



Is lung cancer in never smokers still an unknown disease?

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Lung cancer poses an important public health problem worldwide. We also know that lung cancer does not have the same characteristics in smokers as in never-smokers. In the current issue of *Translational Cancer Research*, Banks *et al.* (1) highlighted these differences in a cross-sectional analysis of almost 18,000 patients diagnosed with lung cancer between 2007 and 2018, which are representative of the general population in Northern California [United States (US)]. The authors combined data from a cancer registry with electronic health records as the main data sources for their study. Their conclusions are in line with those from recent studies, supporting that lung cancer in smokers and lung cancer in never-smokers are two different clinical entities and they should be considered as such.

It is widely known that tobacco smoking is the most important risk factor for lung cancer since it causes approximately 80–90% of all lung cancers (2). Nevertheless, other risk factors for lung cancer besides smoking have been identified, such as exposure to second-hand tobacco smoke, residential radon, occupational exposures, air pollution, or genetic predisposition. In addition, it is speculated that alcohol consumption, diet and other lifestyle habits may influence the development of this type of cancer.

Currently, between 10–20% of all lung cancer cases are diagnosed in people who have never smoked. This proportion varies according to the geographical area, being three times higher in Asian countries compared to Europe or the US (3). Never-smokers lung cancer accounts for

16,000 to 24,000 deaths per year in the US (3). Additionally, there is evidence pointing to an increase in the incidence of lung cancer in never-smokers in the last decades. A study conducted in the United Kingdom pointed out a 15% increase in the proportion of lung cancer in never-smokers between 2008 and 2014 (4). Two other studies observed the same increasing trend. It should be noted that these studies noticed a greater increase in incidence in never-smoking women than in never-smoking men (5,6). However, studies analysing the incidence of lung cancer in never-smokers are scarce and have important limitations, thus making it not possible to reach a conclusion. Nevertheless, many countries show a decrease in the prevalence of tobacco consumption, leaving room for an increase in the number of never-smokers lung cancer cases associated to exposure to another risk factors. However, recent studies do not confirm this increasing trend (7). In any case, more evidence is necessary in order to assess whether lung cancer incidence in never-smokers has varied over time.

Banks *et al.* (1) concluded in their study with important sociodemographic and clinical disparities in subjects diagnosed with lung cancer depending on their smoking status. Banks *et al.* found that never-smokers diagnosed with lung cancer were more frequently women, Asian/Pacific Islanders and Hispanic patients and had adenocarcinoma or carcinoid tumours. Other recent investigations have also analysed differences in genetic and environmental factors (8,9). The amount of evidence regarding this issue has

led several authors to consider that lung cancer in never-smokers is a unique entity and much different from lung cancer in smokers.

In line with the available evidence (10,11), Banks *et al.* (1) found that women diagnosed of lung cancer are more likely to be never-smokers in comparison to men. It is also noteworthy that this difference is maintained in almost all age groups, races/ethnicities and histological types of lung cancer, as seen in other investigation (7). Never-smoking women have two to three times more risk of developing lung cancer compared to never-smoking men (12). Different authors have attempted to provide an explanation for this notorious sex difference. However, no study has yet been able to conclude that these differences are due to genetic, hormonal, or other characteristics of women that may contribute to an increased susceptibility to developing lung cancer. One possible explanation is that women are more exposed to carcinogens other than tobacco consumption, compared to men. As mentioned above, residential exposures such as radon and second-hand tobacco smoke may play an important role in explaining the differences found between men and women (13). Also, women have historically been more exposed to biomass from cooking, which are known to cause lung cancer and other respiratory diseases (10). Cooking oil fumes may contribute to increase the burden of disease in women, especially in South America and also in some Asian countries, where it is still common for women to be exposed to them.

In addition to differences by sex, Banks *et al.* (1) conclude that there are also differences by race/ethnicity, level of deprivation of the neighbourhood and histological type at diagnosis. These findings are supported by the results of other studies conducted in different countries. As the authors pointed out, these differences found between smokers and never-smokers lung cancer may influence the time at which this disease is diagnosed and therefore its prognosis. The knowledge and attitudes towards lung cancer differ whether the subject is a smoker or not, since this type of cancer is closely associated with smoking, as it is its main risk factor. Therefore, lung cancer is less likely to be suspected in never-smokers who present symptoms compatible with lung cancer. In fact, in many never-smokers, the diagnosis is made accidentally, following imaging tests that were originally intended to detect other pathologies (4). It has been suggested that lung cancer in never-smokers might be diagnosed later and therefore in more advanced stages, which would imply a worse prognosis of the disease. In two studies, 57% and 62% of lung cancer

cases in never smokers were diagnosed at stage IV, compared to 48–49% among former and current smokers (14,15). A study carried out in Portugal concluded that the median number of months elapsed from the onset of symptoms to the first medical appointment was 2 for smokers and 3 for never-smokers (14). Although the difference is small, this may suggest that the patients themselves do not suspect of lung cancer, partly because they are never-smokers and lung cancer is closely linked to tobacco, showing a lack of knowledge regarding this disease. Lung cancer symptoms may also be different between smokers and never-smokers as shown recently (16).

