Editorial

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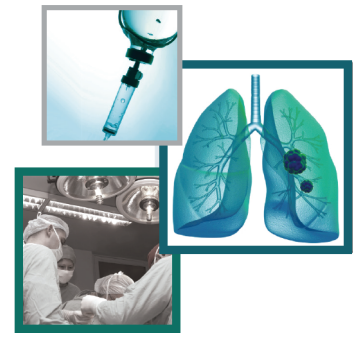
Lung Cancer Management



Understanding sex disparities in lung cancer incidence: are women more at risk?

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"The higher rate of lung cancer among never-smoking women compared with men is clearly a key driver of the changing lung cancer demographics cancer worldwide"

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Sex-based differences in global lung cancer incidence have dramatically shifted over the past 50 years. This is particularly evident in the western world, including in the USA, where women now have an increased risk relative to men of developing lung cancer, despite a decreasing incidence of lung cancer overall among both groups [1–5]. Sex-based disparities in lung cancer incidence are characterized primarily by rising rates of adenocarcinoma and are particularly magnified among younger women and never-smokers, two increasingly at-risk populations who we notably do not currently have screening guidelines for [4–7]. There are a number of endogenous and exogenous factors that may uniquely contribute to a woman's risk of developing lung cancer, suggesting that lung cancer may be increasingly characterized as a truly distinct disease process in women compared with men [1,8,9]. Further exploration of these sex-based differences will be of monumental importance, as we refine our risk stratification and screening processes to reflect the changing demographics of the lung cancer population.

Changes in smoking habits, particularly in the last part of the 20th century, are partly responsible for the shifting demographics in lung cancer incidence. In the USA, for example, women did not begin smoking at high rates until after World War II, and therefore the decline in smoking rates that started in the late 1960s was delayed and much slower for women compared with men [10]. Lung cancer incidence thus peaked later for women (early 2000s) compared with men (1980s), and is now declining, but at a slower rate [9]. In contrast, in many developing nations where smoking rates are declining among men, they alarmingly continue to rise among women [3]. Despite these trends, the majority of women diagnosed with lung cancer globally today are still smokers and thus public health initiatives to address smoking behavior, particularly in women, are of ongoing importance [9].

From the early 1990s to present day, many have questioned whether women may be more susceptible to the carcinogens in tobacco than men and therefore at a higher risk of developing lung cancer at similar levels of exposure. A few large prospective cohort studies have not shown this to be the case [8,10,11]. However, some speculation remains as to whether women who smoke may harbor a different genetic profile than men who smoke that could predispose them to the development of lung cancer. For example, women who smoke have a higher frequency of a point mutation in the *TP53* gene compared with women who do not smoke, a finding which does not apply to men [12]. Women also are more likely to have mutations in the *GSTM1* gene, which normally functions to inactivate toxic metabolites and has been linked to the development of lung cancer in smokers [1,12]. Although variations in smoking patterns between sexes may explain the smoking-associated sex-based lung cancer incidence disparities particularly in western countries, it does not explain the disparities in the never-smoker population, for whom there are clearly additional factors at play.

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Up to 50% of women diagnosed with lung cancer worldwide are never-smokers compared with only 15–20% of men, and these proportions have been rising in both genders [2,13]. One cross-sectional secondary analysis of six prospective cohorts in the US found that among never-smokers, women were at higher risk of developing lung cancer compared with men, with age-adjusted incidence rates ranging from 15.2 to 20.8 per 100,000 person years compared with 11.2–13.7 per 100,000 person years, respectively [6]. A retrospective cohort analysis of the UK Million Women study found that the incidence rate of lung cancer in women who were never-smokers was similar to the US study at 14.3 per 100,000 person years over an average of 14 years of follow-up from study recruitment in 1998 [7]. The higher rate of lung cancer among never-smoking women compared with men is clearly a key driver of the changing lung cancer demographics cancer worldwide [4,5,12].

There are also alarmingly higher rates of lung cancer in women compared with men among younger populations (less than 65 years old). One retrospective cohort study evaluated the incidence of lung cancer between 1995 and 2014 in US populations aged 30–64 using data from the National Health Interview Survey. While age-specific incidence rates declined during the last two decades in both sexes, the rate declined faster for men than for women, such that the incidence of lung cancer in young women now surpasses that of men [4,5,12]. These patterns of increased lung cancer incidence among younger women are reflected in global trends as well. One systematic analysis examined cancer incidence rates in patients aged 30–64 between 1993 and 2012 across five continents. In all countries analyzed, age-specific incidence rates of lung cancer declined in men, but in women there was significant variation. Western nations in particular including the UK, USA, The Netherlands, Denmark, New Zealand and Germany were found to have rising and now higher incidence rates of lung cancer among women compared with men over the study period, and this trend is suspected to occur in developing countries in the future [4].

Why do women have such an increased risk of lung cancer, especially women who are never-smokers and those who are younger? As described among the smoking population, there are some theories regarding genetic variations between the two sexes among the nonsmoking population. Women with polymorphisms in the *CYP1A1* gene, which causes increases in DNA adducts and promotes carcinogenesis, have increased odds of developing lung cancer regardless of smoking history [9,12,14]. Overexpression of the X-linked gastrin-releasing peptide receptor has been linked to the development of lung cancer and has a higher rate of overexpression in both smoking and nonsmoking women compared with men [2,9]. Lending to the theory that genetics may play a role in lung cancer development, family history of lung cancer is posited to be a risk factor in both men and women, but it is unclear if that effect is more pronounced in women [7,15].

