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Early-onset lung cancer in Asia: a narrative review

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Introduction: The incidence of early-onset lung cancer (EOLC), often defined as those that occur in adults under the age of 50, is increasing globally. Asia accounted for almost 76% of EOLC cases worldwide. This presents a challenge given previous limited studies and the socioeconomic implications.

Methods: References were identified through a PubMed, Scopus and Web of science search for relevant articles published in 2000 to April 2025 using the terms 'lung carcinoma or cancer', 'early-onset' or 'young adults', and 'Asia'.

Results: Early-onset lung cancers are more common in female, primarily presenting as adenocarcinoma, and tends to be diagnosed at an advanced stage. There is a high prevalence of potentially targetable genomic alterations: 30-56.3% EGFR mutations and 16.1-50% ALK rearrangements. Comparative analyses show higher prevalence of actionable genetic alterations ROS1, and RET fusions and ERBB2 mutations compared to older patients. Air pollution is a significant risk factor for lung cancer in Asia. MUC16, a transmembrane glycoprotein, is overexpressed in lung cancer, particularly in patients exposed to indoor air pollution. Patients with EOLC exhibit impaired cell-mediated immunity with reduced T cell infiltration. This suggests a potentially limited response to immune checkpoint inhibitor therapies in this patient group.

Conclusion: The incidence of EOLC is increasing in Asia. This accounts for 75.9% of global cases. The research conducted in the region are mostly retrospective and, majority are single-institution studies. Due to its unique clinical and molecular features, EOLC requires dedicated research efforts and tailored interventions.

KEYWORDS

lung cancer, familial lung cancer, early-onset lung cancer, young adults, Asia

1 Introduction

Lung cancer remains the most common cause of cancer-related deaths globally. It represents 12.4% of all cancer cases and 18.7% of cancer mortality (1). Risk factors of lung cancer include tobacco smoking, environmental tobacco smoke or second-hand smoking, occupational exposures, air pollution, previous respiratory diseases, advanced age and genetic susceptibility (2–4). The occurrence of lung cancer increases significantly in individuals over

the age of 50. The studies that have been conducted focused on the risk factors in these age group and in older population. There is inadequate information on early-onset lung cancer (EOLC), often defined as those that occur in adults under the age of 50 (5). Assessing risk factors, distinct clinicopathologic features and behavior, tumor molecular characteristics, and management outcomes for early-onset lung cancer present a challenge given previous limited studies and socioeconomic implications. This article reviews the clinical and molecular characteristics of EOLC in Asia based on retrospective analyses, research studies, and reviews currently available in the scientific literature.

2 Methods

2.1 Study design, search strategy and selection

References for this Review were identified through a comprehensive search of PubMed, Scopus and Web of Science for relevant publications from 2000 until April 2025. The search was limited to articles that were published in English language. The search terms used included “lung carcinoma or lung cancer”, “early-onset” or “young adults”, and “Asia”. The search covered a wide range of publication types, including original research articles, reviews, editorials, cohort and cross-sectional studies, as well as letters to the editor. Additional articles were sourced from the authors’ personal archives and by reviewing the reference lists of pertinent studies to identify papers not retrieved through the initial electronic search. The final list of references was selected based on originality, recency, and relevance to the objectives and scope of this review. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (6) were followed to systematically search the literature to identify studies relevant to this review. Duplicate papers, papers not written in English, those containing non-human and aged 65+ years were manually removed through the study screening process.

2.2 Results

The PRISMA flow diagram (Figure 1) shows the study selection process. The search strategy initially identified 1,196 records. The included articles were published between 2000 and April 2025. The subsequent process involved several stages to refine the initial search results. Before screening, 243 duplicate records were systematically removed. This left 953 unique records. The final list of references that included 523 articles was selected based on originality, recency, and relevance to the objectives and scope of this review.

3 Epidemiology

The incidence of early-onset cancers is rising globally (7). In 2019, the incidence exceeded 3.26 million cases (7). This was 79.1% increase since 1990 (6). Asia accounted for almost 76% of EOLC

cases globally (1). China, Türkiye and Korea have the highest incidence in the region based on age-standardized rate per 100,000 (8; Figure 2). China, India and Indonesia have the highest number of EOLC cases in 2022 (8). China contributes 64.1% of these cases (8). EOLC incidence and mortality are expected to increase, with 110,000 new cases by year 2035 (9) (Figure 3).

