000 population) by sex (male and female), 1990–2023; Figure 2C. Age-standardized lung cancer mortality rates (per 100,000 population) globally and in Europe, 1980–2023.

the only WHO region worldwide to have missed this benchmark among women, with over 62 million adult female smokers — representing more than 40% of the global female smoking burden — residing within the region (37).

## Histological Subtype Distribution

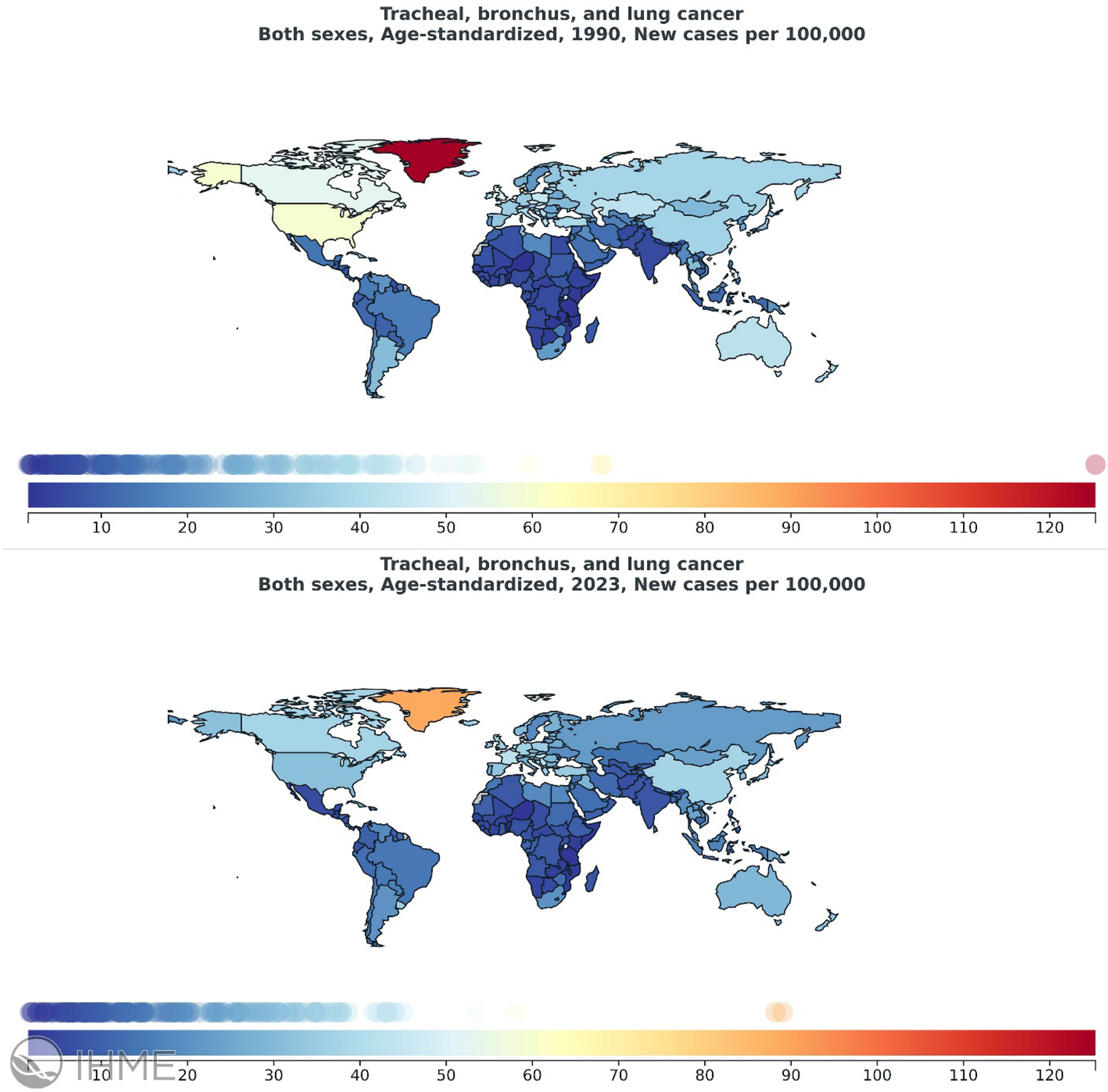
Squamous cell carcinoma was historically the predominant NSCLC subtype, particularly in men, owing to its strong etiological link with central-airway tobacco carcinogenesis (5, 12). Since the 1990s, adenocarcinoma has overtaken squamous cell carcinoma to become the most common NSCLC subtype in most high-income regions, accounting for approximately 40% of NSCLC globally, compared with 25% for squamous cell carcinoma (5). Adenocarcinoma is particularly prevalent in women (27–54% of cases across populations), never-smokers (53–70%), and this shift has extended more recently to LMICs (3, 5). Temporal analyses have documented parallel declines in squamous cell carcinoma and SCLC incidence in high-income countries, tracking reductions in smoking (10-12). The prevalence of adenocarcinoma in NSCLC has direct implications for molecular testing: it is the subtype most likely to harbor targetable driver mutations. These include *EGFR* alterations (exon 19 deletions, L858R substitutions, exon 20 insertions), *ALK* rearrangements, *KRAS G12C* mutations, *ROS1, RET,* and *NTRK1-3* fusions, *BRAF* V600E mutations, *ERBB2* mutations, and *MET* exon 14 skipping mutations ((38-43).

## Mortality Trends and Premature Burden

### *Global and European Temporal Trends*

Global age-standardized lung cancer mortality rates rose from approximately 25.6 per 100,000 in 1980 to a peak of approximately 27.8 per 100,000 in the early 1990s before declining progressively to approximately 22.2 per 100,000 by 2023 (1). In Europe, rates peaked at approximately 36.0 per 100,000 in the early 1990s, then declined to approximately 26.3 per 100,000 by 2023, remaining consistently above the global average throughout (1). Temporal trends in lung cancer ASMRs globally and in Europe are illustrated in Figure 2C. The inflection point in the early 1990s indicates the population-wide effects of tobacco control efforts that began in the 1960s and 1980s, resulting in reductions in cancer mortality after a lag of two to four decades (22).