In never-smokers, exposure to residential radon increases two-fold the risk of developing lung cancer, being the main risk factor for lung cancer in people who have never smoked (17). Never-smokers must be exposed to a higher concentration of this gas in order to induce lung cancer compared to smokers. There is also evidence suggesting that there is a synergistic interaction between exposure to residential radon and tobacco smoke, including second-hand tobacco smoke (9,18). Exposure to second-hand tobacco smoke is also known to increase the risk of lung cancer (19). This exposure might play an important role in the case of never-smoking women. Garrido *et al.* observed that the majority of never-smoking women diagnosed with lung cancer were exposed to second-hand tobacco smoke, especially in their homes (13). These results are consistent with those presented by Couraud *et al.*, who found that exposure to carcinogens in the home was higher in women than in men who developed lung cancer (20).

In recent decades, different studies have linked lung cancer to various specific substances, occupations, and industries. Over the years, the International Agency for Research on Cancer (IARC) has identified multiple substances that increase the risk of developing lung cancer, such as asbestos, wood dust, diesel fumes or endotoxins, among others (21). In this case, the weight of occupational exposures in the burden of lung cancer falls mainly on men (20) since women have not typically been employed in jobs with high exposure to these carcinogens until relatively recently. Therefore, the risk of developing lung cancer may be as well influenced by the occupation itself and this is especially relevant in manual jobs such as blue-collar occupations (construction, agriculture, mining, etc.).

It is known that the exposure to environmental pollution plays an important role in the development of different types of cancer, including lung cancer. An association between exposure to particulate matter 2.5 and 10 (PM_{2.5}

and PM10) and lung cancer morbidity and mortality has been observed previously (22). International organizations have regulated the concentrations of these substances in order to control the harmful effects on the health of the population. Despite this, a large European study has observed that exposure to environmental pollution below the limits established by organizations such as the US Environmental Protection Agency (EPA) or the World Health Organization (WHO) also increases the risk of mortality from lung cancer (23). It appears that exposure to PM2.5 poses a higher risk of developing lung cancer in former smokers and never-smokers, compared to smokers, while exposure to PM10 acts in the opposite way by entailing a higher risk among current smokers. It should be noted that the differences found based on smoking status are not significant in the available evidence (22).

It is speculated that different lifestyle habits, such as alcohol consumption, a low intake of fruits/vegetables or too short/long hours of sleep may influence the risk of developing lung cancer in never-smokers. At the moment, these associations are not clear due to the lack of research performed exclusively in never-smokers. A recent study conducted in Canada in never-smokers found significant association between these habits and lung cancer risk, except for alcohol consumption (24). However, a pooling study conducted in Spain, which included 438 cases of lung cancer in never-smokers, found a significant association between the consumption of spirits and the development of lung cancer. This association has not been observed with other types of alcoholic beverages (25).

Banks *et al.* (1) observed that there is a higher prevalence of never smoking lung cancer cases in wealthier areas. This is mainly due to the lower tobacco consumption in such population but not to the presence of other risk factors of lung cancer (i.e., occupation, environmental tobacco smoke or higher environmental pollution). Occupational exposures that pose a risk of developing lung cancer are generally associated with manual occupations (blue-collar occupations), which historically have been less paid than white-collar occupations. Even in countries without universal health care, such as the US, these workers may have less access to health care. With regard to radon exposure, on the one hand, there is much evidence that concludes a relationship between a lower socioeconomic level and a lower concentration of residential radon. This could be explained by the fact that homes with less economic resources tend to be not as heated and draft-proofing as wealthier ones, and this contributes to decrease

the underpressure of the dwelling relative to the air beneath it, decreasing the rate at which radon gas concentrates inside the house (26). On the other hand, it could be also possible that a significant proportion of homes with high radon concentration lacks protection against this gas, mainly due to a lack of economic resources. Nevertheless, there is limited scientific evidence regarding the potential association between these aspects and the development of lung cancer (27).