Based on current data and projections for the next years, there is the need for research studies and targeted interventions to address this significant public health concern.

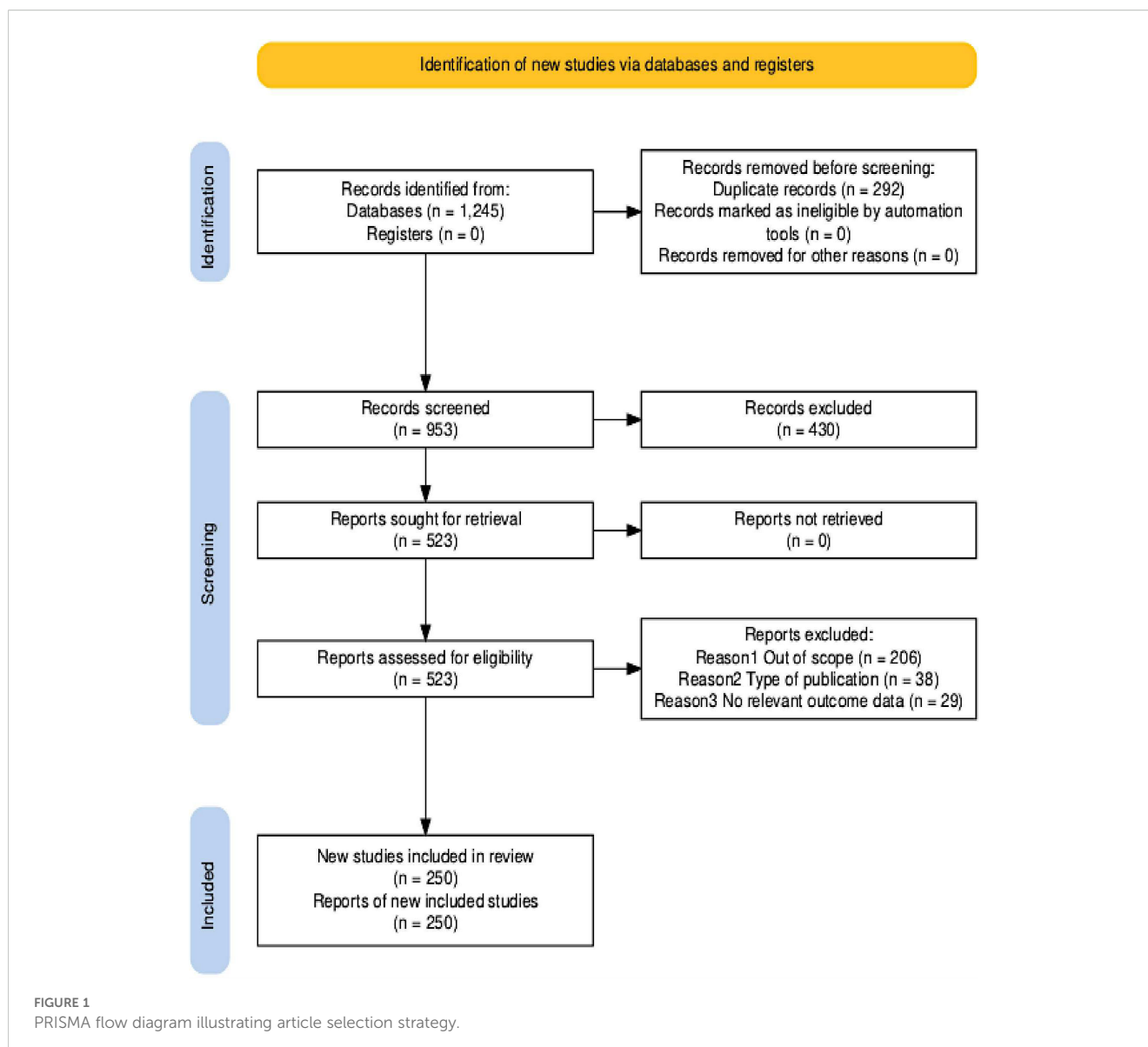
4 Risk factors

A study in Korea by Kang, et al. (10) is the largest cohort to date evaluating the health behaviors, socioeconomic factors, and comorbidities associated with lung cancer risk in individuals under the age of 40. The risk of developing lung cancer was observed to increase with advancing age, and females were found to be at greater risk compared to males (10). While current smoking was significantly associated with a heightened risk, former smoking did not show the same effect. Additionally, metabolic syndrome was linked to an increased likelihood of lung cancer. In contrast, light alcohol intake (less than 10 g/day) seemed to offer a protective benefit, though this effect was not seen with higher levels of consumption (10 g/day or more) (10). Factors such as higher income, regular physical activity, and obesity were associated with a lower risk of developing lung cancer (10).

