The Impact of Age on Non-Small Cell Lung Cancer: A Comprehensive Overview

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Abstract: Lung cancer remains one of the leading causes of cancer-related mortality worldwide, with incidence and mortality rates rising significantly with age. Tobacco use is the primary risk factor, aging itself introduces biological and clinical complexities that influence lung cancer risk, diagnosis, treatment, and prognosis. Age-related factors such as cumulative exposure to carcinogens, genetic and epigenetic alterations, immunosenescence, and comorbidities contribute to increased susceptibility and poorer outcomes in older adults. Non-small cell lung cancer (NSCLC) is more prevalent in this population, though genetic predispositions in younger patients also highlight age-stratified molecular differences. Despite therapeutic advances, older patients remain underrepresented in clinical trials. This mini-review also highlights how genetic variants may differentially influence lung cancer risk across age groups, underscoring the importance of age-specific molecular research.

Keywords: Lung cancer, NSCLC, SNPs, Age

1. Introduction

Lung cancer remains one of the most prevalent and lethal forms of cancer worldwide [1]. In recent years, a decline in cancer-related mortality has been observed, attributed to various factors such as smoking cessation policies, improved disease control and management, and the implementation of effective screening strategies. Although lung cancer ranks as the third most commonly diagnosed cancer in Europe in 2020, it remains the leading cause of cancer-related deaths [2]. While tobacco use is the primary risk factor for lung cancer, age is also a significant, and potentially underrated determinant in clinical studies [2, 3]. The likelihood of developing lung cancer increases markedly with age. According to data from the American Cancer Society and the World Health Organization (WHO), the majority of lung cancer cases are diagnosed in individuals aged 65 years and older, with the median age at diagnosis being approximately 70 years [1, 4, 5]. This mini-review explores the relationship between age and lung cancer, examining how age influences risk, diagnosis, treatment, prognosis, and healthcare strategies, with particular attention to its association with molecular variants.

2. Methodology

In this narrative review has been analyzed published literature obtained from publicly available databases.

3. Results and Discussion

The age-related increase in lung cancer incidence can be attributed to a combination of biological and environmental factors. Cumulative exposure to carcinogens, such as tobacco smoke, air pollution, and occupational hazards (e.g., asbestos, radon), elevates the likelihood of genetic mutations that may lead to cancer development [6]. In addition, aging is associated with genetic instability, whereby cells accumulate genetic and epigenetic alterations. These changes compromise DNA repair mechanisms and increase susceptibility to malignant transformation [7, 8]. Another age-related physiological process is immunosenescence. This diminishes the body's ability to identify and eliminate abnormal or pre-cancerous cells, further contributing to cancer risk in older adults [9]. Lung cancer is broadly categorized into two main subtypes: non-small cell lung cancer (NSCLC), which comprises approximately 85% of cases, and small cell lung cancer (SCLC), a more aggressive form strongly linked to tobacco use [10, 11]. Although lung cancer can occur in younger individuals, particularly in non-smokers or those with genetic predispositions (e.g., EGFR mutations), the disease predominantly affects older populations. Incidence and mortality rates are significantly higher among individuals aged 65 years and older. While the overall distribution of lung cancer subtypes does not vary significantly with age, older patients are more frequently diagnosed with NSCLC, particularly the adenocarcinoma subtype. Younger patients, especially non-smokers, are more likely to harbor genetic mutations such as EGFR, ALK, or ROS1, which can inform personalized treatment strategies using targeted therapies [2, 11]. Despite therapeutic advances, overall survival rates for lung cancer remain low, with five-year survival estimates of approximately 32% for NSCLC and 9% for SCLC. Older age is associated with poorer prognosis, primarily due to advanced stage at diagnosis, limited treatment options, and higher prevalence of comorbidities [12, 13].

