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Review

Geographic differences in lung cancer: focus on carcinogens, genetic predisposition, and molecular epidemiology

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Juan Carlos Laguna*, **Miguel García-Pardo***, **Joao Alessi**, **Carlos Barrios**, **Navneet Singh**, **Humaid O. Al-Shamsi**, **Herbert Loong**, **Miquel Ferriol**, **Gonzalo Recondo** and **Laura Mezquita**

***Abstract*:** Lung cancer poses a global health challenge and stands as the leading cause of cancer-related deaths worldwide. However, its incidence, mortality, and characteristics are not uniform across all regions worldwide. Understanding the factors contributing to this diversity is crucial in a prevalent disease where most cases are diagnosed in advanced stages. Hence, prevention and early diagnosis emerge as the most efficient strategies to enhance outcomes. In Western societies, tobacco consumption constitutes the primary risk factor for lung cancer, accounting for up to 90% of cases. In other geographic locations, different significant factors play a fundamental role in disease development, such as individual genetic predisposition, or exposure to other carcinogens such as radon gas, environmental pollution, occupational exposures, or specific infectious diseases. Comprehensive clinical and molecular characterization of lung cancer in recent decades has enabled us to distinguish different subtypes of lung cancer with distinct phenotypes, genotypes, immunogenicity, treatment responses, and survival rates. The ultimate goal is to prevent and individualize lung cancer management in each community and improve patient outcomes.

Keywords: geographic differences, molecular diagnosis, molecular epidemiology, NSCLC

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Correspondence to:
Laura Mezquita
Medical Oncology Department, Hospital Clinic of Barcelona, Calle Villarroel 170, Barcelona 08036, Spain

Laboratory of Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain

Department of Medicine, University of Barcelona, Barcelona, Spain
lmezquita@clinic.cat

Juan Carlos Laguna
Medical Oncology Department, Hospital Clinic of Barcelona, Barcelona, Spain

Laboratory of Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain

Department of Medicine, University of Barcelona, Barcelona, Spain

Miguel García-Pardo
Department of Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain

Department of Medicine, University of Barcelona, Barcelona, Spain

Joao Alessi
Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute

Carlos Barrios
School of Medicine, Porto Alegre, Rio Grande do Sul, Brazil

Navneet Singh
Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Humaid O. Al-Shamsi
Burjeel Medical City, Abu Dhabi, United Arab Emirates

Introduction

Lung cancer is the second most diagnosed tumor worldwide, accounting for 2.2 million new cases globally across both genders. It is also the leading cause of cancer-related deaths, responsible for up to 1.8 million deaths in 2020.[1] While the distribution of lung cancer is relatively consistent, some regions have significantly higher incidence rates than others when adjusting by age. For example, Hungary and Serbia in Europe or French Polynesia in Oceania have high incidence rates. Conversely, Western or Middle Africa has very low lung cancer incidence rates.[1] These disparities can be attributed to variations in the distribution of risk factors, in addition to differences in reporting.

Among the risk factors for lung cancer, up to 80–90% of cases are attributed to tobacco consumption.[2] However, the World Health Organization (WHO) declares many other carcinogens including indoor radon gas, environmental pollution, asbestos, occupational exposure, or radiation.[3] Recent evidence shows that beyond external carcinogens, ethnicity[4] and genetic predisposition (associated with germline pathogenic variants in well-known high/moderate-penetrance cancer predisposition genes)[5] may also play a crucial role in lung cancer risk and the molecular profile of the lung tumor.

From a pathological perspective, lung cancer can be classified into two main subtypes: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), with NSCLC representing around 85% of cases.[6] Molecular characterization of NSCLC has revolutionized the treatment and management of these patients by identifying

Herbert Loong
Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong SAR, China

Miquel Ferriol
Laboratory of Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain

Barcelona Neural Networking Center, Universitat Politècnica de Catalunya, Barcelona, Spain

Gonzalo Recondo
Medical Oncology Department, CEMIC, Buenos Aires, Argentina

*These authors contributed equally

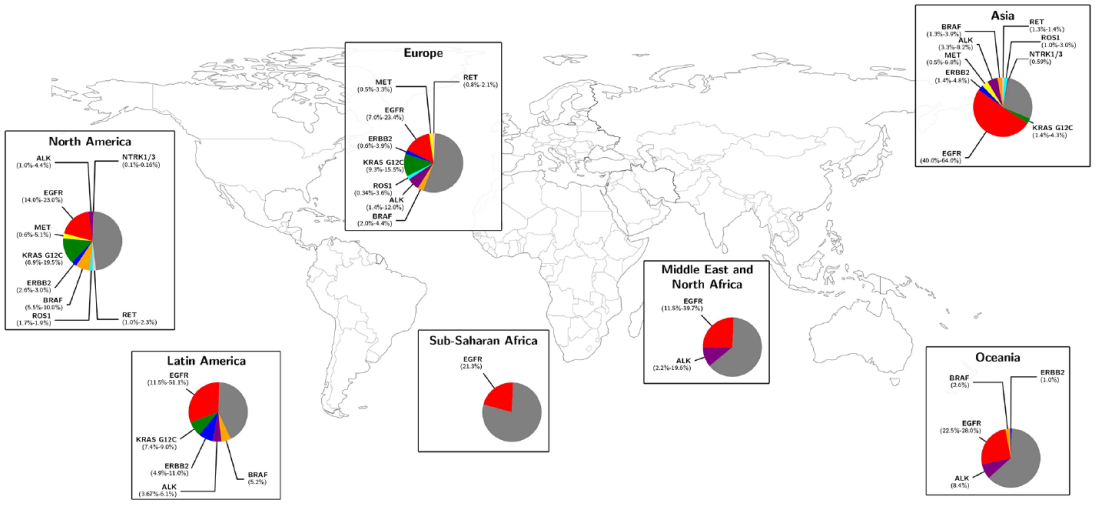

Figure 1. Distribution of the main actionable genomic alterations in non-small-cell lung cancer across the five continents. The gray proportion of each sector graphic represents 'non-reported' molecular information. Studies used for collecting the prevalence of each alteration are represented in Supplemental Table 1S.

specific driver oncogenic alterations, for which targeted therapies have been developed. Thus, testing for oncogenic drivers – such mutations in *EGFR*, *KRAS*, *BRAF*, *MET*, *ERBB2*, fusions, or rearrangements in *ALK*, *ROS1*, *RET*, *NTRK1/3*, among others – is essential in NSCLC management.[7] Emerging evidence suggests that the prevalence of these genetic alterations in NSCLC varies significantly across different regions, influenced by epidemiological factors such as geography, ethnicity, smoking, or gender.[8] For instance, mutations in *EGFR* are more frequent in women with lung adenocarcinoma, especially among Asian descent and non-smokers,[9] while *KRAS G12C* mutations in NSCLC are associated with smoking history.[10] Distribution of main actionable genomic alterations across continents is represented in Figure 1.