4.1 Air pollution

Air pollution is a significant risk factor for lung cancer in Asia (11–14). Both ambient air pollution, specifically fine particulate matter (PM_{2.5}), and household air pollution from the use of solid fuels like coal have been associated with increased lung cancer risk in various Asian populations, including those in China, Korea, and Taiwan (15–17). The International Agency for Research on Cancer (IARC) has classified outdoor air pollution and particulate matter as Group 1 carcinogens (18, 19).

A study from North China (12) provides specific insights on EOLC and air pollution. This large multicenter case–control study involved over 14,000 subjects. It identified being younger than 50 years old as a risk factor for lung cancer overall (12). More specifically, in areas categorized as heavily polluted, being male, consistent alcohol consumption, a family history of cancer, having ever smoked, and having quit smoking were all identified as risk factors for lung cancer (12). Being younger than 40 years old, having a family history of cancer, and smoking or having smoked in the past were found to be higher risk factors in the heavily polluted areas (12). This finding suggests a potential interaction where heavy air pollution exposure may contribute to earlier onset of the disease, particularly when combined with genetic predisposition or family history and smoking history. The study also highlighted that PM_{2.5} was the main factor affecting the occurrence of lung cancer in this North China cohort (12).



The higher levels of air pollution (20) is one possible reason to explain the higher familial risk of lung cancer in Asia. The traditional indoor cooking methods by burning coal or solid fuel are still practiced in certain rural areas in China (21) and in some countries in Southeast Asia. Xuanwei county has the highest lung cancer rates in China which was attributed to household air pollution from cooking and heating (22, 23).

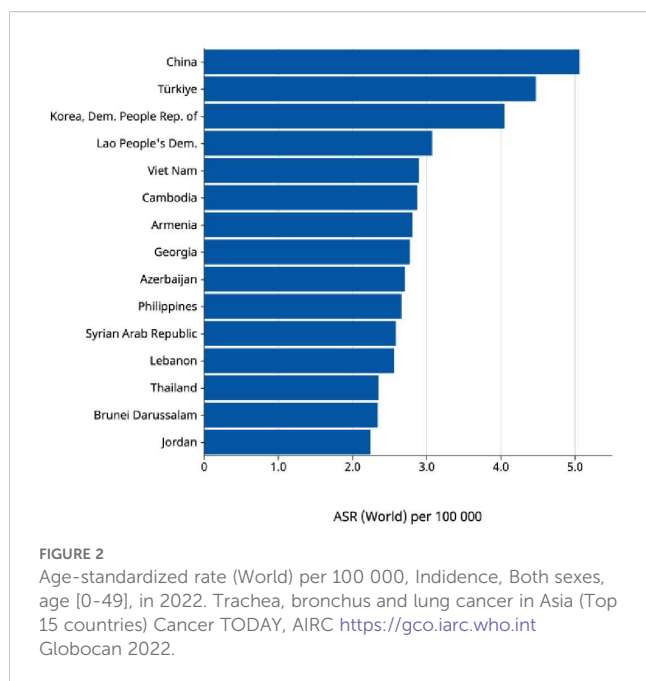
4.2 Familial lung cancer

Earlier research on the familial risk of lung cancer has shown that the risk increases when there is a history of early-onset lung cancer in the family, affected first-degree relatives (FDRs), as well as multiple affected family members (24, 25). Individuals with a family

history of lung cancer among FDRs have approximately 50% higher risk of lung cancer than those without a family history (24).

Characteristics of FLC in Yunnan-Guizhou, China found more individuals under age 50, showed two peaks, i.e. 46 vs. 58 years (26). This suggested genetic or environmental potential risk factors. While not statistically significant, the FLC group showed higher proportions of females, adenocarcinoma histology, stage IV disease, and metastasis to other organs, suggesting a more aggressive cancer (26). A significant difference was observed in tumor location, with FLC patients more commonly having cancer in the left lung (26).

