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Editorial

# Indoor air pollution: An important risk factor for lung cancer among Asian women without a history of smoking

Edited by: Peifang Wei

Data from the GLOBOCAN 2020 estimates of incidence and mortality worldwide for lung cancer show that Asia has the highest rates for both sexes. Although smoking is known as the primary driver of lung cancer, 10–40% of people with lung cancer report no history of smoking (never-smokers).[1] Never-smokers are defined as individuals who have smoked fewer than 100 cigarettes in their lifetime. Reported incidences of lung cancer in never-smokers (LCINS) vary in different world regions, although female incidence rates are higher than those in males, especially in South Asia (83 %).[2] In addition, microsimulation modeling of US data revealed that the absolute number and proportion of LCINS, as well as lung cancer deaths, will increase up until 2065.[3] Generally speaking, LCINS is currently one of the major public health concerns requiring attention.

Each year, almost 4 million people die prematurely from illnesses caused by indoor air pollution; of these, 6% are from lung cancer (World Health Organization [WHO] online database, 2022). Sources of indoor air pollutants associated with lung cancer include coal combustion, tobacco, and building materials.[4] Epidemiological studies among never-smokers have reported that exposure to second-hand smoke (SHS) and combustion products of cooking oil fumes and indoor heating are significantly related to increased incidence rates of lung cancer in Asian women without a history of smoking.[5,6] According to the WHO online database (2022), deaths from trachea, bronchus, and lung cancer attributable to household air pollution (HAP) among females are extremely high in China. Generally, the risk for women is higher because of their roles in food preparation. Furthermore, a large-scale prospective cohort study of Chinese never-smokers investigated the association between SHS and HAP with lung cancer mortality.[7] The study demonstrated a 4% increased risk for every five-year increment of HAP exposure duration, with the highest risk among the group aged 40.1–50.0 years compared with the never-exposed group. However, no significant association was observed between SHS and lung cancer death, nor was there evidence of a statistical association between HAP and SHS. For SHS, relatively limited heterogeneity in exposure increments may obscure a real connection with lung cancer mortality. Hence, further study in younger cohorts with sufficient follow-up time may help to clarify this conundrum.

In addition, radon exposure has been reported as the second most important risk factor for lung cancer, with the most important being tobacco exposure, and is one of the leading risk factors for LCINS worldwide. Among Chinese women, a trend analysis reported that the burden of lung cancer attributable to residential radon had shown an upward trend from 1990 to 2019, while the burden of lung cancer attributable to solid fuels showed a gradually decreasing trend.[8] Both solid fuels and residential radon are important factors influencing lung cancer among the female population. However, according to the risk estimates of lung cancer from residential radon exposure among never-smokers, women appear to be at lower risk of lung cancer than men. The excess relative risk was 9% for women, but 46% for men ($P = 0.027$).[9]

Components of indoor air pollutants can typically be classified into biological, organic, inorganic, or radioactive categories.[10] A variety of components have been identified as being associated with the development of lung cancer. Pleural fluid analysis performed in patients with lung cancer and non-malignant controls found that Chinese cooking practices and incense burning increased the risk of lung cancer, especially in women. This study also indicated that concentrations of naphthalene ethylbenzene and o-xylene in the pleural fluid were important biomarkers for predicting the lung adenocarcinoma in women.[11] Lung cancer associated with naphthalene exposure has been reported in animal studies; researchers observed that some female mice developed lung tumors while inhaling naphthalene vapors daily for a lifetime. Nevertheless, more epidemiological research is needed to provide sufficient evidence.[12] To better understand the effects of cooking oil fumes on the lungs, researchers conducted an *in vivo* respiratory toxicology study on rat lungs. The results showed that inflammation, oxidative stress, and apoptosis may be the potential toxicological mechanism.[13]

SHS, another known human carcinogen, includes smoke released from actively burning tobacco products. Data from the WHO show that more than 7000 chemicals have been identified in tobacco smoke, at least 250 of which are known to be toxic or carcinogenic (http://www.who.int/publications/i/item/WHO-CED-PHE-EPE-19.12.13). SHS can generate reactive oxygen species [14] and promote the $T_H2$ cytokine response (decreased inteferon [IFN]-gamma levels, increased interleukin [IL]-4, IL-5, and IL-13 levels),[15] which is associated with an active allergic response. Some studies have suggested that carcinogens not only cause cancer through directly inducing DNA damage, but also cause undetectable multiple DNA mutational signatures in tumors.[16,17] Furthermore, the genomic landscape of LCINS shows no strong tobacco exposure-related signatures, even in populations with SHS exposure. As for the genomic characteristics of LCINS, *EGFR* was the most frequently mutated gene (30.6 %).[18] Among *EGFR*-driven lung cancer cases, there is a significant relationship between particulate matter (PM) and the development of lung cancer.[19] PM released from cooking and combustion is also one of the main components of indoor air pollu-

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tion.[10] Recent data suggest that PM mediates an altered progenitor state in alveolar type II cells with *EGFR* mutations through the macrophage release of IL-1β, which promotes lung cancer.[19]

Addressing sources of indoor air pollution will likely be required to reduce the adverse health impacts of indoor air pollutants.[20] The good news is that clean fuels and technologies for cooking are beginning to be increasingly adopted worldwide, which may alleviate the HAP-attributable lung cancer burden to a certain extent.

Tobacco dependence persists as the key barrier in reducing SHS exposure, despite effective interventions being available. Multiple types of interventions have achieved varied success, including sending letters, telephone interviews,[21] and brief advice.[22] Other interventions described by the WHO include quit lines, intensive behavioral support, cessation clinics, nicotine replacement therapies, and non-nicotine pharmacotherapies (http://www.who.int/publications/i/item/WHO-CED-PHE-EPE-19.12.13). Additionally, more systemic research, predictive modeling, and implementation studies should be encouraged in the future. Based on the current knowledge of risk factors and predictive models, advocating lung cancer screening for Asian women without a history of smoking should also be considered.

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Xiangling Chu[#]
*School of Medicine, Tongji University, Shanghai 200092, China*

Qi Wang[#], Chunxia Su[*]
*Department of Medical Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai 200433, China*

[*]Correspondence to: Department of Medical Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai 200433, China.
*E-mail address:* susu_mail@126.com (C. Su)
[#] Xiangling Chu and Qi Wang contributed equally to this work.

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