Intra-European mortality trends diverge substantially by subregion. Lung cancer mortality is declining in men throughout Europe, but the rate of decline is considerably slower in Central, Eastern, and Southern European countries than in Western counterparts (15, 20). Among European women, overall mortality stopped increasing in 2023, though this aggregate stabilization masks ongoing increases in Central and Eastern European countries (21). Reductions in population-level mortality in the US since 2013 have been partially ascribed to the adoption of targeted therapies for *EGFR*-mutant and *ALK*-rearranged NSCLC, alongside the effects of tobacco control. A contributory role of treatment in reducing mortality is also likely to become evident in European registry data with further analysis (44). Years of life lost (YLL) rates, which weight deaths at younger ages more heavily, provide an important complement to mortality rates (23). Globally, age-standardized YLL rates due to lung cancer peaked at approximately 690 per 100,000 in the early 1990s and declined to approximately 500 per 100,000 by 2023 (Figure 3) (1). In Europe, YLL rates were significantly higher throughout, peaking at around 940 per 100,000 and decreasing to roughly 610 per 100,000 by 2023, consistently surpassing the global average, suggesting that a disproportionate share of European lung cancer deaths occurs below the expected life expectancy (1).




Percentage of total years of life lost (YLL) attributable to lung cancer, all ages, globally and in Europe, shown from 1990 to 2023. Source: Global Burden of Disease (GBD) 2023, Institute for Health Metrics and Evaluation (GBD Compare tool) (1).

Figure 3. Globally age-standardized years of life lost (YLL) rates due to lung cancer, 1990-2023.

## Survival Trends in Lung Cancer

### *Population-Level Survival and the Stage Problem*

Five-year relative survival for lung cancer remains substantially lower than for most other common solid tumors. Systematic review of registry data finds that five-year relative survival rarely exceeds one-third across settings, with most countries reporting estimates below 25% (22). In the US, overall five-year survival has improved gradually to approximately 25–29% for patients diagnosed between 2015 and 2021, a gain attributable to both earlier-stage diagnosis through LDCT screening and to survival improvements with targeted therapy and immunotherapy in advanced disease (45, 46). The fundamental determinant of population survival remains at the stage of diagnosis: patients identified at stage IA have a five-year survival exceeding 75%, while survival falls below 5% at stage IV (47). Given that approximately 70% of cases continue to be diagnosed at stage III or IV, observed overall survival rates are a direct arithmetic consequence of this stage distribution rather than any inherent therapeutic ceiling (5, 6).

Across Europe, five-year relative survival for lung cancer averages around 13–15%, with notable variation between countries, ranging from 10% in Lithuania to 20% in Switzerland (20). In comparison, data from Bosnia and Herzegovina show similar outcomes: a recent study reported a median overall survival of 19 months in complete responders, while patients with progressive disease and those receiving no treatment had substantially worse outcomes, with median survival of 6 months and 1 month, respectively (48). International population-level analyses have identified stage at diagnosis as a partial but important mediator of national survival differences, with countries achieving earlier stage distributions, through screening and diagnostic pathway investment, demonstrating comparatively better outcomes (28).

### *Screening and Stage Migration*

From a survival perspective, stage migration, the shift in the proportion of cases detected at stage I–II versus stage III–IV, is the primary driver of mortality benefit. NELSON trial data confirmed that LDCT screening in high-risk populations produced a significant shift toward an earlier-stage distribution, with approximately half of screen-detected cancers found at stage I, compared with approximately a quarter in the control arm (18). Patients diagnosed at stage IA achieve five-year survival exceeding 75%, compared with below 30% at stage IIIA and below 5% at stage IV (47). Despite the demonstrated benefits of LDCT screening programs in promoting earlier-stage detection rates and improving survival, its impact on a population level remains limited by low uptake among individuals. In the US, the uptake of lung cancer screening programs in 2024 was 24.5%, even though it doubled from a rate of 12.8% in 2018; it remains substantially lower than rates of other well-established screening programs, including colorectal (67.4%), cervical (75.4%), and breast cancer screening (80.0%) (49, 50).

## Impact of Targeted Therapy and Immunotherapy on Survival

Targeted therapy has produced transformative survival gains for molecularly defined NSCLC subgroups. In *EGFR*-mutant disease, more prevalent in East Asian populations (38–50%) than in European or North American populations (~14%), Osimertinib, a third-generation *EGFR* tyrosine kinase inhibitor, achieved a median overall survival of 38.6 versus 31.8 months compared with earlier-generation agents in the FLAURA RCT (HR 0.80, 95% CI 0.64–1.00) (38). *ALK* inhibitors, such as alectinib and lorlatinib, have demonstrated five-year progression-free survival rates in ALK-rearranged NSCLC that were previously unattainable with current treatments. *KRAS* G12C mutations, found in about 13% of NSCLC cases, mainly in tobacco-exposed adenocarcinoma patients, are now targetable with drugs such as sotorasib and adagrasib (39). *MET* exon 14 skipping mutations (3–4% of NSCLC) respond to capmatinib and tepotinib (39). Furthermore, in *RET* fusion-positive NSCLC, selpercatinib and pralsetinib have demonstrated substantial survival benefit, with median progression-free survival reaching approximately 22–25 months for selpercatinib and around 12.6 months for pralsetinib (40). Another trial analysis reported that *NTRK*-positive NSCLC may benefit from larotrectinib, with a median progression-free survival of approximately 35 months and an overall survival exceeding 40 months (41). In *HER2*-mutant NSCLC, trastuzumab deruxtecan showed significant benefit in the DESTINY-Lung01 trial, with median PFS of 8 months and OS of 17.8 months (42).

Collectively, these targeted agents represent the biological basis for the treatment-attributable component of population-level mortality improvement in the US between 2013 and 2019 (44). For patients without targetable driver mutations, the KEYNOTE-189 phase III trial established that pembrolizumab combined with platinum-pemetrexed chemotherapy in non-squamous NSCLC produces significantly improved five-year overall survival (19.4% vs. 11.3%) compared with chemotherapy alone (24, 51). These immunotherapy-based regimens are now standard first-line care for this population in settings with appropriate access. The survival benefits of molecular targeted therapy and immunotherapy have not been equitably distributed. Real-world analyses document persistent disparities in molecular testing rates across racial, ethnic, and socioeconomic groups, with direct downstream consequences for access to targeted agents (52). Fewer than half of patients globally receive the molecular testing required for treatment selection (53). This inequity in testing is the primary reason, as biological advances fail to translate into population-level improvements in survival outside high-income settings.