A systematic review and meta-analysis done by Ang et al. (27) found that sex, smoking status, type of FDR, early onset of lung cancer in affected relatives, and having at least one affected relative was significantly associated with increased familial risk of lung cancer. Familial risk of lung cancer was found to be greater in Asian



populations compared to those in Western regions, in younger individuals compared to older ones, and in those with two or more affected relatives as opposed to those with only one (27). Asians were observed to have a higher familial risk of developing squamous cell carcinoma compared to Western counterparts. Higher familial lung cancer risk among younger individuals suggests a genetic component favoring a tumor suppressor model with cellularly recessive effects that are commonly found in familial cancers such as breast cancer (28). Evidence of Mendelian codominant inheritance caused by a rare major autosomal gene for the pathogenesis of early onset familial risk of lung cancer has been previously reported (29).

Familial risk of lung cancer is complex. It involves both genetic and the shared environmental factors including environmental tobacco smoke, air pollution, and geographical region among family members (30). The effects of smoking and smoking behavior cannot fully explain and account for familial risk of lung cancer. Genetic factors, including polymorphisms in DNA repair genes, impaired DNA damage, and defective DNA repair mechanisms, may contribute to the susceptibility of familial lung cancer in both never-smokers and ever-smokers (31–33). Germline genetic mutation of epidermal growth factor receptor (*EGFR*) T790 M were identified in families with high density of lung cancer cases (34, 35).

Individuals with a family history of early-onset lung cancer have a significantly increased risk of developing the disease, whereas this link was not observed in those with relatives diagnosed at a later age. A rare major autosomal gene could play a role in early-onset lung cancer (36). A prior study conducted in Anhui, China, reported that female relatives, particularly mothers, had a higher risk of lung cancer compared to male relatives (37). The control for household exposure to tobacco smoke did not negate the finding that females with family history of lung cancer were more susceptible to lung cancer risk than their male counterparts (33).

4.3 Pulmonary tuberculosis

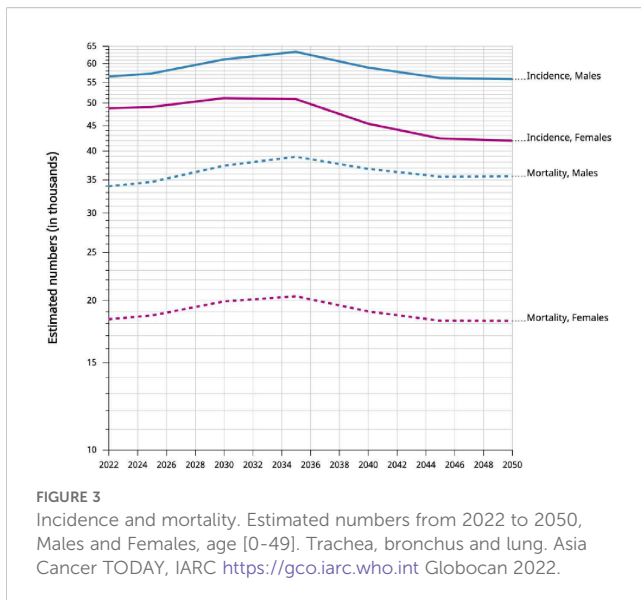
History of TB infection has been considered as a significant independent risk factor for lung cancer (38). Hwang SY, et al. did a comprehensive systematic review and meta-analysis (39) that showed a statistically significant association between a prior TB diagnosis and subsequent lung cancer. This association was found to be more pronounced in younger patients diagnosed with pulmonary TB (39). The link is particularly evident in regions with a high or upper-middle burden of TB, such as in East Asia and the Pacific (39). The increased risk is independent of smoking status. Several mechanisms have been proposed explaining this correlation, including TB-induced chronic inflammation, potential immunosuppressive effects, and the capacity of *Mycobacterium tuberculosis* to induce cellular DNA damage (40–42). The effective control and treatment of TB, including latent TB infection, may play a role in mitigating the risk of future lung cancer development.