Hence, the geographic distribution of lung carcinogens and their interaction with the specific particularities of each individual may impact the different patterns of lung cancer phenotypes and genotypes, immunogenicity, response to therapies, and even survival in different populations. Understanding the basis for different susceptibilities is essential to develop proper preventive measures and personalize lung cancer management for each population. In this review, we aim to examine the worldwide differences in lung cancer, with a particular focus on molecular alterations.

Lung cancer in America

Lung cancer in North America

Lung cancer incidence and mortality. Lung cancer remains a major health challenge in the United States (US) and Canada, with high incidence and mortality rates. In 2020, there were 227,875 new diagnoses of lung cancer in the US, comprising 10% of all tumor cases and ranking as the second most prevalent cancer type, following breast cancer. Lower incidence was observed in Canada, with 25,574 new lung cancer cases accounting for 9.3% of all cancer cases and ranking as the third leading cause of cancer in the country.[1] While historically lung cancer primarily affected men, the American Cancer Society projects that its incidence is rising among women. By 2023, it is estimated that out of 238,340 cases in the United States, 51% will be diagnosed in women.[11] In addition, lung cancer is the leading cause of cancer death in North America, accounting for approximately 160,000 deaths in the US and 23,000 deaths in Canada annually.[11,12]

Lung cancer carcinogens in North America. Tobacco smoking is the main cause of lung cancer in North America and is responsible for the high incidence rates.[11] Pan American Health Association published in their last report that 23% of adults in the US and 13% in Canada smoke tobacco, with higher rates among men.[13] Throughout the Americas, tobacco consumption is overall

declining but mainly among men, while it has increased among women. This leads to a relatively similar male-to-female ratio in tobacco use compared to the global average (1.9 in the Americas *versus* 4.7 worldwide).

Beyond tobacco, other environmental factors contribute to the increased risk of developing lung cancer in both Canada and the US.[14] Radon, a radioactive gas that arises naturally as a decay product of uranium-238, stands as the second leading cause of lung cancer in the US.[15] Because there is no known safe level of radon exposure, the United States Environmental Protection Agency (EPA) recommends fixing homes with radon levels at or above 4 pCi/L (equivalent to 148 Bq/m^3).[16] Despite this recommendation, some US territories such as Colorado, Idaho, Montana, Alaska, South Dakota, etc. are well above this limit.[17] Conversely, the median residential radon in Canada is 82 Bq/m^3. However, high uranium concentrations in glacial tills and derived soils in the Western Prairies make the regions of Alberta and Saskatchewan in Canada the second-highest worldwide for indoor radon levels.[18,19]

Air pollution, specifically environmental particles measuring $\leqslant 2.5\,\mu m$ (PM2.5), has been associated with an increased lung cancer risk.[20] It is recommended that annual exposure to PM 2.5 should not exceed 5 $\mu g/m^3$.[21] Both Canada and the US consistently record average levels lower than 10 $\mu g/m^3$ but regions such as California, New York, and Pennsylvania in the US[22,23] are significantly higher.

In addition, industries such as mining, construction, manufacturing, and transportation often entail exposure to hazardous agents such as asbestos, silica, diesel exhaust, and various chemicals.[14] Doll and Peto attributed up to 4% of US cancer deaths to occupational factors, with lung cancer being the major contributor.[24] Steenland *et al.* later estimated a similar range of 2.4–4.8% for such contributors.[25] The Occupational Cancer Research Centre reported that up to 8% of the lung cancer cases in Canada were caused by occupational asbestos and 2.5% of the cases by diesel engine exhaust.[26]

Intrinsic factors related to lung cancer in North America. Differences in lung cancer incidence based on ethnicity or race have been described in the US. Data from the Surveillance, Epidemiology, and End Results Program show the highest rates of lung cancer (76.1 per 100,000) among African Americans compared to other ethnic groups, despite a lower prevalence of smoking. This suggests the existence of other factors that may make these populations more susceptible to lung cancer.[27] The Multiethnic Cohort study has investigated disease rates and genetic variations among five different ethnic groups in the US revealing disparities in genes involved in metabolism and carcinogen exposure, which could play a role in cancer predisposition.[28] Interestingly, when considering individuals who smoked less than 30 cigarettes daily, African Americans and Native Hawaiians had a notably higher risk of developing lung cancer compared to other populations.

These data further support ethnic and racial differences in lung cancer risk and carcinogenesis, which could be explained by a genetic background not completely understood. Mukheree *et al.* studied 5118 patients with NSCLC and SCLC at the Memorial Sloan Kettering Cancer Center in New York, finding pathogenic germline variants (PGV) in high/moderate penetrance genes in 4.3% of the patients, mainly in DNA damage repair (DDR) pathway genes. Other studies reported the prevalence of PGV across ancestry in the US, showing that individuals of European ancestry have a higher prevalence of genetic variants in DDR genes including *BRCA2*, *CHEK2*, *ATM*, and *BRCA1*.[29,30]

Molecular characterization of lung cancer in North America. The prevalence of oncogenic driver alterations in NSCLC, including *EGFR, ALK, MET*, and *BRAF V600E*, has been extensively studied in North America. A study conducted by Kris *et al.* in 2014 analyzed the prevalence of *EGFR* mutations in patients with NSCLC from the Lung Cancer Mutation Consortium database, which included a large number of patients from North America. The study reported that *EGFR* mutations were present in approximately 17% of NSCLC patients in North America, with a higher prevalence observed in female patients, non-smokers, and adenocarcinoma histology.[31] Another report analyzed data from The Cancer Genome Atlas and found a similar prevalence of *EGFR* mutations in North American patients with NSCLC.[32] The prevalence of *ALK* fusions in patients with NSCLC in North America has also been investigated in several studies. For example, a study by Shaw *et al.* reported a prevalence of *ALK* fusions of approximately 4% in patients

with NSCLC in North America.[33] *MET* aberrations, including amplifications and mutations, are less frequent compared to *EGFR* and *ALK* alterations. A study by Frampton *et al.* in 2015 analyzed data from a commercial next-generation sequencing panel and reported a prevalence of *MET al*terations of ~2% in NSCLC in North America.[34] More recently, data from a nationwide real-world database[35] updated the prevalence of oncogenic drivers in NSCLC in the US, reporting rates of 35.5%, 17.8%, 2.8%, 2.3% of *KRAS*, *EGFR*, *ERRB2*, and *BRAFV600E* mutations; and 4.3%, 1.2%, 1.1%, and 0.1% in *ALK*, *RET*, *ROS1*, and *NTRK* fusions, respectively.

