Air pollution and adenocarcinoma in never smokers

Exposure to atmospheric fine particles smaller than 2.5 μm (PM$_{2.5}$) was recently estimated to have contributed 223,000 deaths from lung cancer worldwide in 2010. More than half of the lung cancer deaths attributable to ambient PM$_{2.5}$ were estimated to have been in China and other East Asian countries. In a US study long-term exposure to PM$_{2.5}$ was associated with lung cancer mortality. Mortality rates among male and female never smokers were estimated 17.1 and 14.7 per 100,000 person years, respectively. CT-screening studies in high risk smoker cases show a lung cancer detection of about 1% in US and Europe leading to a mortality reduction of 20% in National Lung Cancer Screening Trial and reductions in mortality in women in the screened group after 8 years that were consistently higher than in men, respectively 39-61% vs 24-26% in the NELSON Study. Lung cancer screening in 12,000 Taiwanese never-smokers showed an increased lung cancer detection of 2.34% in participants between 55 and 75 years and having one of following risk factors: family history of lung cancer within third-degree relatives, passive smoking or cooking air pollution exposure. The reason for the increased incidence of adenocarcinomas in the never-smoker population might be air pollution in and around the household and passive smoking. The genetic susceptibility is still poorly quantified but may modify the lung cancer risk.

Air pollution
Household air pollution attributed to solid fuel burning for heating and cooking is the leading disease burden in Southeast Asia. Coal use was associated with a 30% increased risk of lung cancer (odds ratio (OR) 1.3, 95% CI, 1.0-1.6). Wood, agricultural residues and coal are solid cooking fuels burned in simple cook stoves by about 40% of people worldwide. The health effects of air pollution from cooking fuel in and around household are estimated as 3 to 4 million premature deaths annually and induce 3 to 5% disability-adjusted life years. In 2015 it was shown that ambient PM$_{2.5}$ air pollution is the 5th risk factor for global mortality contributing to about 4.2 million deaths. Also in never-smokers, a significant association was found with respiratory mortality (hazard ratio (HR) 1.27; 95% CI, 1.03-1.56). Many studies have confirmed these mortality associations over time.

In a European study of 312,944 cases with a follow-up of 12.8 years, 2095 (0.7%) incident lung cancers were diagnosed. The risk for lung cancer and PM$_{10}$ were associated (HR 1.22 (95% CI, 1.03-1.45) per 10 μg/m$^3$). This suggests an effect even below the current European Union air pollution limit values of 40 μg/m$^3$ for particulate matter with PM$_{10}$ and 25 μg/m$^3$ for particulate matter with PM$_{2.5}$. The same increments of PM$_{10}$ and PM$_{2.5}$ were associated with HRs for adenocarcinoma of the lung of 1.51 (1.10-2.08) and 1.55 (1.05-2.29), respectively. However, the lung cancer risk associated with air pollution is much smaller than that associated with smoking (relative risk (RR) 23.3 for currently smoking men and 12.7 for currently smoking females).

Air pollution is not only caused by fuel burning, but also by traffic. Traffic air pollution concentrations were associated with adenocarcinoma incidence in subjects who had never smoked, with a relative risk of 1.47 (95% CI, 1.01-2.16) for a 10 μg/m$^3$ increase in smoke concentration. Diesel exhaust at high exposure level in non-smokers was associated with lung cancer.

Passive smoking
It is not always easy to dissect the non-smoking causes of pulmonary adenocarcinoma. The
OR for passive smoking and lung cancer risk is 1.58 (95% CI 1.42 – 1.77). In China the population fraction of lung cancer attributable to passive smoking (PAF) is about 25%, indicating that 25% of the lung cancer cases could be prevented by eliminating passive smoking in never-smokers. This percentage is higher than in Britain (15%) or US (2.7%)15, 16.

*Genetic susceptibility*

Genomic studies also suggest that adenocarcinoma from non-smokers and smokers have different aetiologies17. The carcinogenic effect of coal exposure varies by region (OR 2.15) with the highest risk for lung cancer in Taiwan and China (OR 2.27, and 3.27, respectively)18. The interaction between air pollution exposure and genetic variation may modify the risk for lung cancer. Genetic variation in HLA class II showed an association with coal use.19 Variants in *CLPTM1L-TERT* locus of chromosome 5p15.33 and *CHRNA5–CHRNA3* locus on chromosome 15q25.1 are also associated with increased lung cancer risk, most notably adenocarcinoma in non-smokers in contrary to smokers from European descent where lung cancer risk is associated with three other regions on chromosomes 5p15.33, 6p21.33, and 15q2520. Genetic polymorphisms, such as Ile462Val of *CYP1A1* and Arg399Gln of *XRCC1* seems also to be related with increased lung cancer risk in never-smokers. At last, a lower DNA methylation index and MGMT methylation has been observed in never-smokers21, 22.

Chien-Hua Tseng et al., presented a nationwide study from Taiwan where they linked risk factors for lung cancer to the prevalence of tobacco smoking and air pollution. The incidence of adenocarcinomas increased in males and females while the ever smoking patterns over a time span of 20 years decreased in men and stayed low in women. Air pollution was estimated from atmospheric visibility trends over this time period prior to the cancer diagnosis. PM$_{2.5}$ level changes predicted the rise and fall of predominant adenocarcinoma in never-smokers. This is in line with another study where ambient concentrations of PM$_{2.5}$ were associated with an increased lung cancer related mortality2324.

Potential bases bias from a lung cancer screening program was reduced (as good as possible) by excluding stage I disease. Calculating the population fraction attributable to smoking for lung cancer was used to estimate the magnitude of this factor over time. They also took into account the multicollinearity between highly correlated factors such as smoking, gender and EGFR mutation status. The harmful effect of air pollution was only significant in those who never smoked and in EGFR wild-type lung adenocarcinoma female patients. This suggests that air pollution effects are larger for females than for males. Patients with EGFR mutations treated with TKI did not seem to have a dismal effect of air pollution. Moreover, this study also suggests that the benefit of EGFR-TKI was larger than the risk of air pollution on survival of advanced adenocarcinoma patients.

In conclusion, air pollution and passive smoking are associated with non-smoker adenocarcinomas in the lung. The proportion of adenocarcinomas in never smokers is increasing; about 25% of mainly Chinese lung cancer cases could be prevented by eliminating passive smoking in never-smokers. Still a substantial number of adenocarcinomas in non-smokers remain, not being explained by passive smoking, and most likely caused by air pollution. Whether EGFR mutations are induced by air pollution needs to be determined.
References

6. de Koning, H., et al. Effect of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population based trial. IASLC; 2018; page 2, PL02.05