## Survival by Histological Subtype and Racial Equity

SCLC carries the worst prognosis among major lung cancer subtypes, with overall five-year survival rates remaining below 7% across populations, reflecting aggressive biology, near-universal presentation at advanced stage, and limited therapeutic progress (4, 5, 54). Within NSCLC, adenocarcinoma demonstrates better stage-specific survival than squamous cell carcinoma, 79% versus 47% at stage I and 27% versus 13% at stage III in large multi-institutional series, partially reflecting the higher prevalence of molecularly targetable mutations in adenocarcinoma (55, 56). SEER data (2015–2021) document clear racial and ethnic disparities in five-year lung cancer survival: Non-Hispanic Asian/Pacific Islander patients achieve approximately 34–35%, while Non-Hispanic American Indian/Alaska Native patients achieve approximately 22–23%, a gap of 11–12 percentage points (57). Non-Hispanic Black patients (approximately 25–26%) remain consistently below the overall average of approximately 28% (57). Similar inequities are also observed in Europe, where rates vary substantially across regions, ranging from below 10% in Eastern Europe to over 15% in Western and Northern European countries (58). These disparities stem from varying rates of late-stage diagnosis, unequal access to molecular testing and guideline-based treatment, a higher burden of comorbidities, and the cumulative impact of socioeconomic disadvantages throughout the care process continuum (59).

## Risk Factors Across the Globe

### *Tobacco Smoking*

Tobacco smoking is the dominant cause of lung cancer, increasing risk by 10 to 30-fold in a dose-dependent relationship with cumulative exposure (60, 61). Cigar, pipe, and bidi smoking also confer elevated risk, with bidi particularly relevant in South Asia (16, 62). Globally, smoking prevalence declined from 32.7% in 2000 to 20.9% in 2022, reflecting the cumulative effect of taxation, smoke-free legislation, advertising restrictions, and cessation support programs under the WHO Framework Convention on Tobacco Control (FCTC), adopted in 2003 (61, 63). Global smoking rates have decreased by approximately 27% since 1990, though these declines have occurred predominantly in economically developed countries; rates in numerous LMICs have seen little reduction (46).

Region-specific population attributable fractions (PAFs) for tobacco and other risk factors, derived from the GBD 2023 study, are summarized in Table 2 (1). Tobacco PAFs reach 67.1% in Eastern Europe and 65.1% in Central Europe, highlighting that tobacco control is the single most impactful lever for lung cancer prevention in these regions. Europe presents a specific policy challenge: tobacco smoking prevalence reached 25.3% in 2022, with female prevalence at 18.5%, among the highest for women globally, and has had the slowest decline rates in any WHO region over the past decade (63). Only eight of 27 European Union countries have achieved fully smoke-free public environments, and cigarettes have become more affordable in 14 European countries since 2014 (16).

Table 2. Population Attributable Fractions (PAF%) for Common Risk Factors for Different Regions in 2023

| Region | Smoking (PAF%) | Ambient particulate matter pollution (PAF%) | Occupational carcinogens (PAF%) | Household air pollution (PAF%) | Residential radon (PAF%) |
|---|---|---|---|---|---|
| Global | 58.25 | 14.18 | 14.32 | 2.97 | 4.09 |
| Central Asia | 60.34 | 15.96 | 11.17 | 2.35 | 7.34 |
| Central Europe | 65.11 | 10.71 | 12.43 | 0.62 | 5.62 |
| Eastern Europe | 67.08 | 7.12 | 9.85 | 0.19 | 6.80 |
| High-income Asia Pacific | 49.52 | 9.39 | 21.48 | 0.04 | 2.39 |
| Latin America and the Caribbean | 44.93 | 10.23 | 12.10 | 1.41 | 4.17 |
| North Africa and the Middle East | 60.78 | 19.83 | 12.79 | 1.14 | 3.70 |
| South Asia | 41.45 | 16.60 | 9.54 | 15.72 | 4.27 |
| Southeast Asia, East Asia, and Oceania | 62.93 | 20.25 | 9.24 | 3.03 | 3.42 |
| Southern Latin America | 51.65 | 11.83 | 16.86 | 0.12 | 2.85 |
| Sub-Saharan Africa | 30.47 | 9.58 | 9.75 | 20.67 | 4.33 |
| Western Europe | 58.22 | 5.48 | 29.31 | 0.05 | 5.91 |

Regions are defined according to the Institute for Health Metrics and Evaluation Global Burden of Disease (IHME GBD) classifications. Central Asia: Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan; Central Europe: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czechia, Hungary, Montenegro, North Macedonia, Poland, Romania, Serbia, Slovakia, and Slovenia; Eastern Europe: Belarus, Estonia, Latvia, Lithuania, Moldova, Russia, Ukraine; High-income Asia Pacific: Brunei, Japan, Singapore, South Korea; Latin America and the Caribbean: Brazil, Mexico, Colombia, Peru, Chile, Argentina, Cuba, Dominican Republic, Jamaica, and others; North Africa and the Middle East: Algeria, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, United Arab Emirates, Yemen; South Asia: Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan. Southeast Asia, East Asia, and Oceania; Southeast Asia: Cambodia, Indonesia, Laos, Malaysia, Maldives, Myanmar, Philippines, Sri Lanka, Thailand, Timor-Leste, Vietnam; East Asia: *China, North Korea, Taiwan;* Oceania: Fiji, Papua New Guinea, Solomon Islands, Vanuatu, and other Pacific island nations; Southern Latin America: Argentina, Chile, Uruguay; Sub-Saharan Africa: All African countries south of the Sahara (e.g., Nigeria, South Africa, Kenya, Ethiopia, Tanzania, Ghana, Uganda); Western Europe: Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom; PAF=Population attributable fractions.

Second-hand smoke exposure confers an estimated 20–30% increase in lung cancer risk, proportional to the degree of exposure (64, 65). Mortality attributable to second-hand smoke continues to rise in parts of southern Asia and Latin America, a direct consequence of inadequate enforcement of smoke-free policies (66).