The influence of genetic ancestry on molecular profile has also been assessed in the US. *EGFR* mutations were more associated with Asian ancestry while *MET* dysregulations were more frequently observed in patients of Ashkenazi Jewish ethnicity. A rare variant in the *ATM* gene was linked to an increased risk of lung adenocarcinoma in the latter population.[36]

Lung cancer in Latin America

Lung cancer incidence and mortality. Lung cancer is one of the leading causes of cancer-related deaths in Central America, South America, and the Caribbean accounting for about 86,627 deaths in 2020.[37] Specifically, it is the fourth cancer in incidence and first cause of mortality in South America and the Caribbean. However, in Central America, lung cancer is being surpassed by other cancer types as the main cause of death like liver, stomach, colorectal, breast, and prostate cancer.[37]

Lung cancer carcinogens in Latin America. Tobacco usage rates vary considerably among the adult population in Latin America. In Central America, the estimated prevalence of tobacco use is generally less than 10% in most countries, including Panama, El Salvador, and Costa Rica. By contrast, South America exhibits notably higher prevalence rates, with countries such as Chile (29.2%), Argentina (24.5%), and Uruguay (21.5%) at the forefront.[13]

According to WHO and the World Air Quality, Chile, Peru, Colombia, and Mexico are among the Latin American countries with the highest air pollution rates in the region.[38] A recent study in Chile showed a significant association between the level of PM2.5 across different boroughs and higher lung adenocarcinoma incidence.[39] Interestingly, these countries also have the highest incidence of *EGFR* mutant lung cancers. While the link between air pollution and *EGFR* mutant lung cancers in this region remains under investigation, the correlation becomes particularly intriguing in light of the preclinical and epidemiological studies conducted by the TRACERX consortium.[20] Exposure to indoor air pollution from wood smoke during cooking and heating has also been associated with lung cancer and studied in Mexico particularly. In a cohort of 914 patients with lung cancer, approximately 35% had been exposed to wood smoke. This subgroup exhibited higher rates of lung adenocarcinoma histology, with around 50% showing *EGFR* mutations and a lower incidence of *KRAS* mutations (6.7%) compared to smokers.[40]

Arsenic water intake is a major carcinogen, associated with an increased risk of lung cancer. By the year 2012, it was estimated that 4.5 million Latin Americans were exposed to high levels of arsenic concentrations across multiple countries. The main areas of high levels of drinking water arsenic exposure are the Antofagasta region in Chile, central Argentina and Andes region, Bolivia, Peru, Ecuador, southeastern Brazil, Nicaragua, and Mexico.[41] In Antofagasta (Chile), the relative risk for mortality due to lung cancer is 3.61 higher in men and 3.26 in women compared to regions with no arsenic water contamination.[42] Arsenic is predominantly associated with squamous cell carcinoma histology, and in this Chilean region, it accounts for about two-thirds of lung cancers.[43,44] A study performed using comparative genomic hybridization showed differential copy number alterations to non-arsenic exposed tumors; however, the mutational profile of arsenic-associated lung cancers remains to be elucidated.[43]

Other carcinogens, such as residential radon gas exposure, have been scantly studied in Latin America. A recent systematic review analyzing 31 studies[45] was conducted in Brazil, Argentina, and Peru and less in Costa Rica, Chile, Colombia, Ecuador, Paraguay, and Venezuela. The range of radon concentration in these studies was 0–3.723 Bq/m^3, with the highest concentrations reported in Lages Pintadas, Belo Horizonte, and Poços de Caldas in Brazil. However, there are no studies on the molecular biology of lung cancer in

areas with high residential radon exposure in Latin America.

Intrinsic factors related to lung cancer in Latin America. Cranford *et al.* studied lung cancer incidence by ethnicity of people living in Florida, including the Hispanic population.[46] They found that, among the Hispanic population, individuals of South American origin had a higher lung cancer incidence adjusted by age compared to those from Central America. In this study, Cubans had the greatest incidence among Hispanics.

Regarding genetic cancer predisposition syndromes, germline *TP53* mutations (Li-Fraumeni Syndrome) are a rare condition characterized by a predisposition to multiple tumors, including lung cancer.[47] In Southeastern Brazilian populations, it is estimated that up to 0.3% of the population carries germline *TP53* mutations.[48] This high frequency is attributed to a founder mutation, the *TP53* p.R337H. Of particular interest is the established association between germline *TP53* alterations and the development of lung cancer with somatic *EGFR* mutations. In one study, patients with germline *TP53* mutations in codon 337 had a rate of *EGFR* mutations as high as 89%.[49] This, among other factors, may contribute to the high *EGFR* mutation rates observed in Brazil.[50,51]

Molecular characterization of lung cancer in Latin America. In this vast region, which includes 33 countries, multiple factors affect lung cancer prevention and patient care. Socioeconomic barriers and inequity in access to fragmented and underfinanced healthcare systems directly impact biomarker testing and access to targeted therapies in the region.[52,53] Consequently, there is limited information about the prevalence of molecular drivers of lung cancer beyond *EGFR* mutations, *ALK* and *ROS1* fusions, and PD-L1 expression, which are the minimum biomarkers to be tested.