Early detection significantly improves outcomes. However, diagnosis in older adults is often delayed due to non-specific symptoms, such as chronic cough, fatigue, or weight loss, which may be misattributed to aging or existing comorbid conditions. Although screening is recommended for high-risk individuals aged 50 to 80, older adults are frequently under-screened, particularly those with multiple comorbidities [14–16]. Consequently, lung cancer is more often diagnosed at an advanced stage in this population, diminishing the likelihood of curative treatment. Moreover, older patients are underrepresented in clinical trials and screening studies, limiting the research findings to this age group [17, 18]. The management of lung cancer in older adults requires a comprehensive assessment of physiological age, functional status, comorbidities, cognitive function, psychosocial factors, and patient preferences. Chronological age alone should not determine treatment eligibility; however, it often influences therapeutic decision-making [17-19]. Surgical resection remains the standard of care for early-stage NSCLC. Nevertheless, in older patients there are concerns about anesthesia risks and postoperative complications. Chemotherapy can be effective, but older adults are more susceptible to treatment-related toxicity. So, the targeted therapies and immune checkpoint inhibitors are often better tolerated in older patients with actionable biomarkers [2, 17, 20]. Depending on the disease stage, a radiation therapy (RT) is also used [21, 22].

A growing body of research suggests that genetic variants may influence lung cancer risk in an age-dependent manner or contribute specifically to early-onset disease. Several studies have hypothesized that genetic susceptibility may vary with age, potentially affecting both cancer risk and disease progression. One study investigated the association between single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and epigenetic modifications in relation to patient age. Among the findings, a higher frequency of DNA methylation changes was observed in younger patients [23]. In a two-stage genome-wide association study (GWAS), researchers identified four novel susceptibility loci for early-onset NSCLC: 5p15.33 (rs2853677), 5p15.1 (rs2055817), 6q24.2 (rs9403497), and 12q14.3 (rs4762093). These SNPs demonstrated stronger associations in younger patients compared to older cases, supporting the existence of age-dependent genetic risk factors [24]. Similarly, another study identified the SNP rs28757157, along with rs3751592 and rs59429575, as being significantly associated with increased lung cancer risk specifically among individuals under 60 years of age [25]. These findings underscore the importance of age-stratified genetic analyses in understanding lung cancer susceptibility.

4. Conclusions

Age is a important factor influencing the epidemiology, diagnosis, treatment, and outcomes of lung cancer. Although older adults are most affected by the disease, they also encounter distinct challenges in accessing timely and appropriate care. Addressing these challenges necessitates a nuanced understanding of the aging process, the adoption of individualized treatment strategies, and the implementation of age-sensitive healthcare approaches. As the global population continues to age, optimizing lung cancer management for older adults will be essential for improving clinical outcomes and enhancing quality of life.

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References

[1] World Health Organization, *Lung cancer,* [Internet resource] [Accessed: August 10, 2025]
[2] R.L. Siegel, T.B. Kratzer, A.N. Giaquinto, et al., *Cancer statistics, 2025*, CA: A Cancer Journal for Clinicians, 75 (2025) 10–45.
[3] T. Dyba, G. Randi, F. Bray, et al., The European cancer burden in 2020: *Incidence and mortality estimates for 40 countries and 25 major cancers*, European Journal of Cancer (Oxford, England : 1990), 157 (2021) 308–347.
[4] American Cancer Society, *Key statistics for lung cancer*, [Internet resource] [Accessed: August 10, 2025]
[5] F. Venuta, D. Diso, I. Onorati, et al., *Lung cancer in elderly patients*, Journal of Thoracic Disease, 8 (Suppl 11) (2016) S908–S914.
[6] GBD 2019 Respiratory Tract Cancers Collaborators, *Global, regional, and national burden of respiratory tract cancers and associated risk factors from 1990 to 2019: A systematic analysis for the Global Burden of Disease Study 2019*, The Lancet Respiratory Medicine, 9 (2021) 1030–1049.
[7] B. Milholland, A. Auton, Y. Suh, J. Vijg, *Age-related somatic mutations in the cancer genome*, Oncotarget, 6 (28) (2015) 24627–24635.