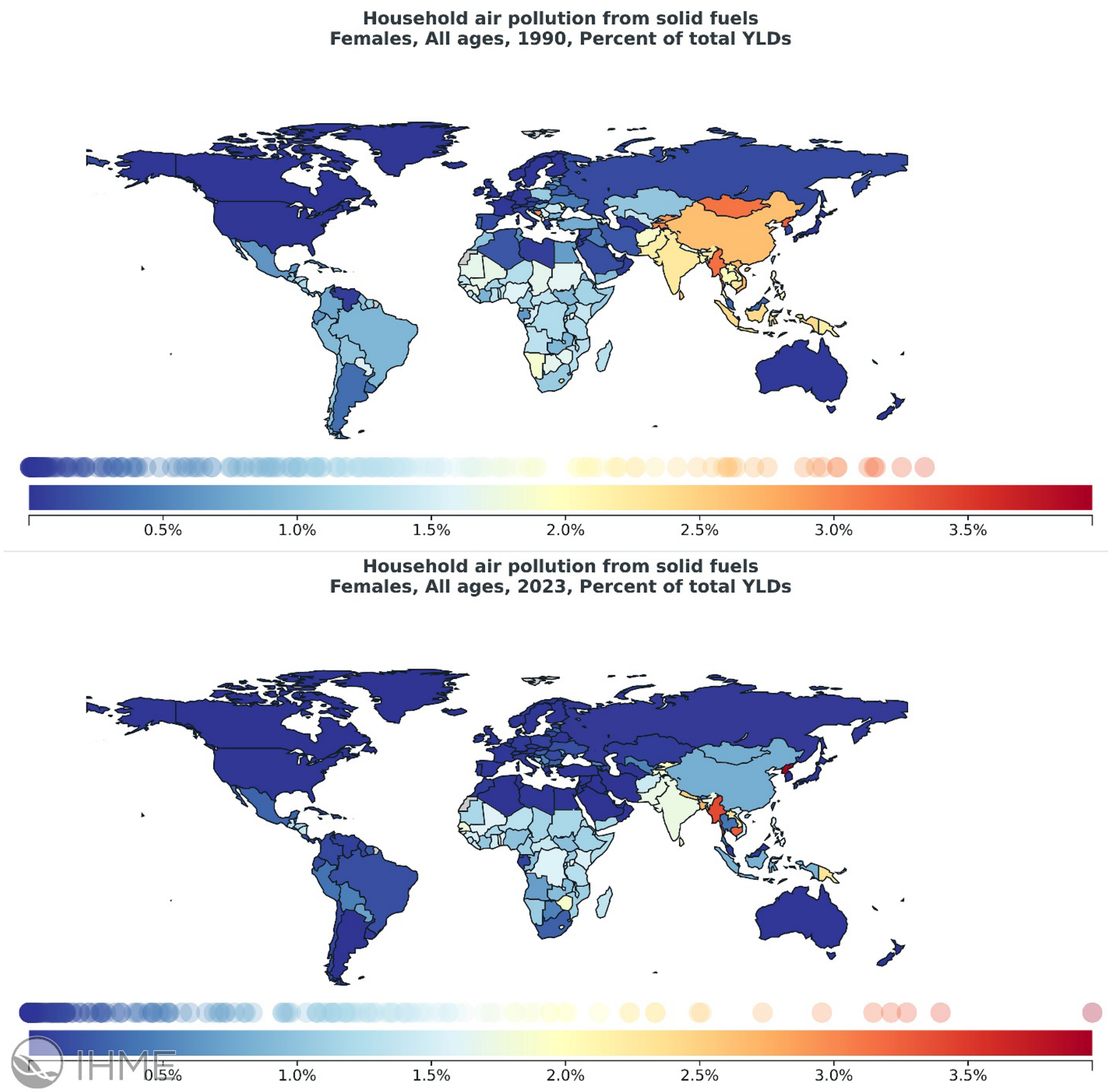
### *Environmental and Occupational Carcinogens*

The International Agency for Research on Cancer (IARC) has classified ambient particulate matter (PM2.5), household biomass fuel combustion, asbestos, diesel exhaust, crystalline silica, radon, arsenic, and several other occupational agents as Group 1 lung carcinogens (11). Ambient PM2.5 was responsible for approximately 374,210 lung cancer deaths globally in 2021, approximately 18.7% of all lung cancer deaths that year (67). GBD 2023 PAF estimates for ambient PM2.5 range from

5–10% in Western Europe and North America to approximately 16–20% in Southeast Asia, East Asia, and Oceania (Table 2) (1).

Household air pollution from biomass fuel combustion, affecting approximately 2.1 billion people globally, predominantly in LMICs, has a PAF of 20.7% in Sub-Saharan Africa and 15.7% in South Asia, making it the second largest attributable risk factor in these regions (Table 2; Figure 4) (1, 68). The excess risk is higher in women than in men owing to greater cumulative domestic exposure (38, 56, 69).

Residential radon exposure is an important and modifiable risk factor in high-income countries




Percentage of total years lived with disability (YLDs) attributable to household air pollution from solid fuels, females, all ages, shown for 1990 and 2023. Source: Global Burden of Disease (GBD) 2023, Institute for Health Metrics and Evaluation (GBD Compare tool) (1).

Figure 4. Global distribution of burden attributable to household air pollution from solid fuels, 1990 and 2023.

with older housing stock. A meta-analysis of 39 case-control studies reported a relative risk of 1.38 (95% CI 1.19–1.60) for lung cancer associated with elevated residential radon (70). In Eastern Europe, the GBD 2023 radon PAF is estimated at 6.8%, the second-largest attributable factor in that region, after tobacco (Table 2) (1). A separate meta-analysis of 24 studies estimated an adjusted excess relative risk of 0.15 per 100 $Bq \cdot m^{-3}$ specifically in never-smokers (30). Occupational carcinogens carry particular weight in Western European settings: the GBD 2023 PAF for occupational carcinogens in Western Europe is 29.3%, nearly double the global average of 14.3% and the highest regional estimate in Table 2, reflecting the legacy of mid-20th century asbestos, diesel exhaust, and crystalline silica exposure (1, 71, 72). Arsenic contamination of drinking water is a further Group 1 lung carcinogen relevant to specific geographic settings, addressable through source substitution and point-of-use removal systems (52, 73, 74).

### *Emerging Exposures*

The lung cancer risk from e-cigarettes cannot yet be confidently quantified due to their recent market entry and the long latency of lung cancer, which takes two to four decades from the 2010s. Available evidence pertains to short-term pulmonary effects, including oxidative stress, airway inflammation, and E-cigarette or Vaping Use-Associated Lung Injury (EVALI). It documents the presence of known carcinogens, such as polycyclic aromatic hydrocarbons, in e-cigarette product aerosol (75). The absence of long-term carcinogenicity data reflects methodological constraint rather than evidence of safety. Given the scale of adolescent uptake in high-income countries, this question will carry substantial public health consequences when the relevant cohorts reach middle age (76). For cannabis, a meta-analysis of eight observational studies found no statistically significant association with lung cancer risk. However, the available studies are characterized by inadequate adjustment for confounders and small sample sizes (31). A specific clinical phenotype, younger dual cannabis and tobacco users presenting with atypical histological subtypes, has been described but requires further characterization (32).