The prevalence of *EGFR* somatic mutations in lung adenocarcinomas varies significantly across countries: from 14% in Argentina and 18% in Uruguay, 22% in Chile, 25% in Brazil and Colombia, 27% in Panama, 31% in Costa Rica or 34% in Mexico to 51% in Peru.[51,54–56] Notably, the prevalence of *EGFR* mutations in Argentina and Uruguay is like in Spain, potentially linked to the predominance of Spanish immigration and European ancestry. On the other hand, in other countries where the preponderance of Native and African American ancestry predominates, the higher prevalence of *EGFR* mutations might be related to distinct ethnic and ancestry patterns. In a study including 601 lung cancer cases from Mexico and 552 from Colombia, ancestry was assessed using single nucleotide polymorphism (SNP) in tumor samples. Native American ancestry was positively correlated with *EGFR* mutations and negatively correlated with *KRAS* and *STK11* mutations, as observed in Asian populations.[57]

Regarding other molecular drivers, the distribution of *KRAS* mutations in the region does not vary significantly between countries such as Mexico, Colombia, and Peru, where rates have been reported at 12.9% and 16.8%, which is lower than rates reported in the United States and Europe. In Brazil, the reported prevalence of *KRAS* mutations is 24.2% and 23% in Argentina.[50,58] In the case of *ALK* fusions, there are no significant differences in the reported prevalence in the region, ranging from 3.7% in Chile to 9.5% in Costa Rica.[50,59,60]

Overall, testing for oncogenic drivers in clinical practice remains an unmet need in most countries in the region and unfortunately, most patients are managed without this critical information.

Lung cancer in Asia

Lung cancer incidence and mortality

Lung cancer is the most diagnosed cancer among men in Asia, and the second most common cancer among women, after breast cancer. In 2020, 1.3 million people were diagnosed with lung cancer and it was the most common cause of death from cancer (slightly over 1.1 million deaths) in the region.[61] Incidence and mortality rates of lung cancer in East Asia are particularly concerning, with 34.4 and 28.1 cases per 100,000, respectively, which is higher than in Europe and the United States.[62] Sex disparities have been reported, with higher incidence (ratio 2.46) and mortality (ratio 2.5) for males compared to females.[63]

Lung cancer carcinogens in Asia

About half of the world's smokers live in Asia.[64] Male smoking rates remain high; indeed, half of the world's male smokers live in three Asian countries: China, India, and Indonesia.[65] Tobacco use among children is also concerning in this

area; about 34% of the world's children aged 13–15 years using various forms of tobacco belong to the South-East Asia region.[66]

Although tobacco smoking continues to be the leading global contributor to lung cancer, the incidence of lung cancer in non-smokers is increasing, particularly among non-smoking Asian women. Epidemiological studies conducted in East Asian countries such as the People's Republic of China, Japan, Mongolia, North Korea, and the Republic of Korea showed that approximately one-third of all lung cancer patients in East Asia have never smoked[62] which is significantly higher than in Western countries.

Regarding residential radon, similarly to the published residential radon studies in North America and Europe, the China pooling study observed that long-term indoor radon exposure increases lung cancer risk, with an OR of 1.33 (1.01–1.36) at 100 Bq/m^3.[67] National radon risk registries and communication strategies, as opposed to Europe or North America, are lacking in Asia. According to 2019 WHO data, China, Turkey, and Syria are the only Asian countries conducting national radon surveys,[68] and additionally, some large-scale radon studies are ongoing in several countries, including India, Israel, Japan, Korea, and the Philippines.[69] Data from national surveys show low median radon concentrations in China (37 Bq/m^3), India (32 Bq/m^3), or Japan (18 Bq/m^3) and higher rates in Vietnam (79 Bq/m^3) and Korea (91 Bq/m^3).[70]

Outdoor air pollution and particulate PM2.5 are a concerning health issue in Asia. China has the highest attributable death rate for lung cancer caused by PM2.5, and there is an increasing trend in all of East Asia except for South Korea and Japan.[71] Industry, traffic, and household biomass combustion for heating and cooking, prevalent in Asia, have become major sources of air pollutant emissions and have a larger impact on premature mortality.[72] However, the implementation of national environmental protection policies in Asian countries is still pending.

Diesel exhaust and other occupational expositions play a relevant role in lung cancer risk, in Asia with millions of Asian workers exposed, particularly for squamous cell and small cell carcinoma.[73] The risk of occupational exposure to crystalline silica and lung cancer is also well known. There is an increased risk of lung cancer with cumulative occupational exposure to silica in workers both with and without silicosis, regardless of smoking status, and also with a multiplicative risk with smoking and silica exposure for overall lung cancer risk. This is especially relevant in Asia since there are 11.5 million workers in India, and millions in China, of workers exposed to crystalline silica while manufacturing and installing stone countertop materials for household use and sandblasting denim for fashionwear.[74,75]

Intrinsic factors related to lung cancer in Asia

There are significant differences in the clinical and molecular profile of lung cancer between Asian and Caucasian patients. In addition to exposure history, differences in ethnicity and ancestry background are thought to be the major reason for the observed differences in germline and somatic alterations between Asian and Western patients with lung cancer.

In China, germline mutation landscape has been assessed in 1794 patients with NSCLC[76] reporting a prevalence of PGV in genes related to cancer risk, mainly in DNA repair pathways, of 5.9%. Interestingly, among PGV carriers, somatic oncogenic drivers were significantly prevalent especially *MET* dysregulation (7.6% in PGV carriers *versus* 3% in non-carriers) and *KRAS* mutations (16.8% *versus* 8.3%).

Specific germline alterations have also been studied in the Asian population. Hu *et al.*[77] reported a prevalence of 1.03% of germinal *BRCA* alterations among 6220 Asian patients with NSCLC with a high prevalence of somatic oncogene drivers, *EGFR* the most frequently mutated gene (53% of patients) among BRCA carriers. Germline *EGFR* mutations in East Asian and *ERBB2* in Japanese patients with NSCLC have been described targeting never-smokers.[78]

Molecular characterization of lung cancer in Asia

The proportions of actionable genetic alterations in Asia vary considerably across published studies and by histological subtype. Compared with Caucasian patients with NSCLC, Asian patients have a much higher prevalence of *EGFR* mutations (about 30–40% *versus* 7–15%, respectively), mainly among patients with adenocarcinoma and never-smokers. Around 5% of Asian and White

patients with NSCLC have *ALK*-positive tumors.[79] On the other hand, *KRAS* mutations are less frequent in Asian patients (8–10% *versus* 20–30%). For *KRAS G12C* mutations, different studies reported a prevalence of 1.5–4.3% in NSCLC in Asia, which is significantly lower than the 10–15% described in Caucasian patients.[80]

Data from a large lung cancer genomic screening project including more than 206 institutions in Japan, Taiwan, and China (LC-SCRUM-Asia) showed frequencies of oncogenic fusions in *ALK*, *ROS1*, *RET*, or *NTRK* to be similar in Asian and white populations.[81] In particular, some studies have reported a high prevalence of *ALK* fusions (10%) among South Asian patients.[82] For *ERBB2*, the prevalence in Asia is between 1.5% and 4%.[81,83] *MET* exon 14 skipping mutation is found in about 2% of patients, also similar to Western countries.[84] Final data from ongoing national registries would allow us to better understand the real prevalence of molecular driver alterations in NSCLC in Asia.