[8] D.J. Zabransky, E.M. Jaffee, A.T. Weeraratna, *Shared genetic and epigenetic changes link aging and cancer*, Trends in Cell Biology, 32 (4) (2022) 338–350.
[9] J. Lian, Y. Yue, W. Yu, et al., Immunosenescence: a key player in cancer development, Journal of Hematology & Oncology, 13 (2020) 151.
[10] K. Inamura, *Lung cancer: understanding its molecular pathology and the 2015 WHO classification*, Frontiers in Oncology, 7 (2017) 193.
[11] A.G. Nicholson, M.S. Tsao, M.B. Beasley, et al., *The 2021 WHO Classification of Lung Tumors: impact of advances since 2015*, Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 17 (3) (2022) 362–387.
[12] American Cancer Society, *Lung Cancer Survival Rates*, [Internet resource] [Accessed: August 10, 2025]
[13] F. Tas, R. Ciftci, L. Kilic, S. Karabulut, *Age is a prognostic factor affecting survival in lung cancer patients*, Oncology Letters, 6 (5) (2013) 1507–1513.
[14] M.S. Kale, K. Sigel, A. Arora, et al., *The benefits and harms of lung cancer screening in individuals with comorbidities*, JTO Clinical snd Research Reports, 5 (3) (2024) 100635a
[15] S. Advani, D. Zhang, M. Tammemagi, et al., Comorbidity profiles and lung cancer screening among older adults: U.S. Behavioral Risk Factor Surveillance System 2017–2019, Annals of the American Thoracic Society, 18 (11) (2021) 1886–1893.
[16] P. Pacheco, V. Melo, C. Martins, H. Ribeiro, *Lung cancer screening with low-dose CT: a systematic review*, Cureus, 16 (12) (2024) e75515.
[17] G. Wu, X. Gu, D. Yuan, et al., *Diagnosis status and pathological diagnosis derived treatment of elderly lung cancer patients over 75 years old*, Translational Cancer Research, 8 (1) (2019) 87–95.
[18] N.L. Christensen, A. Gouliaev, S. McPhail, et al., *Lung cancer among the elderly in Denmark – a comprehensive population-based cohort study*, Lung Cancer, 191 (2024) 107555.
[19] G.R. Tarchand, V. Morrison, M.A. Klein, E. Watkins, *Use of comprehensive geriatric assessment in oncology patients to guide treatment decisions and predict chemotherapy toxicity*, Federal Practitioner : For The Health Care Professionals of The VA, DoD, and PHS, 38 (Suppl 2) (2021) S22–S28.
[20] C. O'Leary, L. McSorley, B. Hennessy, et al., *Challenges associated with systemic therapy for older patients with inoperable non-small cell lung cancer,* Expert Opinion on Pharmacotherapy, 21 (17) (2020) 2185–2194.
[21] N. Giaj-Levra, P. Borghetti, A. Bruni, et al., *Current radiotherapy techniques in NSCLC: challenges and potential solutions*, Expert Review of Anticancer Therapy, 20 (5) (2020) 387–402.
[22] Q. Chen, S. Ying, J. Qin, L. Zhang, *Optimization of treatment strategies for elderly patients with advanced non-small cell lung cancer*, Frontiers in Oncology, 14 (2024) 1384906.
[23] S. Meucci, U. Keilholz, D. Heim, et al., *Somatic genome alterations in relation to age in lung squamous cell carcinoma*, Oncotarget, 9 (2018) 32161–32172.
[24] J. Fan, T. Hong, X. Zhao, et al., A two-stage genome-wide association study identified four potential early-onset non-small cell lung cancer risk loci based on 26,652 participants in Chinese population, Molecular Carcinogenesis, 62 (9) (2023) 1263–1270.
[25] C. Zhang, Y. Cheng, W. Chen, et al., *Association of CYP19A1 rs28757157 polymorphism with lung cancer risk in the Chinese Han population*, World Journal of Surgical Oncology, 20 (1) (2022) 400.