### *Genetic Susceptibility*

Family history of lung cancer confers a 1.51-fold increased risk after adjustment for smoking and other confounders (77). Twin studies estimate heritability at approximately 18% (78). Genome-wide association studies (GWAS) have identified 18 or more susceptibility loci collectively accounting for approximately 12% of the added familial relative risk; polygenic risk scores incorporating these loci show promise in improving risk stratification for screening eligibility (79-81). The molecular landscape of NSCLC varies substantially by population. *EGFR* mutations are more prevalent in East Asia (38–50% of NSCLC) than in Europe (~14%) or the Americas (~24%), and are enriched in adenocarcinoma, women, and never-smokers (82, 83). *ALK* rearrangements (approximately 4–5% overall) and other driver alterations associated with non-smoker status, including *ROS1* fusions and *ERBB2* mutations, are enriched in similar populations (33). *KRAS* mutations, present in approximately 27% of NSCLC cases globally, are predominantly found in tobacco-exposed adenocarcinoma patients and vary geographically (approximately 25% in the USA vs. 8% in China) (84, 85). These population differences in mutation frequency have direct implications for the design of molecular testing pathways and for estimating the population-level benefit of targeted agents across different healthcare settings.

Other established independent risk factors include chronic obstructive pulmonary disease (COPD), which confers approximately a sixfold increased risk independent of smoking history, and HIV infection, which increases lung cancer risk two to fivefold through immunosuppression and direct viral mechanisms independent of tobacco (86-90). Dietary factors can also influence the risk of lung cancer. For instance, red and processed meat consumption increases the risk, while fruit and vegetable intake is inversely associated

(91, 92). Furthermore, RCTs have established that β-carotene supplementation paradoxically increases lung cancer risk among smokers (93, 94).

## Strengthening Multi-Level Prevention of Lung Cancer

### *Primary Prevention*

Tobacco control is the highest-yield primary prevention intervention for lung cancer at the population level. The WHO FCTC, adopted in 2003 and ratified by 182 countries as of 2021, provides the international framework for evidence-based tobacco control through taxation, smoke-free legislation, advertising bans, and mandatory health warnings (61). As of 2025, approximately one-third of reporting countries had improved implementation of plain packaging and pictorial warnings (62). However, implementation gaps remain substantial, particularly in Europe, where cigarettes have become more affordable in 14 European countries since 2014 (16). Only eight of 27 EU member states have fully smoke-free public environments, and the European region has the slowest rate of tobacco decline among WHO regions (16).

School-based and community-level interventions complement population-level policy. The ASSIST trial, a peer-led school-based smoking prevention program in the UK, demonstrated significant reductions in adolescent smoking sustained at two-year follow-up (95). Cessation programs that incorporate counseling, behavioral therapy, and pharmacotherapy extend these benefits to adult populations (96, 97). Consistent with the 2019 ACC/AHA Primary Prevention Guidelines, physicians, particularly those in primary care, should routinely identify tobacco users and assist in cessation by providing brief cessation counseling, prescribing pharmacotherapy when appropriate, and reinforcing smoking abstinence through repeated follow-up (98). Population-level campaigns such as the CDC's 'Tips From Former Smokers' program and occupational health interventions targeting indoor air quality have demonstrated measurable reductions in carcinogen exposure at scale (64, 99). A network meta-analysis of more than 400 studies, 200 of which were meta-analyses, showed a significant reduction in tobacco use, evidenced by increased quitting ratio and decreased smoking prevalence and cigarette sales, in countries where campaigns were paired with health warnings, taxation, and flavor bans (100). Although most included studies were from high-income countries, such as the US, UK, Australia, and New Zealand, similar trends, albeit with less pronounced effects, were observed in LMICs (100). Beyond tobacco, primary prevention must address the full range of modifiable carcinogen exposures (69). A meta-analysis of 15 studies from LMICs showed the greatest reductions in household air pollution, with reductions in kitchen PM levels, followed by personal PM exposure and carbon monoxide (CO) levels, after interventions such as improving cookstoves or health education campaigns that promote outdoor cooking (101). However, using a plancha instead of an open fire did not result in a difference in personal PM or CO levels (SMD 1.0). Indoor radon testing and mitigation, particularly in high-radon geological zones across Northern and Eastern Europe, where the GBD 2023 radon PAF reaches 6.8% in Eastern Europe, represents an underutilized prevention opportunity (1). Enforcement of occupational carcinogen regulations, including diesel exhaust emission controls and asbestos abatement in legacy materials, addresses the 29.3% Western European occupational PAF (1).

### *Secondary Prevention*

Secondary prevention in lung cancer focuses on early diagnosis and timely treatment, as outcomes are strongly stage-dependent, with higher survival rates when the disease is detected at an early, localized stage. Low-dose computed tomography (LDCT) screening enables the detection of asymptomatic, early-stage tumors and reduces morbidity and mortality. Hence, many countries have moved toward implementing national LDCT screening programs. In 2020, Croatia became the first country in the European region to fully implement a nationwide CT-based lung cancer screening program. Within five years, over 50,000 individuals were screened, with 4.5% yielding positive findings (102). Since then, several other countries in the region have followed, initiating national screening programs either at full scale or through pilot implementation (Table 3).

A meta-analysis of nine RCTs found a significant reduction in lung cancer mortality with LDCT compared with no screening (RR 0.87, 95% CI 0.78–0.98) and significantly higher early tumor detection compared with chest radiography (RR 2.84, 95% CI 1.76–4.58) (112). The National Lung Screening Trial (NLST) and Dutch–Belgian Randomized Lung Cancer Screening Trial (NELSON) trials provide the most definitive evidence. Their findings form the basis for current screening guidelines in the USA (2021 U.S. Preventive Services Task Force: ages 50–80, ≥20 pack-years, current or quit ≤15 years) and in Europe, where the EU issued a position statement in 2017 recommending that member states establish implementation timelines (18, 75). Table 4 summarizes the characteristics and outcomes of the major RCTs evaluating LDCT-based lung cancer screening.