Lung cancer in the Middle East and North Africa

Lung cancer incidence and mortality

The Middle East and North Africa (MENA) region comprises countries that are part of the Arab League, including the Gulf Cooperation Council countries such as the United Arab Emirates, Oman, Kuwait, Bahrain, Saudi Arabia, and Qatar. In addition, it includes Yemen, Iraq, the Levant region consisting of Jordan, Lebanon, and Syria, as well as North African countries like Egypt, Morocco, Libya, and Algeria. While all these countries fall under the Arab League's umbrella, they exhibit significant variation in their social and economic standings.[85] In the MENA region, the incidence adjusted by age of lung cancer is reported to be lower than international rates showing the lowest rates in Yemen (4.6 per 100,000) and the highest in Lebanon (18.7 per 100,000).[86] In the MENA region, lung cancer caused 15,396 and 57,114 deaths in women and men, respectively, in 2019. However, accurate data collection regarding cancer incidence is hindered by the absence of comprehensive and up-to-date population registries in many of these countries.[85]

Lung cancer carcinogens in the MENA region

With a combined population of approximately 360 million, up to 46% of the population in the MENA region are smokers,[85] with a high prevalence in countries such as Jordan (35.0%), Saudi Arabia (30.4%), and Lebanon (26.3%).[87] The MENA region has also a unique smoking issue with the widespread water pipe/hookah smoking.[88] The overall highest rate of current smoking (cigarette and water pipe) is seen among students in Egypt (46.7%), Kuwait (46%), and KSA (42.3%).[87] Lebanon and Tunisia also face significant issues with hookah smoking among young people. A recent study conducted on 3384 students from 17 universities in Lebanon revealed that 23% of them were current hookah smokers, while 19.2% reported being cigarette smokers.[89] In addition, among 13- to 15-year-olds in Lebanon, the Global Youth Tobacco Survey indicated a current hookah smoking rate of 34.8%,[90] compared to 11.3% for cigarettes.[91]

Besides smoking, various environmental factors play a role in lung cancer development in the MENA region. Indoor radon exposure is prevalent in some areas, and a study in Iran reported that high radon concentrations were associated with an increased risk of lung cancer among non-smokers.[92] Median radon exposure in Iran (198 Bq/m^3) is one of the highest in the region,[70] consistent with regions with high natural background radiation reported as Ramsar, an Iran city on the Caspian Sea. Particularly, Ramsar has been established as one the most radioactive cities of the world[93] with mean radon levels of 650 Bq/m^3 and maximum levels of 3700 Bq/m^3 because of the deposition of 226 Radium in local rocks and its use in the construction of houses.[94] Radon exposition also stands as a public health issue in countries such as Uzbekistan and Kyrgyzstan with one of the highest mean radon expositions in the world (219 and 200 Bq/m^3, respectively).[70] In addition, in some ex-Soviet Republics in central Asia as Kazakhstan, Kyrgyzstan, Tajikistan, and Uzbekistan, extensive uranium mining and milling activities generated large amounts of uranium tailing materials and waste rock deposits, often dumped in inhabited areas or their close vicinity[95] estimating that about 0.7–7.2% of the total population is exposed to radiation risk.[96]

MENA is among the regions worldwide with the highest death rates attributable to air pollution. A systematic analysis for the Global Burden Disease

of 2019[97] investigated the effect of PM2.5 and ozone air pollution in 21 countries of the region. Up to 12.8% of all the deaths were attributable to air pollution, particularly, 21.3% of lung cancer deaths with the highest rates reported in Afghanistan, Egypt, and Yemen.

Occupational carcinogens are the third reason for lung cancer deaths in North Africa and the Middle East after smoking and air pollution with a 2.4 age-standardized rate of deaths by lung cancer per 100,000 habitants[98] with different patterns between men and women. Retrospective studies in North Africa revealed as main exposition in occupations like masonry construction and painting (47.1%), agriculture (30.8%), and transportation sectors (12.8%) in men with lung cancer; while women were more exposed to cleaning products (50%) and coal smoke (42.8%).[99]

Intrinsic factors related to lung cancer in the MENA region

Genetic contribution to lung cancer development has been studied in a few countries of the region. In Tunisia and Egypt, SNPs in five genes were associated with high lung cancer risk (*CYP1A2*, *CYP1A1*, *IL-17A/F*, *IL-8*, and *TNFα/β*).[100] Other genetic polymorphism has been evidenced in Iran cohorts[101] linked to lung cancer risk including C-allele of the rs2245214 ATG5 gene polymorphism or C allele rs2645429 in Farnesyl-Diphosphate Farnesyltransferase 1, among others.

Molecular characterization of lung cancer in the MENA region

Molecular information related to lung cancer profile in the MENA region is limited to *EGFR* and *ALK* alterations. In a systematic review and meta-analysis including 1215 patients with NSCLC from the Middle East and Africa, 41.1% of the patients were never-smokers, and 85.8% were diagnosed with adenocarcinoma. In 8 out of 10 studies assessed, *EGFR* mutations were analyzed by polymerase chain reaction, with an overall prevalence of 21.2%. with an enrichment in the female, non-smoker population with adenocarcinoma histology.[102] The exon 19 deletion was the most observed, in 58% of cases.

Regarding *ALK* fusion, in real-world data of ALK-positive NSCLC in the MENA, the prevalence of *ALK* fusions was 8.7% among 448 tissue samples analyzed using Immunohistochemistry.[79]

Widespread access to molecular profiling platforms for tumor assessment remains limited in many of the MENA regions due to the cost and limited specialized molecular laboratories; however, the establishment of reference central laboratories in each country could play a pivotal role in facilitating access to these tests, particularly as the technology becomes more cost-effective and convenient over time.[85]

Lung cancer in Sub-Saharan Africa

Lung cancer incidence and mortality

Infectious diseases account for the greatest burden of disease across sub-Saharan Africa (SSA); however, the health burden due to cancers is increasing.[103] It is estimated that by 2030, there will be a significant rise in cancer.[104] Importantly, survival from cancer is low in SSA in comparison to other world regions.[105] Viral diseases are important drivers for cancers such as cervical cancer, Burkitt's lymphoma, Kaposi's sarcoma, or hepatocellular carcinoma.[103]