Women, when compared with men, are also at particular risk to develop adenocarcinoma, now the most common histologic subtype worldwide, particularly among the young and never-smoker populations. This finding further supports that there may be a molecular distinctness of the disease between the two sexes [9,16]. For example, women are more likely to develop mutations in the *EGFR* and *KRAS* genes, both of which are found primarily in the adenocarcinoma subtype. Polymorphisms in genes related to estrogen synthesis have been associated with overexpression of EGFR, but there are no conclusive mechanisms described in the literature to explain this phenomenon [2,3]. The estrogen receptor is known to be over expressed in many lung cancers, but there is no clear consensus on the impact of estrogen and hormone replacement therapy (HRT) on the development of lung cancer in women [7,14,16]. A meta-analysis performed by Greiser e*t al.* analyzed the associations between ever-use of hormonal therapy and risk of lung cancer, and revealed that ever-use was associated with a 27% decrease in lung cancer risk irrespective of smoking history; however, a subgroup analysis of adenocarcinoma found an increased risk with ever-use of HRT [17]. These findings have not been consistently replicated in recent large cohort studies [1].

Are exogenous exposures responsible for the increased lung cancer incidence among women? There is conflicting evidence regarding the impact of second-hand smoke exposure. One study showed a 24% increased risk of developing lung cancer among women who lived with men who smoked, but, like many studies evaluating second hand smoke, lacked detailed data on exposure duration and intensity [18]. In contrast, the UK Million Women study did not identify second hand smoke as a significant factor in the development of lung cancer among never-smoking women [7]. Indoor cooking with coal, which is a known carcinogen, is posited as another culprit, particularly in Asian countries where the proportion of never-smoker lung cancer among women is particularly high. One study showed that among women who live in Asia, those who cook with coal compared with those who do not have an increased odds of 5.4 of developing lung cancer [19]. Others have postulated infectious etiologies. Human papillomavirus and mycobacterial tuberculosis have been shown to be associated with lung cancer development in

women, particularly in the Asian subcontinent, but their exact role in the pathogenesis of lung cancer has not been defined [9].

For decades, lung cancer was characterized predominantly as a disease in men who smoke, and our current guidelines for screening, molecular testing and treatment are largely based on these historical patterns. Today's epidemiologic data, however, tell a different story. Decline of smoking rates in men and women alike in the western world is a public health success story, but there has been a parallel rise of incidence of lung cancer in never-smokers, a phenomenon that overwhelmingly favors women, is expected to continue to rise, and is not currently well understood. It is essential that we better characterize the biological and environmental factors that influence the development of lung cancer in women in order to accordingly refine and expand our practices for the prevention and management of this disease.

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References

1. Rivera MP. Lung cancer in women: differences in epidemiology, biology, histology and treatment outcomes. *Semin. Respir. Crit. Care Med.* 34(6), 792–801 (2013).
2. MacRosty CR, Rivera MP. Lung cancer in women: a modern epidemic. *Clin. Chest Med.* 41(1), 53–65 (2020).
3. Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. *Ann. Glob. Health* 85(1), 8 (2019).
4. Fidler-Benaoudia MM, Torre LA, Bray F, Ferlay J, Jemal A. Lung cancer incidence in young women vs young men: a systematic analysis in 40 countries. *Int. J. Cancer* 147(3),811–819 (2020)
5. Jemal A, Miller KD, Ma J *et al.* Higher lung cancer incidence in young women than young men in the United States. *N. Engl. J. Med.* 378, 1999–2009 (2018).
6. Wakelee HA, Chang ET, Gomez SL *et al.* Lung cancer incidence in never smokers. *J. Clin. Oncol.* 25(5), 472–478 (2007).
7. Pirie K, Peto R, Green J, Reeves GK, Beral V. Lung cancer in never smokers in the UK Million Women study. *Int. J. Cancer* 139(2), 347–354 (2016).
8. Barrera-Rodriguez R, Morales-Fuentes J. Lung cancer in women. *Lung Cancer (Auckl).* 3, 79–89 (2012).
9. Kligerman S, White C. Epidemiology of lung cancer in women: risk factors, survival and screening. *AJR Am. J. Roentgenol.* 196(2), 287–295 (2011).
10. Prescott E, Osler M, Hein HO *et al.* Gender and smoking-related risk of lung cancer. The Copenhagen center for prospective population studies. *Epidemiology* 9(1), 79–83 (1998).
11. Bain C, Feskanich D, Speizer FE *et al.* Lung cancer rates in men and women with comparable histories of smoking. *J. Natl Cancer Inst.* 96(11), 826–834 (2004).
12. Yim SH, Chung YJ. Molecular epidemiology of female lung cancer. *Cancers* 3(2), 1861–1876 (2011).
13. Thun MJ, Hannan LM, Adams-Campbell LL *et al.* Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies. *PLoS Med.* 5(9), e185 (2008).
14. Berardi R, Verdecchia L, Paolo MD *et al.* Women and lung cancer: clinical and molecular profiling as a determinate for treatment decisions: a literature review. *Crit. Rev. Oncol. Hematol.* 69(3), 223–236 (2009).
15. Isla D, Majem M, Viñolas N *et al.* A consensus statement on the gender perspective in lung cancer. *Clin. Transl. Oncol.* 19(5), 527–535 (2017).
16. North CM, Christiani DC. Women and lung cancer: what's new? *Semin. Thorac. Cardiovasc. Surg.* 25(2), 87–94 (2013).
17. Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of lung cancer: systematic review and meta-analysis. *Maturitas* 65(3), 198–204 (2010).
18. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 315(7114), 980–988 (1997).
19. Hosgood HD, Boffetta P, Greenland S *et al.* In-home coal and wood use and lung cancer risk: a pooled analysis of the international lung cancer consortium. *Environ. Health Perspect.* 118(12), 1743–1747 (2010).