Despite this evidence base, major implementation barriers persist. False-positive rates exceed 90% in some settings, with attendant psychological burden and the risk of unnecessary invasive procedures (113). Cumulative radiation exposure from repeated low-dose scans warrants consideration. In LMICs, higher rates of pulmonary tuberculosis and other granulomatous infections inflate false-positive rates; the first Brazilian lung cancer screening trial (BRELT1) recorded a positive screen rate of 40% compared with 26% in the NLST (114). Cost-effectiveness varies widely, with incremental cost-effectiveness ratios ranging from approximately $8,376 per QALY in broad-eligibility analyses to $200,921 per QALY in cohorts restricted to ≥30 pack-years; nevertheless, 90.3% of 31 cost-effectiveness studies included in a meta-analysis met national thresholds in their respective countries (115-117).

Table 3. National Lung Cancer Screening Programs and Guidelines by Country

| Country | Year | Recommendation & Interval | Age Range | Eligibility Criteria (beyond age) | Reference |
|---|---|---|---|---|---|
| Croatia | 2020 | LDCT screening; annual | 50–75 | ≥30 pack-years; current smokers or quit ≤15 years | Croatian Ministry of Health (103) |
| Czech Republic | 2022 | LDCT screening; annual | 55–74 | ≥20 pack-years; current or former smokers | Lung Cancer Policy Network (104, 105) |
| Poland | 2020 | LDCT screening; annual | 50–74 | ≥20 pack-years; includes additional risk factors (e.g., COPD, occupational exposure) for ages 50-54 | Ministry of Health, Republic of Poland (106) |
| Hungary | 2023 (Pilot) | LDCT screening; annual | 50–75 | ≥20 pack-years; current/former smokers | HUNCHEST pilot program (107) |
| Italy | 2021 (Pilot) | LDCT screening; annual | 55–74 | ≥30 pack-years; current or quit ≤15 years | Rete Italiana Screening Polmonare (RISP) Pilot; European Country Cancer Profile: Italy 2025 (108) |
| Spain | 2022 (Pilot) | LDCT screening; annual | 50–75 | ≥20 pack-years; current or quit ≤15 years | (Cancer Screening, Smoking Cessation, AND Respiratory Assessment) CASSANDRA trial protocol (109) |
| Germany | Approved 2024, launched 2026 | LDCT screening; annual | 50–75 | ≥25 pack-years; current or quit ≤10 years | German Federal Joint Committee (G-BA) (110) |
| United States | 2021 | LDCT screening; annual | 50–80 | ≥20 pack-years; current smoker or quit ≤15 years | United States Preventive Services Task Force (111) |

LDCT=Low-dose computed tomography.

Table 4. Characteristics of Major Randomized Controlled Trials Investigating Lung Cancer Low-dose Computed Tomography Screening

| Trial | Population | Country | Participants (N) (inv/comp) | Screening frequency (yrs) | Follow-up (median yrs) | Comp | LC Mortality (95%CI; P-value) | Secondary outcomes | ACM benefit | Key interpretation | Trial Verdict | Role in evidence-based |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NLST (156, 157) | Age 55–74, ≥30 PY, current smoker or quit ≤15 yrs | USA | 53454 (26722/2673) | At 1 yrs | ~6.5 (Extended 11.3) | CXR | 20% rate reduction. Extended RR: 0.92 (0.85-1.00; 0.05) | ACM; LC incidence | 3.2% ACM rate reduction | LDCT should be used for screening high-risk populations, but may cause overdiagnosis | Screening with LDCT reduces mortality from lung cancer | Landmark, practice-changing trial, strongest RCT, major guidelines changes |
| NELSON (158) | Age 50–74, current heavy smokers/ex-smokers | Netherlands & Belgium | 15792 (7900/7892) | At baseline, 1 yr, 3 yrs, 5.5 yrs | 10 | UC | RR: 0.76 (0.61-0.94; 0.01) | ACM; LC incidence; stage at diagnosis | No benefit (rate ratio: 1.01; 95% CI, 0.92-1.11) | LDCT reduces LC mortality with fewer late-stage diagnoses | LDCT screening effective in high-risk populations | Landmark European trial, second strongest after NLST; influenced European policy changes |
| MILD (159) | Age ≥49, ≥20 PY | Italy | 4099 (1190 annual, 1186 biennial/ 1723) | Annual vs Biennial | 10 | UC | HR: 0.61 (0.39-0.95; 0.02) | ACM; LC incidence; annual vs biennial benefit | No significant benefit (HR: 0.80; 95% CI: 0.62–1.03; P-value: 0.07). | Biennial screening is safe and reduces the number of scans needed in comparison to annual screening. | Suggests flexible intervals possible | Supports risk-adapted screening |
| UKLS (160) | Age 50–75, high risk (LLPv2 ≥5%) | UK | 4055 (2028/2027) | At baseline | 7 | UC | RR: 0.84 (0.7-0.92; 0.375) | ACM; LC incidence; mortality from all cancers; mortality from causes other than LC | RR: 0.65 (P-value: 0.062) | Pilot trial, underpowered study | Did not show an adverse effect on mortality. | Feasibility study; contributed to UK screening pilots |
| ITALUNG (161) | Age 55–69, current smokers/ex-smokers | Italy | 3206 (1613/1593) | Annual | 8.5 | UC | RR: 0.70 (0.47-1.03; 0.07) | Stage shift; earlier detection | 20% reduction (OR: 0.80; 95% CI: 0.66–0.96) | Underpowered study | Screening reduces LC mortality in high-risk smokers without causing significant overdiagnosis. | Contributed long-term European evidence |
| DLCST (162) | Age 50–70, ≥20 PY | Denmark | 4104 (2052/2052) | Annual | 3 | UC | HR: 1.00 (0.90-1.12; NM) | False positive rate; psychosocial effects | No benefit | Screening does not increase the risk of adverse mental health outcomes | No significant difference in LC mortality or ACM between inv and comp groups. | Highlighted risks of false positives |
| DANTE (163, 164) | Age 60–74, ≥20 PY | Italy | 2472 (1276/1196) | Annual | 3 | UC | HR: 0.993 (0.69–1.43; NM) | ACM; LC incidence; stage at diagnosis; false positive rate; overdiagnosis; compliance & adherence; intervention-related harms | No benefit | Screening increased diagnoses but not survival | Did not show an adverse effect on mortality. | The effect of screening with LDCT on lung cancer mortality might be smaller than anticipated |

