

## Review

# Cancers of the lung, head and neck on the rise: perspectives on the genotoxicity of air pollution

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## Abstract

Outdoor air pollution has been recently classified as a class I human carcinogen by the World Health Organization (WHO). Cumulative evidence from across the globe shows that polluted air is associated with increased risk of lung, head and neck, and nasopharyngeal cancers—all of which affect the upper aerodigestive tract. Importantly, these cancers have been previously linked to smoking. In this article, we review epidemiologic and experimental evidence of the genotoxic and mutagenic effects of air pollution on DNA, purportedly a key mechanism for cancer development. The alarming increase in cancers of the upper aerodigestive tract in Asia suggests a need to focus government efforts and research on reducing air pollution, promoting clean energy, and investigating the carcinogenic effects of air pollution on humans.

**Key words** Air pollution, lung cancer, head and neck cancer, mutagenic effects

On October 17, 2013, the World Health Organization (WHO) announced for the first time that outdoor air pollution is carcinogenic to humans. The International Agency for Research on Cancer (IARC), WHO's specialized cancer agency, officially classified outdoor air pollution and particulate matter (PM) as IARC Group 1 carcinogens. This announcement acknowledges the importance and global impact of air pollution, a leading environmental factor in cancer deaths worldwide<sup>[1]</sup>.

The question is, which cancers are associated with air pollution or PM? The answer lies in recent cancer statistics and reports from countries with heavy industrialization or urbanization. These reports show that cancers of the upper aerodigestive tract, including lung cancer, head and neck cancer, and nasopharyngeal carcinoma (NPC; a head and neck cancer with high prevalence in South China), are associated with air pollution<sup>[2]</sup>. In addition, incidences of breast cancer and bladder cancer are also linked to outdoor air pollution<sup>[3,4]</sup>. Strikingly, these cancers have been long recognized as smoking-related, i.e., cigarette smoking is a known risk factor.

In this focused review, we discuss the key evidence linking air pollution to upper aerodigestive tract cancers, which are

highly prevalent in Asia. We also describe the possible mutagenic and tumorigenic effects of air pollution and pollutants. A better understanding of air pollution and its effects on carcinogenesis is urgently warranted to improve health outcomes and to lessen the economic burden on health care systems and governments.

## Increased Incidence of Lung Cancer and Head and Neck Cancers

Several large-scale studies in the US demonstrated that air pollution is associated with lung cancer risk. In a multi-city study with 8,111 subjects, Dockery *et al.*<sup>[5]</sup> showed that air pollution, similar to smoking, was positively associated with lung cancer mortality. Another study by Beeson *et al.*<sup>[6]</sup> showed that among 6,338 non-smoking adults in California, air pollution [including sulfur dioxide, ozone, and particulate matter 10 (PM<sub>10</sub>)] was associated with increased risk of developing lung cancer during a 15-year follow-up (from 1977 to 1992). Note that PM<sub>2.5</sub> was not included in that study.

Rigorous scientific or epidemiologic studies of the association between air pollution and cancer incidence have not been officially conducted in China or other Asian countries. Nevertheless, a marked increase in lung cancer incidence has been specifically noted over the past 2 to 3 decades in these countries. A recent analysis of cancer trends in China showed a continuous rise in lung cancer incidence from 1973 to 2005. Importantly, lung cancer incidence was much higher in urban populations than in rural populations (40.98/100,000 in urban area vs. 25.71/100,000 in rural area) in 2004–2005<sup>[7]</sup>, likely because urban areas tend to be more polluted

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than rural areas. Additionally, the incidence of breast and pancreatic cancers was relatively higher in urban areas than in rural areas of China<sup>[7]</sup>.

Similar trends in cancer incidence seem to be occurring in India, where urbanization and industrialization are happening at a very rapid rate. Indeed, air pollution is imposing a serious health burden in India. In the US, lung cancer incidence has dropped notably among males and remained relatively unchanged among females<sup>[8]</sup>. In contrast, the incidence of lung cancer in non-smoking women is surging in India<sup>[9]</sup>, and air pollution is likely a key factor.

In a recent study, Grant *et al.*<sup>[2]</sup> revealed that residence in urban areas have increased incidence of lung cancer, which was found to be associated with NPC incidence in the US, suggesting a link between urban pollution and this type of head and neck cancer. Other head and neck cancers, including oral, laryngeal, and pharyngeal cancers, have also been associated with ambient air pollution in other studies<sup>[10,11]</sup>. In India, the incidence of head and neck cancers in males is increasing as well<sup>[9]</sup>.