4.4 Reproductive and hormonal factors

The influence of reproductive and hormonal factors on lung cancer in women suggests a direct hormonal etiology (43, 44). In a pooled analysis of over 308,000 Asian females done by Yin X, et al. revealed that parous women, especially those with one or two children, had a lower risk of incidence as well as mortality from lung cancer when compared to nulliparous women (45). This was found to be even greater among ever-smokers than never-smokers (45). Additionally, an older age at first delivery was linked to a reduced risk of lung cancer incidence and mortality (45). A comprehensive meta-analysis (46) supported these observations. In addition to higher parity and older age at first delivery, longer menstrual cycle length was also significantly associated with a reduced risk of lung cancer (46). These protective effects were notably observed among Asian women (46). Conversely, ever-use of hormone replacements and non-natural menopause increased the likelihood of lung cancer (46). These are often attributed to the potential effects of estrogen on lung cancer proliferation and growth (47). Estrogen receptors are expressed in both normal and cancerous lung tissues, allowing estrogen to directly stimulate gene transcription and transactivate growth factor signaling pathways, particularly the epidermal growth factor receptor (*EGFR*) pathway (48). The factors associated with lower estrogen levels have been correlated with a decreased lung cancer risk (49). Given the prevalence of *EGFR* mutations in adenocarcinoma among East Asian females who are never-smokers, it is hypothesized that higher parity might inversely affect lung cancer risk by inhibiting *EGFR* activation or mutation (50).

5 Clinical presentations

Studies from China, Japan, and India (51–55) offer valuable insights into the clinical presentation and characteristics of early-onset lung cancer in Asia. In a large Chinese cohort (51) early-onset



non-small cell lung cancer (NSCLC) represented 5.27% of all lung cancer cases among individuals aged 15 to 45 years. Studies indicate that this younger population often presents with adenocarcinoma as the predominant histological subtype, reported in 85.7% of patients in India (55) and a high proportion (45%) in a retrospective study reviewing patients aged 18–35 years (51). Furthermore, a significant number of these patients are never smokers (44–79%) (54, 55). Gender distribution appears notable, with one large Chinese study observing a higher female-to-male ratio (2.55 vs 1.19) in early-onset lung adenocarcinoma patients compared to later-onset cases. Diagnosis often occurs at late-stage disease, with 49.21% being stage IV at diagnosis (51). Metastasis occurs frequently, with the pleura being the most common site (38.71%), followed by the bone (35.48%) and lung (25.81%), and most cases (68%) involving metastasis to a single organ (51).

6 Molecular etiology and genomic alterations

Young patients with lung cancer had a higher frequency of genomic alterations (51, 56). The first study to characterize the genomic alterations of lung adenocarcinoma in young never-smokers aged 45 years and younger through whole genome sequencing was done by Luo, et al. (57). Although the sample size was small, there was a high prevalence (63.9%) of potentially targetable genomic alterations in the cohort (57). Several analyses on patients with adenocarcinoma, aged ≤ 40 years found 30–56.3% harbored EGFR mutations, 16.1–50% had ALK rearrangements, and ROS1 in 7% (54, 55, 58–62). Hou et al. (60) reported that in patients with lung adenocarcinoma aged 45 years or younger, there was a higher occurrence of genetic alterations in human epidermal growth factor receptor 2 (HER2) and ALK, along with concurrent EGFR/TP53 mutations. In contrast, the prevalence of EGFR exon 20 mutations, KRAS, and serine/threonine kinase 11 (STK11)

mutations was lower compared to patients older than 45 years. A retrospective Japanese study of 1746 consecutive patients diagnosed with adenocarcinoma identified 81 who were aged 40 years or younger at diagnosis (54). The specific alterations that were observed in the most common actionable targets included the following: HER2 mutations (5.7%), BRAF (3.4%), v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations (2–3.4%), Ret proto-oncogene (RET) (1.1%), CDKN2A (1.1%), HER2 amplification (1.1%), HRAS (1.1%), and MAP2K1 (1.1%) (54).

Most of the available research studies in Asia were on comparative analyses on the genomic alteration between early-onset or younger patients and elder or late-onset lung adenocarcinoma (52, 63). One analysis (64) reveals more frequent ERBB2 mutations and ALK-rearrangement in younger group. A study analyzing 7,858 lung cancer samples through targeted-gene sequencing examined the genomic differences between younger (≤ 45 years) and older (> 45 years) patients (64). The age-dependent trend analysis for genomic alterations showed increases in tumor mutation burden and changes in several genes as age advanced, including KRAS, MET, PIK3CA, CDKN2A, and MDM2. Conversely, the frequencies of ALK, ROS1, and RET fusions, as well as ERBB2 mutations, were found to decrease with age (64).