The table summarizes key trial design features, including study populations, screening protocols, comparator groups, and follow-up duration, alongside primary outcomes (lung cancer mortality) and selected secondary outcomes such as all-cause mortality, stage at diagnosis, and detection rates. These trials collectively assess the effectiveness of LDCT screening compared with usual care or alternative approaches in reducing lung cancer–related mortality and informing evidence-based screening strategies. CXR: Chest X-ray; DANTE: Detection And screening of early lung cancer with Novel imaging TEchnology; DLCST: Danish Lung Cancer Screening Trial; HR: Hazard ratio; Inv: Intervention group; ITALUNG: Italian Lung Cancer Screening Trial; LC: Lung cancer; LDCT: Low-dose computed tomography; LLPv2: Liverpool Lung Project model (version 2); MILD: Multicentric Italian Lung Detection Trial; N: number; NELSON: Dutch-Belgian Randomized Lung Cancer Screening Trial (Nederlands–Leuvens Longkanker Screenings Onderzoek); NLST: National Lung Screening Trial; NM: Not mentioned; OR: Odds ratio; PY: Pack-years; RCT: Randomized controlled trial; RR: Relative risk; UC: Usual care (no screening); UK: United Kingdom; UKLS: UK Lung Cancer Screening Trial; USA: United States of America; Yrs: Years.

Risk-stratified approaches using validated prediction models, the PLCOm2012 model (six-year absolute risk horizon) and the Liverpool Lung Project model version 2 (LLPv2, five-year horizon) have demonstrated superior detection rates compared with conventional smoking-history-based criteria. They are now embedded in the UK screening program (52, 118). Artificial intelligence tools for automated nodule analysis and malignancy probability estimation are increasingly integrated into screening workflows, offering potential to extend screening capacity in resource-constrained settings (119). Liquid biopsy approaches, including cell-free DNA assays and circulating tumor DNA analysis, are under active evaluation as adjuncts to LDCT or as potential alternatives in populations with limited CT access (120, 121).

### *Tertiary Prevention*

Tertiary prevention in lung cancer centers on ensuring that every patient with established disease receives optimal molecular characterization, multidisciplinary treatment planning, and access to evidence-based systemic therapy. Multidisciplinary tumor boards (MTBs) integrating medical oncologists, thoracic surgeons, pulmonologists, radiologists, pathologists, and radiation oncologists are recommended as standard of care by the European Society for Medical Oncology (ESMO) and other major guideline bodies, with documented benefits for adherence to guideline-concordant treatment (74).

Comprehensive molecular profiling is the prerequisite for access to the targeted agents reviewed in Section 4.3. Systematic molecular reflex testing policies under which PD-L1 protein expression, along with *EGFR, ALK, KRAS G12C, MET* exon 14, and other rare genomic alterations, are assessed on all NSCLC diagnostic specimens by default, are the most actionable intervention for reducing the disparity between who biologically could benefit from targeted therapy and who receives it. Real-world analyses have demonstrated persistent inequities in testing rates by race, ethnicity, and socioeconomic status even within settings where testing is technically available, with direct consequences for survival (43). Immune checkpoint inhibitors targeting the PD-L1 pathway, either as monotherapy in highly expressed NSCLC or in pembrolizumab-based combination regimens, are now standard first-line care for patients without targetable driver mutations (24, 51). At the population level, digital health infrastructure — electronic health record linkage, claims data integration, and cancer registry surveillance — is essential for monitoring treatment uptake, identifying care gaps, and evaluating the effectiveness of screening and treatment programs (122, 123).

## Clinical and Public Health Implications

### *Health System Requirements in the Precision Oncology Era*

The transition towards risk-stratified LDCT screening and precision oncology in the management of lung cancer has engendered specific and considerable demands on healthcare infrastructure. This must be addressed as an essential prerequisite for realizing the survival benefits, in which early-stage cancer detection could result in five-year survival rates exceeding 75%. Accessible molecular pathology services capable of performing next-generation sequencing or validated single-analyte assays for *EGFR, ALK, KRAS G12C, ROS1, MET* exon 14, PD-L1, and *NTRK1-3* on diagnostic biopsy samples are essential for all healthcare systems treating lung cancer. This requirement should align with clinical guidelines in each country, and health systems should effectively deliver the treatments that offer the greatest proven survival benefits (53, 124). MTBs have become increasingly important in translating complex genomic data into individualized treatment decisions, particularly for patients with rare or multiple molecular alterations. MTBs focus on the interpretation of next-generation sequencing results, facilitate access to targeted therapies and clinical trials, and promote precision medicine based on updated guidelines (125). More recently, comprehensive Precision Oncology Programs have expanded this model by integrating molecular diagnostics, longitudinal clinical data, and digital health infrastructure into coordinated systems designed to support targeted therapy selection, real-world outcome monitoring, and clinical research (126).

Advanced staging with PET-CT has similarly become integral to accurate mediastinal staging and treatment planning in resectable NSCLC, driving infrastructure investment requirements that are difficult to meet in resource-constrained settings (73). MTB-based care coordination, in which oncologists, radiologists, pathologists, thoracic surgeons, and pulmonologists collaboratively review each case, has shown benefits for guideline adherence and survival outcomes and is recommended as the standard of care by the European Society of Medical Oncology (ESMO) (74, 123). At the population level, electronic health record linkage with cancer registry data enables near-real-time monitoring of incidence, treatment patterns, and outcomes, facilitating identification of care gaps and evaluation of screening program effectiveness (122).

### *Stage Migration, Screening Equity, and Survival Gains*

Shifting the stage at diagnosis toward earlier disease (stage I–II), or shift migration, is the main way through which lung cancer mortality is reduced at the population level, and this effect is closely tied to LDCT screening, rather than better treatment. Survival depends heavily on the stage at diagnosis; early detection greatly improves outcomes, with stage IA patients surpassing 65% five-year survival, compared to under 40% for regional cancer and around 10% at stage IV (57, 127). The NELSON trial demonstrated that LDCT screening in high-risk groups significantly moved diagnoses to earlier stages, with about 50% detected at stage I versus 14.2% in controls (18). This shift, not better treatments, is the primary driver for the 24% lung cancer-specific mortality reduction among men and 33% among women in NELSON, and 20% in NLST (128). Population survival rates, such as the European five-year survival of 13–19%, reflect stage distribution influenced by access to screening (20). Countries investing in screening show better outcomes. Despite coverage since 2015, less than 20% of eligible Americans participate, with disparities among high-risk groups (129). The ASCO notes that improving survival depends on equitable implementation of screening, not just on disease biology (130).