With the aim of reducing the mortality burden of lung cancer, the implementation of a screening program was proposed with the objective of detecting tumours in early stages and thus improving prognosis and survival. In the US, this screening has been covered by Medicare since 2015. Meanwhile, in Europe, only Croatia has implemented a lung cancer screening at the population level. Lung cancer screening is being carried out in people at high risk of developing lung cancer. This risk is based on two variables: age and smoking habit. Currently, to be included in lung cancer screening a person must be between 50 and 80 years old, smoking or having smoked more than 20 pack-years and, in the case of ex-smokers, not having quit smoking more than 15 years ago. There is evidence suggesting that these eligibility criteria exclude an important proportion of people with high risk of developing lung cancer (28). For instance, never-smokers would not be eligible subjects to participate, so cancer cases in these subjects could not be detected by screening. This means that at least 10–20% of all cancer cases cannot be detected by screening, thus resulting in a limited population impact. In addition to smoking, screening also fails to consider other aspects such as sex, occupational exposure to human carcinogens in the workplace or residential exposures. Because of these limitations in the eligibility criteria, several authors consider that the use of risk models applied on an individual basis would allow us to categorize high-risk subjects more rigorously. Generally, these models consider a wider range of variables to calculate the risk of developing lung cancer, such as those previously mentioned as well as age and smoking habit.

In addition, research on never-smokers lung cancer is still scarce compared to studies that have been conducted in smokers. The importance of conducting studies in never-smokers is justified by the differences previously found in lung cancer cases according to smoking habit. It is necessary for future studies to be multicentre and with ample recruitment time to achieve sufficient sample sizes. For example, the LCRINS (Lung Cancer Risk in Never

Smokers) study was carried out in Spain with the aim of finding out the risk factors for lung cancer in never smokers. This is a multicentre study with more than 400 never smokers with lung cancer recruited. Such studies can provide valuable information with a view to identify risk factors of never smokers' lung cancer and thus to establish measures to prevent it (29). In this regard, some organizations such as the UK National Cancer Research Institute (NCRI) are developing research strategies focused on never-smokers lung cancer patients, referring to this disease as "a critical area of focus". It should be also mentioned that Banks *et al.* (1) used information from electronic health records and registries, making it possible to have an important sample size and to reduce patient selection bias. We are of the opinion that the use of integrated health information to conduct scientific studies has the potential to generate useful evidence for clinical decision-making.

In conclusion, there is sufficient evidence to support the existence of important differences in lung cancer between former/current smokers and never-smokers. The sociodemographic and clinical characteristics are not the same in both groups, although the explanation for this is not known for certain at the moment. However, there are still many uncertainties regarding lung cancer in never-smokers. More quality research focused on never-smokers diagnosed with lung cancer is needed to evaluate its risk factors, such as exposure to second-hand smoke, occupational and residential radon exposures, environmental pollution, and genetic factors. Also, more studies are clearly needed to understand the pattern of this disease, as well as its evolution. On the one hand, lung cancer needs to be treated differently depending on the smoking status of the subjects diagnosed. On the other hand, we can never forget that it is essential to carry out smoking cessation programs since tobacco consumption continues to be by far the main risk factor for lung cancer.

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References

1. Banks KC, Sumner ET, Alabaster A, et al. Sociodemographic and clinical characteristics associated with never-smoking status in patients with lung cancer: findings from a large integrated health system. *Transl Cancer Res* 2022;11:3522-34.
2. Centers for Disease Control and Prevention. What Are the Risk Factors for Lung Cancer? *Centers Dis Control Prev*. 2021. Available online: https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm
3. Samet JM, Avila-Tang E, Boffetta P, et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. *Clin Cancer Res* 2009;15:5626-45.
4. Cufari ME, Proli C, De Sousa P, et al. Increasing frequency of non-smoking lung cancer: Presentation of patients with early disease to a tertiary institution in the UK. *Eur J Cancer* 2017;84:55-9.
5. Toh CK, Ong WS, Lim WT, et al. A Decade of Never-smokers Among Lung Cancer Patients-Increasing Trend and Improved Survival. *Clin Lung Cancer* 2018;19:e539-50.
6. Pelosof L, Ahn C, Gao A, et al. Proportion of Never-Smoker Non-Small Cell Lung Cancer Patients at Three Diverse Institutions. *J Natl Cancer Inst* 2017;109:djw295.
7. Siegel DA, Fedewa SA, Henley SJ, et al. Proportion of Never Smokers Among Men and Women With Lung Cancer in 7 US States. *JAMA Oncol* 2021;7:302-4.