Industrialization and urbanization of human activity is closely linked to burning solid fuel such as coal, charcoal, and wood. In fact, a recent study by Sapkota *et al.*<sup>[12]</sup> showed that lifetime exposure to indoor solid fuel (coal and wood) burning increased the risk of head and neck cancers (in particular, hypopharyngeal cancer) and lung cancer. Because large populations in China and India depend on solid fuels for cooking and heating, indoor smoke is believed to contribute heavily to cancer in these countries. Indeed, exposure to domestic woodfire, especially in households with no windows or poor ventilation, is associated with a marked increase in risk of developing NPC in China<sup>[13]</sup>. An independent study in southern Brazil also confirmed the associated risk of developing head and neck cancers, particularly cancers of the mouth, pharynx, and larynx, with the use of wood stoves<sup>[14]</sup>. More strikingly, a large scale, 20-year retrospective study in China (Xuanwei County, Yunnan Province) comparing lung cancer deaths between life-long, domestic users of “smoky coal” (bituminous) and “smokeless coal” (anthracite) showed that smoky coal users were more likely to die of lung cancer before the age of 70 than smokeless coal users; risk of lung cancer death was 20% for smoky coal users versus 0.5% for smokeless coal users<sup>[15]</sup>. Further, the hazard ratios of male and female lung cancer deaths among smoky coal users were 36 and 99, respectively, when compared to the smokeless coal users. These cumulative studies establish clearly that cancers of the upper aerodigestive tract are associated with polluted air.

## Inheritable Mutagenic Effects of Air Pollution

Given the strong link between air pollution and cancer development, the logical next question is, what carcinogenic effects can air pollution potentially impose? Somers *et al.*<sup>[16,17]</sup> conducted two elegant studies using live animals to determine the mutagenic effects of air pollution on germline DNA, and concluded that exposure to air pollution can induce DNA mutations that offspring inherit from parents. In the first experiment, they compared the DNA mutation rates in two

groups of laboratory mice: one housed in a polluted, urban-industrial area near 2 steel mills and a major highway, and the other housed in a rural area 30 km away from the first group of mice<sup>[17]</sup>. Both groups of mice were briefly exposed (10 weeks, equivalent to 1/5 to 1/10 of the life-span of mice) to ambient air in the respective areas, and were then bred within each group in a standardized animal care facility under identical conditions. The investigators found that the mutation rate in germline DNA was 1.5- to 2.0-fold higher in the offspring of mice exposed to polluted air in the urban-industrial area than in offspring of mice from the rural area control group. This demonstrated that exposure to polluted air, likely due to inhalation of airborne mutagens, can induce inheritable germline mutations *in vivo*.

In the second experiment, the investigators compared the rates of inheritable mutations from mice housed in the same air-polluted, urban-industrial site, with one group exposed to ambient air there, while the other group was housed inside a clean air system [equipped with high efficiency-particulate-air (HEPA) filtration system that can remove ~99.99% of 0.1-micron sized particles] for 10 weeks<sup>[16]</sup>. Similarly, another 2 groups of mice were housed in the rural site 30 km away with exposure to either ambient air or HEPA-filtered air. Breedings were then carried out, and the mutation rates of inheritable germline DNA from each group were compared with respective parental or maternal DNA. Strikingly, germline mutation rates were highest among offspring from the group exposed to polluted ambient air at the urban-industrial site (1.9–2.0 higher frequency of mutations from paternal origin). Exposure to cleaned air (HEPA-filtered air) reduced the paternal mutation rate by nearly 52%. Further, the investigators showed that mutation rates were strongly associated with the total concentration of polycyclic aromatic hydrocarbons (PAHs), including seven chemical carcinogens identified by the US Environmental Agency, as well as the mean total concentration of suspended particulate in the air of the polluted site. Somers *et al.*<sup>[16]</sup> concluded that these “airborne chemical mutagens, including PAHs and heavy metals” and PM may reach the bloodstream, likely via the respiratory system, thus affecting the germline.

Although it has been long speculated that air pollutants or PM can have lasting, damaging effects on the integrity of our genome and can potentially cause cancer, these two very well-defined animal experiments solidly established the *in vivo* mutagenic activity of air pollution and the inheritability of such damage. Thus, air pollution poses a genetic risk for humans, which may link to predisposition of diseases including cancer.