Population-based data on lung cancer incidence and mortality in SSA are scarce. Lung cancer incidence rates remain low, except for Southern regions.[1] Incidence age-standardized incidence rate per 100,000 is significantly higher in Southern Africa (27.5 in men and 9.3 in women) compared to Eastern (4.2 and 3.0), Middle (3.4 and 1.8), and Western Africa (2.8 and 1.8, respectively).[106] This is likely due to the low prevalence of smoking (10% in men and $<2\%$ in women), as well as the lower life expectancy of the population.[106] However, reporting of lung cancer incidence and mortality in SSA is limited by the lack of reliable registries, and it is likely underestimated.[106] In addition, the case fatality rate is higher, mainly due to late presentation and poor access to treatment.[107] In a population-based study, cancer survival was lowest in the two African countries (The Gambia and Uganda). This was attributed to the poorly developed health services, with limited availability of cancer diagnostic and treatment facilities.[105]

Lung cancer carcinogens in SSA

Smoking prevalence varies greatly between SSA countries, accounting for about 6% of cancer deaths in Africa,[104] and it is significantly higher in men. Adult smoking prevalence is less than 10% in men and close to 2% in women in many SSA countries, but cigarette consumption is increasing

in parts of this region because of the adoption of Western behaviors associated with economic growth and increased marketing by tobacco companies.[104] High smoking rates are observed among countries in the eastern and southern regions of Africa, mainly among men in Ethiopia, Malawi, Rwanda, and Zambia, and women in Rwanda and rural Zambia.[108]

Working conditions and workforce characteristics facilitate occupational exposures in SSA. Lack of protective devices, lack of training in hazard awareness, slow implementation of safety standards, obsolete technologies and machinery, and lack of monitoring of occupational health are some of the issues affecting workers of the SSA countries.[109] Occupational factors associated with increased lung cancer risk in Africa include asbestos (South Africa, Swaziland, Zimbabwe), exposure in mines to aluminum smelters (South Africa, Guinea, Mozambique, Cameroon, Nigeria, Ghana), beryllium (Mozambique), nickel compounds (South Africa, Botswana, Zimbabwe), or silica dust from gold mines (South Africa).[109]

Indoor combustion of solid fuels for cooking and heating is the main source of air pollution in SSA. In addition, levels of outdoor pollution have risen in urban areas due to a rapid increase in industrial and motor vehicle diesel exhaust. In SSA, average emissions per vehicle are higher as vehicles are on average older, and cheaper, and lower quality fuels are used.[109]

Intrinsic factors related to lung cancer in SSA

Despite the growing evidence suggesting that genetic factors contribute to the risk of developing lung cancer, data on genetic biomarkers for lung cancer risk in African ancestry populations are limited. Analysis of African Americans in North America has been performed, looking for nominal SNPs linked to lung cancer, and there is growing literature pointing toward rs2036527 as an informative polymorphism for smoking exposure and lung cancer risk in African Americans.[110]

Molecular characterization of lung cancer in SSA

Since most countries in SSA do not have any modalities for molecular testing,[111] the frequency of molecular alterations in African patients has been understudied. Most data come from studies conducted on African Americans in the United States.

In South Africa, biomarkers can be tested using immunohistochemistry and fluorescence *in situ* hybridization, and next-generation sequencing is available in the private sector to use in selected cases.[112] *EGFR* mutation prevalence in SSA patients with NSCLC seems to be similar to that in Western countries, compared to the higher prevalence found in Asian patients.[112] In a retrospective study by Chan *et al.*, *EGFR* mutations were present in 21.3% of South African patients (18% in Caucasians, 23% in Africans, and 39% in other races).[113]

Studies exploring the prevalence of *EGFR* mutations in lung tumors from US patients with Afro-American ancestry have been inconclusive; some studies found a significantly lower prevalence of *EGFR* mutations in Afro-American patients compared with Caucasians, whereas other studies did not observe any association of *EGFR* mutation status with ancestry or self-reported race.[114]

In an analysis conducted by Araujo *et al.*, 206 self-reported Afro-Americans from the United States with NSCLC provided samples for molecular analyses. The frequency of driver alterations altogether was lower than that reported in Caucasians but no difference was detected in either *EGFR* or *KRAS* mutations; in addition, the frequency of *ALK* fusions was similar to the lower boundary of the rates reported in unselected populations.[115]

The NSCLC cases from African patients might have a different pattern of somatic driver mutations than from Caucasians; further studies conducted specifically in SSA patients with NSCLC are needed.

Lung cancer in Europe

Lung cancer incidence and mortality

Lung cancer is the leading cause of cancer deaths in Europe,[1] corresponding to almost 20% of all cancer deaths.[116] The share of all deaths attributed to lung cancer was 7.0% among males, more than double the share (3.2%) recorded for females.[117] Overall, prevalence and mortality rates in Europe are higher than the global average, and 5-year survival rates stand at a mere 11.2% for men and 13.9% for women.[118]

By country, the incidence of lung cancer in men is highest in Central and Eastern Europe such as Hungary (138.3 per 100,000) or Serbia (136.4). Whereas the highest rates in women are seen in Ireland (85.1), Denmark (85.1), and Hungary (76.6).[116] Lung cancer incidence is increasing in European women likely due to different time period in which women initiated the smoking habit.

Lung cancer carcinogens in Europe

Smoking prevalence is still very high in some countries, such as Greece (37%), France (36%), and Bulgaria (36%); while there are others as Sweden with only 7% of smokers in the population. Hand-rolled cigarettes have become more popular among smokers in some European countries, including England (27.3%), France (16.5%), and Finland (13.6%), with overall about 10.4% of current smokers using predominantly hand-rolled cigarettes.[4] The implementation of tobacco control policies is contributing to smoking cessation,[119] which could potentially reduce future lung cancer incidence considerably across Europe.[120]

According to the European Indoor Radon Map launched by the Joint Research Centre of the European Commission, more than 30% of the territory has median radon above 100 Bq/m^3, and 4.2% is above 300 Bq/m^3 with several radon-prone areas,[121] such as the Bohemian Massif, the northwest of Spain, the Massif Central, the Fennoscandian shield, the Vosges Mountains, the Central Alps, the North of Estonia and certain volcanic structures in central Italy.[122] The estimated annual indoor radon mean is 78.5 Bq/m^3, ranging from 10 (Iceland) to 184 Bq/m^3 (Serbia).[123] The European pooling study by Darby *et al.* demonstrated a linear increase of 16% (range: 5–31%) of lung cancer risk per 100 Bq/m^3 of indoor radon across all histologies (adenocarcinoma, squamous, SCLC, and others), highlighting that the risk of death from lung cancer is about 25 times greater for cigarette smokers.[124]

Occupational carcinogens affect one in five workers in the European Union (EU): based on EU CAREX (Carcinogen Exposure Database), a substantial proportion of workers in the EU were exposed to carcinogens in the early 1990s.[125] Cancer, and particularly lung cancer, is the main cause of death by occupational exposures in Europe,[126] up to 53% of all work-related deaths. Asbestos exposition is the main contributor to occupational lung cancer deaths in the EU being estimated that 46,919 lung cancer and mesothelioma deaths would be caused by asbestos according to the European Agency for Safety and Health at work,[126] especially relevant in countries such as the United Kingdom, Netherlands, and Italy.

