

Editorial

Lung Cancer in Young Adults

Cáncer de pulmón en adultos jóvenes



Lung cancer (LC) in individuals under the age of 40 was documented more than five decades ago in a brief report. At present, the median age at LC is diagnosed is 71 years old, with an estimated 2.1 million new cases annually worldwide. However, its incidence in adults under 40 is relatively low, occurring in approximately 1–5% of cases,^{1,2} more frequently observed in women,^{3,4} never-smokers, adenocarcinoma histology and diagnosed at an advanced stage.^{2,3}

Tobacco consumption in young adults does not exhibit the same cause-and-effect relationship as observed in older groups, as 71–74% of NSCLC cases in YA occur in non-smokers with a higher risk associated in young males, with an odds ratio (OR) of 26.3 versus 20.9 in older males, for equal exposure periods of 20–39 years.⁵ Second-hand smoking is one such factor, especially between birth and age 25 years compared with exposure during adulthood (adjusted OR, 1.3 v 0.7, respectively) interestingly, the highest risk was observed 15–24 years after exposure and in younger than 55 years.⁴

The subsequent leading risk factor (RF) for LC among never smokers is exposure to indoor radon, the WHO recommends that indoor concentrations should not be higher than 100 Bq/m³. Long-term inhalation of alpha particles increases the risk of LC by 16% for each 100 Bq/m³.⁶ The carcinogenic effect induced by inhaled radon is mainly due to the progenies of radon (polonium 214 and 218), which emit high-energy alpha particles. Ruano et al. considered exposure to radon in the different Spanish Autonomous Regions and the results showed that 3.8% (838 deaths) of LC mortality was attributable to radon exposure of over 100 Bq/m³ (1 out of 26 LC patients in Spain), being the highest population attributable fractions; Galicia, Extremadura, and the Canary Islands.⁷ In Canada the health system recommends testing every home for radon over at least 3 months during the cold weather because radon is responsible for 16% of LC deaths.⁸

Another widely recognized RF is emphysema, where each 1% increase in lung attenuation area (LAA) is independently associated with increased lung cancer risk. Although there is no consensus on the significance of family history, revealing a contribution to NSCLC risk among individuals aged 40 to 59 and non-smokers with a first-degree relative affected by NSCLC. Another genetic consideration is the germline EGFR T790M mutation, particularly prevalent in non-smoker. Furthermore, the proportion of patients with a family history of cancer is higher in the YA compared to the older (12.37% versus 6.32%, $p < 0.001$).⁹

Other RFs are occupational exposure (asbestos, silica, uranium, chromium, alkylating agents), outdoor air pollution: particulate matter with an aerodynamic $\leq 2.5 \mu\text{m}$, responsible for up to 14% of LC deaths, drinking water containing arsenic, high doses of beta-carotene supplements in smokers and former smokers, diesel engine exhaust and welding fumes.⁴

NSCLC in YA is observed to be more prevalent among females,⁷ physiological estrogen promotes CD8⁺ T cells recruitment and activation in normal tissues, alongside heightened activity of M1 phagocytic macrophages, which are crucial in combating infections and antitumor immunity. Conversely, within the tumor microenvironment, M2 macrophages, regulatory T cells (T-reg), and myeloid-derived suppressor cells (MDSC) may be stimulated by physiological or locally synthesized estrogen, potentially facilitating cellular proliferation, promoting obstruction and attenuating antitumor immunity.¹⁰ The risk of chemotherapy-induced infertility with LC treatment remains poorly established and is typically extrapolated from data on other cancer types, in a cohort of premenopausal women with LC receiving platinum-based chemotherapy (with 64% also receiving taxanes and 32% antimetabolites) the self-reported rate of amenorrhea was 64%. For adult women, embryo or oocyte cryopreservation after ovarian stimulation is the preferred method and ovarian tissue cryopreservation is the preferred method when treatment needs to start urgently as it does not require stimulation. In men, sperm cryopreservation is a standard method to preserve fertility.⁴

In YA the bone metastasis being the predominant site¹¹ and the thoracic imaging characteristics observed a higher incidence of central tumors (55% vs. 33%, $p = 0.02$).¹² The genomic profiling of YA recently summarized in a review by Viñal et al. indicated that appears to possess a greater proportion of oncogenic genomic alterations, overall 57–70%⁴; ALK rearrangements (35%), EGFR mutations (24%), and ROS rearrangements (7%) represent the most common alterations compared to NSCLC patients over the age of 40 (mutation is KRAS (23–30%). The increasing availability of next-generation sequencing (NGS) in clinical practice facilitates the identification of potentially deleterious somatic mutations.