8. Thomas A, Mian I, Tlemsani C, et al. Clinical and Genomic Characteristics of Small Cell Lung Cancer in Never Smokers: Results From a Retrospective Multicenter Cohort Study. *Chest* 2020;158:1723-33.
9. Lee KK, Bing R, Kiang J, et al. Adverse health effects associated with household air pollution: a systematic review, meta-analysis, and burden estimation study. *Lancet Glob Health* 2020;8:e1427-34.
10. McCarthy WJ, Meza R, Jeon J, et al. Chapter 6: Lung cancer in never smokers: epidemiology and risk prediction models. *Risk Anal* 2012;32 Suppl 1:S69-84.
11. Tang A, Ahmad U, Toth AJ, et al. Non-small cell lung cancer in never- and ever-smokers: Is it the same disease? *J Thorac Cardiovasc Surg* 2021;161:1903-17.e9.
12. Wakelee HA, Chang ET, Gomez SL, et al. Lung cancer incidence in never smokers. *J Clin Oncol* 2007;25:472-8.
13. Garrido P, Viñolas N, Isla D, et al. Lung cancer in Spanish women: The WORLD07 project. *Eur J Cancer Care (Engl)* 2019;28:e12941.
14. Dias M, Linhas R, Campainha S, et al. Lung cancer in never-smokers - what are the differences? *Acta Oncol* 2017;56:931-5.
15. Löfling L, Karimi A, Sandin F, et al. Clinical characteristics and survival in non-small cell lung cancer patients by smoking history: a population-based cohort study. *Acta Oncol* 2019;58:1618-27.
16. Ruano-Ravina A, Provencio M, Calvo de Juan V, et al. Are there differences by sex in lung cancer characteristics at diagnosis? -a nationwide study. *Transl Lung Cancer Res* 2021;10:3902-11.
17. Torres-Durán M, Ruano-Ravina A, Parente-Lamelas I, et al. Lung cancer in never-smokers: a case-control study in a radon-prone area (Galicia, Spain). *Eur Respir J* 2014;44:994-1001.
18. Kim AS, Ko HJ, Kwon JH, et al. Exposure to Secondhand Smoke and Risk of Cancer in Never Smokers: A Meta-Analysis of Epidemiologic Studies. *Int J Environ Res Public Health* 2018;15:1981.
19. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA, USA: Centers for Disease Control and Prevention, 2014:1081.
20. Couraud S, Souquet PJ, Paris C, et al. BioCAST/IFCT-1002: epidemiological and molecular features of lung cancer in never-smokers. *Eur Respir J* 2015;45:1403-14.
21. World Health Organization. International Agency for Research on Cancer. Globocan 2020. Available online: <https://www.iarc.fr/>
22. Ciabattini M, Rizzello E, Lucaroni F, et al. Systematic review and meta-analysis of recent high-quality studies on exposure to particulate matter and risk of lung cancer. *Environ Res* 2021;196:110440.
23. Stafoggia M, Oftedal B, Chen J, et al. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. *Lancet Planet Health* 2022;6:e9-18.
24. Murphy RA, Darvishian M, Qi J, et al. Lifestyle factors and lung cancer risk among never smokers in the Canadian Partnership for Tomorrow's Health (CanPath). *Cancer Causes Control* 2022;33:913-8. Erratum in: *Cancer Causes Control* 2022;33:919.
25. García Lavandeira JA, Ruano-Ravina A, Kelsey KT, et al. Alcohol consumption and lung cancer risk in never smokers: a pooled analysis of case-control studies. *Eur J Public Health* 2018;28:521-7.
26. Kendall GM, Miles JC, Rees D, et al. Variation with socioeconomic status of indoor radon levels in Great Britain: The less affluent have less radon. *J Environ Radioact* 2016;164:84-90.
27. Couraud S, Zalzman G, Milleron B, et al. Lung cancer in never smokers--a review. *Eur J Cancer* 2012;48:1299-311.
28. Sears CR, Rivera MP. Age, Sex, Smoking, and Race: Is Progress Being Made in Lung Cancer Screening Eligibility? *Chest* 2021;160:31-3.
29. Lorenzo-González M, Ruano-Ravina A, Torres-Durán M, et al. Lung cancer risk and do-it-yourself activities. A neglected risk factor for lung cancer. *Environ Res* 2019;179:108812.

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