Comparisons of young and old patients found that young patients were characterized by a higher prevalence of ALK, ROS1 and RET fusions, and ERBB2 exon-20 insertions and EGFR exon-19 deletions (64). Approximately 88% of younger patients were identified as having at least one actionable genetic mutation. Somatic interaction analysis suggested that younger individuals with EGFR-positive tumors were more frequently associated with additional mutations in genes such as PIK3CA, MET, TP53, and RB1 compared to their older counterparts (64).

The unique genomic landscape of EOLC carries important clinical implications. The use of next-generation sequencing for patients is essential to support individualized treatment approaches. For those with driver gene mutations, the use of targeted therapies is crucial for effective disease management and improved outcomes.

7 Gene expression and immune landscape

MUC16, a large transmembrane glycoprotein (65–67), has been shown to be associated with enhanced cancer cell growth, metastasis and chemo resistance (68–70). MUC16 could be a therapeutic target for patients (71). MUC16 expression and its clinical significance has been investigated in patients with FLC and affected by indoor air pollution (72). The study revealed that there was a significant association between MUC16 overexpression and FLC ($P < 0.05$), indoor air pollution ($P < 0.01$) and later disease stage ($P < 0.01$) (72). It was also noted that there were more metastasis cases when MUC16 was up regulated (18.1% vs. 10.3%). Additionally, patients with more MUC16 up-regulation were noted to have a lower white blood cell (72). This could play a role in immune regulation. Findings from this study provide useful

information on the interaction between environmental carcinogens and genetic background.

A key characteristic of EOLC is deficiency in cell-mediated immunity of younger patients as demonstrated by transcriptomic and immunological analyses (63). There were changes in cellular metabolism and immune-related genes. There were also reduced immune cells infiltration (49). Notably, there is a significant decrease in CD4+, CD8+, and CD3+ T cells at both tumor sites and tumor/non-tumor interface zones (63). This finding indicates an immunosuppressive tumor microenvironment. Although current treatments for NSCLC often rely on immune checkpoint inhibitors to enhance T cell-mediated anti-tumor responses (73), these findings suggest that such therapies may be less effective in EOLC.

8 Considerations for future perspectives

Despite growing interest in EOLC, most existing research remains limited to single-institution studies, with a significant proportion of Asian data derived from small, retrospective cohorts. Consequently, there is a lack of comprehensive, nationwide or regional data on clinical and survival outcomes. There is a need to better understand the disease's underlying biology. The potential contribution of dietary patterns and environmental exposures, including air pollution, remains poorly elucidated and warrants further investigation. Additionally, there is a notable scarcity of clinical trials specifically designed for EOLC, limiting evidence-based approaches to management and care in this population.

Current lung cancer screening guidelines are primarily tailored to older adults (≥ 50 years) with significant smoking histories, thereby excluding a large subset of younger patients who do not meet traditional high-risk criteria. This exclusion may contribute to diagnostic delays and worse prognostic outcomes in patients with EOLC. As screening models may not effectively capture the distinct risk profile of this group, there is a pressing need to refine risk stratification strategies and incorporate novel, efficient biomarkers for earlier detection. Furthermore, future studies should aim to validate emerging molecular findings in larger, more diverse patient populations to better define the genomic landscape of EOLC. These efforts are crucial to developing targeted prevention strategies, as well as in optimizing therapeutic interventions for this underrepresented and often overlooked patient population.

9 Limitations

A limitation of this narrative review is that the article selection process was conducted by a single reviewer. While this approach ensured consistency in the selection criteria, it carries a risk of selection bias, and may have inadvertently led to overlook other

relevant studies. Literature search strategy relied primarily on keywords without the use of Medical Subject Headings (MeSH) terms that may have limited the comprehensiveness of the search.

10 Conclusions

The rising incidence of EOLC, particularly in Asia, which accounts for over 75% of global cases, signals a growing public health concern that remains poorly understood. Given its distinct clinical and molecular features, EOLC demands dedicated research, tailored screening strategies, and targeted interventions. This is particularly significant due to personal, familial, and societal impacts associated with cancers affecting individuals in their most productive years. A better and deeper understanding of the epidemiology, risk factors, and the biology of EOLC will be critical to inform public health strategies and improve outcomes.

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RD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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