Intrinsic factors related to lung cancer in Europe

Wide populational cohorts in Europe have assessed lung cancer risk in first-degree relatives of cancer with lung cancer – relative risk of 2.36 in the Swedish Family-Cancer Database.[127]

Genetic variations and SNPs associated with lung cancer risk have been studied with genome-wide association studies in European ancestry populations. In a study by *Hung et al.*, never-smokers of lung cancer risk in never-smokers of European ancestry were associated with genetic variation in the 5p15.33 TERT-CLPTM1Ll region.[128] Interestingly, top variants previously shown to be associated with lung cancer risk only conferred risk in the presence of tobacco exposure, underscoring the importance of gene–environment interactions in the etiology of lung cancer.[128]

On the other hand, some authors have analyzed the clinical and molecular features of European patients with lung cancer carriers of a PGV in cancer predisposition genes. For instance, in 22 patients with Li-Fraumeni syndrome and lung cancer, 90% harbored a somatic driver alteration in the lung tumor, mainly *EGFR* mutations.[47] Going further, Mezquita *et al.* characterized molecularly by whole exome sequencing the lung tumors of 22 patients PGV carriers finding a prevalence of oncogene-driven tumor of 68%.[129] Future studies assessing the family and clinical/molecular characteristics of patients with lung cancer harboring germline alterations would help to identify a high-risk population. Recent data from a Spanish cohort show a prevalence of PGV in 7.3% of 55 patients with NSCLC, including young individuals, non-smokers, or those with oncogene-addicted tumors, primarily in DNA repair genes[130]

Molecular characterization of lung cancer in Europe

Across Europe, there is a significant variability in the adoption of biomarker testing for advanced NSCLC. Limitations to the use of biomarker

testing across Europe include a lack of reimbursement of targeted therapies and testing in some countries. Between 2011 and 2016, the proportion of patients with advanced non-squamous NSCLC who underwent single-gene molecular testing ranged from 65% to 85% across Germany, Italy, and Spain.[131] Molecular testing rates typically increase with time.

The largest study in Europe assessing routine nationwide molecular profiling of patients with advanced NSCLC was performed in France collecting 18,679 molecular analysis data from 17,664 patients with NSCLC.[132] The authors found a prevalence of 29% *KRAS* mutations, 11% *EGFR* mutations, 5% *ALK* fusions, 2% *BRAF* mutations, 2% *PIK3CA* mutations, and 1% *ERBB2* mutations. Another large cohort in Germany ($n=3717$ patients with NSCLC)[133] studied separately molecular biomarkers in non-squamous and squamous NSCLC. The most common alterations found in non-squamous tumors were *KRAS* mutations (39.2%), *TP53* (51.4%), and *EGFR* (15.1%) while in squamous tumors were *TP53* (69.1%), *MET* (11.1%), and *EGFR* (4.4%). It is worth noting that up to 29.3% of the squamous tumors were not tested for biomarkers compared to 7.8% of the non-squamous tumors.

Some studies have linked lung cancer carcinogens with certain molecular features. Hill *et al.* found a consistent relationship between PM2.5 air pollutants and EGFR-driven lung cancer incidence in England, Taiwan, and South Korea based on a mechanistic basis for PM-driven lung cancer.[20] Interestingly, two studies in Spain have reported radon levels above 100 Bq/m^3 in patients with *EGFR* mutant and *ALK*-positive NSCLC.[134,135] In line with this data, large ecological studies performed in France observed a higher prevalence of driver oncogenic alterations (*EGFR*, *BRAF*, *ALK*, *ROS1*, and *ERBB2*) in patients with lung cancer living in high radon risk areas according to the Radon map in France.[136,137] The 1920 – EORTC Bioradon study[138] is currently ongoing in five European countries in Europe to assess prospectively this potential association between radon and molecular alterations in NSCLC.

Lung cancer in Oceania

Lung cancer incidence and mortality

Oceania, an island continent located in the Pacific Ocean, encompasses more than 10,000 islands. Despite having the largest geographic area among continents, its population is one of the smallest, with the majority concentrated in Australia and New Zealand, accounting for over two-thirds of the total population of the continent.[139]

According to Globocan, 16,975 new cases of lung cancer were diagnosed in Oceania in 2020, making it the fourth most common tumor in incidence after breast cancer, prostate cancer, and melanoma. It is also the leading cause of cancer-related death when considering both genders, with 12,012 deaths in 2020.[1] However, there are significant intra-continental epidemiological differences, even within each country: while lung cancer ranks fifth in overall incidence among individuals of European descent in Australia/New Zealand, Māori in New Zealand or Indigenous Australians have higher incidence rates (some of which are the highest in the world[140,141]). They also have significantly higher mortality rates compared to the non-aboriginal population (three times higher in the case of Māoris) and die at younger ages.[141–143] In contrast to Australia/New Zealand, in Polynesia and Micronesia, lung cancer is the most incident tumor,[1] fact not completely explained by tobacco consumption.