In young patients, treatment was initiated sooner than in older patients (mean 30.2 days versus 38.1 days, $p < 0.001$).³ At stage I, 64% of YA received surgery only versus 55% of the older patients ($p < 0.0001$).³ At stage I, 14% of the older patients received radiation therapy only compared with 1% of YA. At stage II, 12% of older patients received radiation therapy only compared with 3% of YA

($p < 0.0001$).³ At stage II, 29% of YA underwent adjuvant therapy whereas only 16% of the older patients received that treatment ($p < 0.0001$). YA were more likely to receive any treatment across all stages (82% versus 71%, $p < 0.0001$) and at each individual stage. For advanced stages YA more frequently receive combinations of ICBs and chemotherapy than ICBs alone.⁴ YA with LC receiving EGFR-TKIs experience a greater negative impact on QoL from skin toxicity/and symptoms than older patients.⁴

The median survival times for YA at stages I through IV were more than 60, 59, 18 and 9 months, for the older patients were 49, 22, 13 and 6 months with overall survival duration for YA stands at 12 months contrasted with 8.2 months.³

Screening initiatives utilizing low-dose CT in high-risk adult populations have demonstrated a 20% reduction in LC mortality; thus, it would be prudent to conduct a risk assessment for individuals under 50–55 years of age, particularly focusing on women, emphysema, geographical exposure to radon, and/or a first-degree family history of LC, to initiate annual screening protocols.

In our opinion, lung cancer is a complex disease across its course, from diagnosis, through treatment to long-term outcomes. The average age at diagnosis is 71 years, with advanced stages at diagnosis in 70% of cases. In this scenario, the proximity to the average age of life expectancy is between 12 and 14 years, where all efforts are focused on treating the patient for survival. However, this disease also occurs in patients under 50 years of age, where the time distance to 83 years adds up to more than 3 decades, although the incidence is less than 5%, the prognosis is also very unfavorable: 80% are in an advanced stage at diagnosis, possibly facing death too early. We believe that, as this population is excluded from current lung cancer screening programs, given our resources and knowledge, it should be essential to continue working to achieve a panel of risk factors within this population group by initiating a screening program in order to be able to diagnose early stages and offer them curative therapies where the disease can be recorded as cured in their personal history.

Artificial intelligence involvement

The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript.

Funding

No financial support was provided for the preparation of this article.

Author's contributions

All authors have participated equally.

Conflicts of interest

The authors declare that they have no conflicts of interest in the preparation of this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.opresp.2025.100497](https://doi.org/10.1016/j.opresp.2025.100497).

References

1. Fang YW, Liu CY. Determining risk factors associated with depression and anxiety in young lung cancer patients: a novel optimization algorithm. *Medicina*. 2021;57:340.
2. Jones S, Mullet T, Davenport D, Saha S. Lung cancer in young adults: a single-center experience. *South Med J*. 2022;115(6):366–70.
3. Arnold BN, Thomas DC, Rosen JE, Salazar MC, Blasberg JD, Boffa DJ, et al. Lung cancer in the very young: treatment and survival in the national cancer data base. *J Thorac Oncol*. 2016;11:1121–31.
4. Laguna JC, Tagliamento M, Lambertini M, Hiznay J, Mezquita L. Tackling non-small cell lung cancer in young adults: from risk factors and genetic susceptibility to lung cancer profile and outcomes. *Am Soc Clin Oncol*. 2024;44(3):e432488.
5. Kreuzer M, Kreienbrock L, Gerken M, Heinrich J, Brunker I, Müller K, et al. Risk factors for lung cancer in young adults. *Am J Epidemiol*. 1998;147:1028–37.
6. Urrutia-Pereira M, Chatkin JM, Chong-Neto HJ, Solé D. Radon exposure: a major cause of lung cancer in non smokers. *J Bras Pneumol*. 2023;49:e20230210.
7. Ruano-Ravina A, Varela L, García M, García M, González S, Santiago-Pérez M, et al. Lung cancer mortality attributable to residential radon exposure in Spain and its regions. *Environ Res*. 2021;199:11372.
8. Silvina C, Mema MD, Baytalan G. Radon and lung cancer risk. *CMAJ*. 2023;195:E850.
9. Shi J, Li D, Liang D, He Y. Epidemiology and prognosis in young lung cancer patients aged under 45 years old in northern China. *Sci Rep*. 2021;11:6817.
10. Siegfried JM. Sex and gender differences in lung cancer and chronic obstructive lung disease. *Endocrinology*. 2022;163:1–8.
11. Yang L, Fang F, Chan J, Chen B, Luo W, Zhu Q, et al. Metastatic patterns and prognosis of young lung cancer patients: a population-based study by age. *Ann Transl Med*. 2021;9:1159.
12. Garrana SH, Dagogo-Jack I, Cobb R, Kuo AH, Mendoza DP, Zhang EW, et al. Clinical and imaging features of non-small cell lung cancer in young patients. *Clin Lung Cancer*. 2020;22:23–31.

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