The survival benefit of stage migration is uneven across racial, ethnic, and socioeconomic groups, operating at three points in the screening-to-survival pathway, leading to racial inequity (131, 132). First, screening eligibility itself favors white men; Black men with lung cancer are less likely to be eligible, a disparity that persists despite expanded criteria (133). This reflects that women and minorities, like Black persons, are at higher lung cancer risk at lower cigarette use levels, so eligibility criteria based on pack-year thresholds reinforce disparities (133). Second, screening uptake among eligible individuals is lower in marginalized groups, with barriers worsening disparities in incidence and mortality (134). Third, access to molecular testing after diagnosis is limited for Black patients and those in poorer areas, reducing access to targeted therapies that significantly improve survival. Black patients are also less likely to be diagnosed at an early stage, further worsening survival disparities (132). These layered inequities in lung cancer detection and treatment have mainly benefited White, insured, urban, and socioeconomically advantaged patients (135, 136). Globally, disparities undermine overall reductions in lung cancer incidence, and recent treatment gains are not equitably shared, highlighting the need for investing in equitable screening, biomarker testing, and addressing socioeconomic barriers to ensure early diagnosis and cure (43, 131).

### *Healthcare Policy Responses in Southeastern Europe*

The data examined across Sections 2–6 coalesce into a specific, actionable policy challenge for Southeastern Europe. In Southeastern European nations, including the countries of the former Yugoslavia, such as Bosnia and Herzegovina and

Serbia, as well as Romania and Bulgaria, a confluence of a high tobacco burden, limited LDCT infrastructure, incomplete cancer registration, and restricted access to targeted therapies results in a preventable excess of lung cancer mortality that is inadequately reflected in pan-European statistics. The GBD 2023 PAF estimates presented in Table 2 suggest that tobacco control alone, if implemented fully in accordance with FCTC standards, could theoretically avert 65–67% of lung cancer fatalities in Central and Eastern Europe (1). Against this, only eight of 27 EU member states have achieved fully smoke-free environments, and the Eastern European sub-region demonstrates the least compliance with FCTC measures of any European subregion (16).

Five-year survival for early stages NSCLC in Central and Eastern European countries averages approximately 50%, compared with 63% in Western European counterparts, a gap that reflects structural differences in health systems rather than biological variation (15, 20, 58). Bridging this gap involves three simultaneous efforts: (i) speeding up FCTC implementation, especially focusing on cigarette taxes and smoke-free laws, where the evidence of impact is strongest; (ii) testing LDCT screening programs in urban areas with high disease burden, using PLCOm2012 or LLPv2 risk models that are more effective than traditional smoking-history criteria in identifying high-risk individuals; and (iii) developing molecular pathology capabilities to support biomarker-guided NSCLC treatment at national reference centers, which can then expand through hub-and-spoke networks (52, 118).

The regional trends in lung cancer incidence and mortality could be partially explained by the long-term effects of the profound political and socioeconomic instability that affected Southeastern Europe during and after the 1990s (137). The dissolution of Yugoslavia, associated armed conflicts, economic collapse, sanctions, and large-scale displacement likely influenced lung cancer rates through multiple indirect mechanisms, including changes in smoking behavior, disruption of healthcare infrastructure, and major demographic shifting (138-140). Refugee movements from Croatia and Kosovo into Serbia, alongside internal displacement of two million individuals within Bosnia and Herzegovina, may have altered national smoking prevalence, age structures, occupational exposures, and healthcare access (137, 141-143). Similar demographic transitions were observed more broadly across Europe following the Fall of the Berlin Wall and subsequent intra-European economic migration, as well as more recent migration from the Middle East and Africa into Western Europe (144).

#### *Future Research Priorities*

Several epidemiological questions remain inadequately characterized and represent priority areas for the next decade of lung cancer research. The increasing burden of lung cancer among never-smokers, especially women in East and Southeast Asia, and more broadly in other regions, necessitates comprehensive multi-disciplinary research into causes. This includes quantifying indoor air pollution exposure, mapping residential radon levels, and conducting multi-omics profiling of tumor molecular landscapes in populations without tobacco exposure.

The long-term carcinogenic potential of electronic cigarettes remains unanswerable with current data, given the inherent latency constraint discussed in Section 5.3. Longitudinal cohort infrastructure must be established now to document e-cigarette exposure histories in current adolescent and young adult cohorts, so that lung cancer risk in these populations can be characterized when they reach the relevant age range.

In parallel, advances in multi-omics integration offer a potential solution for addressing these emerging epidemiological gaps. By combining genomic, transcriptomic, proteomic, and metabolomic data, multi-omics approaches enable a more detailed characterization of tumor heterogeneity and the biological mechanisms underlying lung cancer in both smokers and never-smokers (145). This is particularly relevant for understanding the rising incidence in populations without traditional risk factors, where distinct molecular pathways may predominate. Integrating multi-omics data with environmental and clinical exposures may improve risk stratification, identify novel etiological pathways, and support more targeted prevention and treatment strategies (145). However, translating these insights into population-level benefit will require standardized data frameworks, longitudinal datasets, and equitable access to advanced molecular technologies across regions.

## Conclusion

Lung cancer remains the leading cause of cancer-related death globally, and the patterns of incidence and mortality documented in this review make clear that this status will persist for decades in many populations unless the modifiable determinants of the disease are addressed with sustained policy commitment. The evidence reviewed here supports five conclusions. First, tobacco control is the highest-yield and most cost-effective intervention available for lung cancer prevention at the population level. Second, LDCT screening has established its efficacy through multiple RCTs and should be scaled in high-income settings using validated risk prediction models, PLCOm2012, and LLPv2, to maximize detection yield while minimizing harms. Third, advances in molecular targeted therapy and immune checkpoint inhibitors have led to transformative improvements in survival for biologically defined NSCLC subgroups. Fourth, in Southeastern Europe and the MENA region, the convergence of high tobacco burden, limited early detection infrastructure, incomplete cancer registration, and restricted access to targeted therapy creates a preventable excess of lung cancer mortality that demands specific and targeted policy investment. Finally, the evolution of lung cancer risk from more never-smokers with adenocarcinoma and targetable mutations, influenced by indoor pollution and radon, calls for new risk assessment and prevention frameworks. Integrating polygenic risk scores, multi-omics tumor profiling, and better exposure measures into future risk tools is key for advancing lung cancer research.

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