Lung cancer carcinogens in Oceania

The epidemiological cancer registry and associated risk factors exhibit significant disparities between the Australia/New Zealand regions and other Pacific populations, where there is a significant lack of epidemiological data.[144] Tobacco smoking is the leading cause of lung cancer, accounting for about 90% of lung cancers in males and 65% in females in Australia/New Zealand.[145] In 2007, approximately 20% of Australians/New Zealanders over the age of 14 were current smokers.[146] These rates are even higher in lower socioeconomic strata, and are of particular concern among Aboriginal Australians, with smoking rates reaching up to 50% in the population aged >18 years.[147]

In Australia and New Zealand, the annual average of indoor radon concentrations are 45 Bq/m^3,[148] and 23 Bq/m^3,[149] respectively. No radon-prone areas have been reported according to national agencies.[149,150] In Australia, the average radon levels in homes along the Great Dividing Range are typically higher than levels in homes on the coastal plan, mainly due to differences in the nature of the underlying geology (rock and

soil).[150] Data for the rest of the islands in the Pacific continent are limited. Although it is expected that their indoor radon concentrations are low given the absence of granitic bedrocks in Pacific islands' soil, coverage of volcanic rocks by karst limestone plateau, composed largely of fossilized foraminifera and corals with high amounts of uranium, can increase radon concentrations in some islands.[151]

As for other risk factors, air pollution is low on the continent.[152] It is worth noting the nuclear test of Moruroa and Fangataufa between 1966 and 1996.[153] It has been estimated that around 110,000 inhabitants may have received doses greater than 1 mSv/year, constituting about 90% of the total Polynesian population in 1974.[154] This exposure may influence the risk of developing in cancer in the affected area.[155]

Finally, concerning work-related risk factors, it is estimated that around 37% of the population were exposed to at least one occupational carcinogen in their current job,[156] such as diesel engine exhaust, silica, or wood dust, according to the Australian Worker Exposure Study. It is worth noting that in the 1950s, Australia had the highest per capita consumption of asbestos in the world. Production and importation were banned in 2003.[157] This situation has led to Western Australia having one of the highest rates of malignant mesothelioma in the world[157]

Intrinsic factors related to lung cancer in Oceania

Before the arrival of Europeans over 40 1000 years ago, Oceania was inhabited by migrant groups from Africa,[158] who dispersed across the continent leading to the development of a wide variety of ethnicities. The current count exceeds 1000 distinct ethnic groups. Differences in cancer incidence based on ethnicity have been described. For instance, in Australia, Indigenous Australians have a higher likelihood of being diagnosed with lung cancer compared to non-Indigenous Australians, even when accounting for differences in smoking rates.[143] A similar situation occurs with the Māori population in New Zealand.[142] While high smoking rates contribute to the disparity, other factors may also make these populations more susceptible to lung cancer. Epidemiological research is crucial in identifying occupational exposures, diet, socioeconomic status, and genetic differences that may contribute to these disparities.

A notable case was the discovery of germline mutations in the E-cadherin gene associated with gastric and breast cancer, initially identified in three Māori families.[159] Further genetic studies may help identify specific mutations associated with higher lung cancer incidence in certain ethnic groups.

Molecular characterization of lung cancer in Oceania

When examining the molecular profile of lung cancer in Oceania, it is important to consider the variation in access to molecular characterization across different regions. Australia and New Zealand benefit from established public healthcare systems that provide government-funded access to molecular study techniques and targeted therapies.[143] However, except in French Polynesia or Hawaii, the population in the remaining Pacific Islands faces challenges in accessing specialized healthcare and high-quality molecular diagnosis due to factors such as geographical distance and cultural barriers.[160] Consequently, molecular profiling data in Oceania are incomplete, with a focus on wealthier and more populated regions, while other areas have limited available data.

In the few reported series, the frequency of *EGFR* mutations in the Australian population with lung cancer ranges between 19% and 28%,[161–165] including *T790M* mutations (9.3%) and exon 20 insertions (4.8%).[165] This reflects a higher prevalence compared to other series in the Caucasian population (10–15%). In the largest series of Australian patients with NSCLC, the authors also described the prevalence of other driver alterations such as *KRAS* (38.3%), *BRAF* (5.1%), or *ERBB2* (1.7%) mutations.[165] Some studies have attempted to determine the differences in biomarkers prevalence among different ethnicities in northern Australia,[166] but due to the small sample size, no significant differences were found in the prevalence of *EGFR* or *KRAS* mutations. In the New Zealand population, in a cohort of 384 patients with NSCLC,[167] the overall prevalence of *EGFR* mutation was 22.5%, with a higher prevalence among the Asian population (51.8%), followed by Pacific Islanders (29%) and New Zealand Europeans (16.5%), while Māori had the lowest proportion (10.9%). Scarce

information is available about gene fusions in Oceania. It has been published an 8.4% of *ALK* fusion incidence in a retrospective study in New Zealand with a higher incidence among Asian, Pacific, or Māori ethnic groups than in New Zealand Europeans (22.0%, 10.8%, and 6.9%, respectively, *versus* 4.4% in New Zealand Europeans).[168]

Conclusion

Cultural, socioeconomic, and geographic differences in each region can lead to unequal exposure to the mentioned carcinogens in lung cancer. The interaction of all potential risk exposures that contribute to the risk of developing lung cancer, combined with endogenous factors in each individual, such as genetic predisposition, ancestry, sex, and other factors, impacts the development of lung cancer in a multifactorial and complex pathway. These factors may influence the profile of lung cancer, including the pathological, genomic, and immunological biomarkers, which can guide treatment selection and subsequently affect clinical outcomes. One example of this is the differences in clinical and molecular profiles among different populations, such as the higher prevalence of lung cancer in non-smoking Asian populations compared to Western populations, especially among women with adenocarcinoma tumors and those with alterations in *EGFR* or *KRAS*.[62] While this evidence remains limited, an increasing number of studies are being conducted to gain a deeper understanding of these geographic and genetic differences across different countries and world regions, generating new hypotheses on the interaction between environmental and genetic factors. Collectively, these efforts will contribute to generate knowledge, improving the understanding of lung cancer across different world regions, and promoting cancer policies and prevention strategies worldwide.

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Disclaimer

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Author contributions

Juan Carlos Laguna: Conceptualization; Data curation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Miguel García-Pardo: Conceptualization; Data curation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Joao Alessi: Writing – original draft; Writing – review & editing.

Carlos Barrios: Writing – original draft; Writing – review & editing.

Navneet Singh: Writing – original draft; Writing – review & editing.

Humaid O. Al-Shamsi: Writing – original draft; Writing – review & editing.

Herbert Loong: Writing – original draft; Writing – review & editing.

Miquel Ferriol: Resources; Writing – original draft.

Gonzalo Recondo: Writing – original draft; Writing – review & editing.

Laura Mezquita: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

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ORCID iDs

Miguel García-Pardo https://orcid.org/0000-0001-6339-8501

Laura Mezquita https://orcid.org/0000-0003-0936-7338

Supplemental material

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