A well-controlled experiment cannot be easily conducted in humans to directly demonstrate the mutagenicity of air pollution. Nevertheless, a recent large-scale human study looked at potential association of chemical carcinogens in the blood of two generations of women (mothers and daughters) with their rates of developing breast cancer<sup>[18]</sup>. The study stemmed from the question of why women without any currently known risk factor for breast cancer develop the disease. The investigators hypothesized that part of the answer may lie in early exposure to environmental pollutants. The study determined if exposure to pollutants in the environment at various stages of life, including prenatal (in mother’s womb) or during puberty or pregnancy, are associated with increased risk of developing breast

cancer. Women with higher levels of polychlorinated biphenyl 203 (PCB 203) in their postpartum serum were six times more likely to develop breast cancer than the general population. Thus, exposure to PCB (in particular PCB 203) during pregnancy may predict increased risk for early breast cancer. A Spanish study also revealed that postmenopausal women who were highly exposed to traffic-related air pollution had an increased incidence of breast cancer<sup>[3]</sup>.

A compatible, well-planned, long-term study has yet to be conducted to determine whether blood-penetrating pollutants (presumably absorbed through inhalation or exposure) can directly induce upper aerodigestive tract cancers in humans and their offspring. However, several large scale studies in the US and Europe showed that air pollution is associated with cancer mortality rates, most evidently in lung cancer<sup>[19,20]</sup>. These findings coincide with recent reports in India that there is an alarming surge of new lung cancer cases among non-smoking women<sup>[9]</sup>, which is likely due in part to the increasing air pollution problem in India.

## DNA and Protein Damages Caused by Air Pollution

The upper aerodigestive tract cancers described here are closely or etiologically associated with smoking, but what remains to be investigated is whether these cancers are being caused by the physical particles, chemicals, or both found in smoke and air pollution. Chemicals in polluted air can cause DNA damage and protein adducts. Cancer may develop if PM in pollutants induces bodily reactions or immune responses such as long-term inflammation and oxidative stress<sup>[21,22]</sup> in the upper aerodigestive tract. Notably, persistent DNA or protein damage, including DNA adducts or protein adducts, have been found in human populations in polluted regions and may be linked to cancer<sup>[23]</sup>. In a large-scale study in Europe, Peluso *et al.*<sup>[24,25]</sup> demonstrated that the levels of detected DNA adducts were significantly higher in healthy, non-smoking subjects who eventually developed lung cancer than in those who did not develop lung cancer. Thus, detectable DNA adduct formation was associated with subsequent risk of lung cancer. No such DNA adduct association study has been conducted for head and neck cancers in Asia, where air pollution is an increasing environmental problem. Thus far, PAH-DNA adducts, bulky DNA adducts, and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG) have been detected among humans who worked or lived in highly polluted environments. Those affected include non-smoking police officers, bus drivers, traffic workers, and students with different pollution exposures<sup>[26-32]</sup>. Similarly, protein adducts caused by air pollution, including benzopyrene-hemoglobin adducts and 4-aminophenyl-hemoglobin adducts, have been detected in human adults and children, respectively, in polluted areas<sup>[33,34]</sup>. The cancer-causing effects of these adducts have yet to be investigated experimentally.

Recently, researchers have been developing specific DNA markers, including mutations of cancer-related genes such as the

tumor protein 53 (*TP53*) and Kirsten rat sarcoma viral oncogene homolog (*KRAS*)<sup>[35-39]</sup>, as well as markers for hypoxanthine phosphoribosyltransferase (*HPRT*), cyclin-dependent kinase inhibitor 2A (called *CDKN2* or *p16<sup>INK4A</sup>*), death-associated protein kinase (*DAPK*) and retinoid acid receptor beta (*RAR-beta*) to investigate the mutagenic effects of heavily polluted air on the human genome. Large-scale human studies are needed to assess their potential as pollution-reflecting biomarkers. In addition, although smoking is known to cause G>T transversion in the human genome, it remains to be determined whether this transversion rate in aerodigestive cancers can reflect the direct DNA damaging effects of air pollution in humans.

In addition to DNA biomarkers, researchers are also exploring protein biomarkers to reflect the effects of air pollution in humans. A study by Rossner *et al.*<sup>[40]</sup> showed that plasma levels of p53 and p21<sup>WAF1</sup> proteins associated with environmental exposure to benzo[a]pyrene (B[a]P) and carcinogenic PAHs, as well as to levels of total DNA adducts. More studies are needed to examine the penetrating effects of air pollution on our genome and proteins that cause cancer.

## Actions to Reduce Aerodigestive Cancers Induced by Air Pollution

Although it remains to be examined if lung cancers and head and neck cancers associated with air pollution are etiologically or genetically the same as those caused by cigarette smoking, efforts to reduce these aggressive cancers are much needed, given the climbing rates of these cancers in never-smokers in Asia. Therefore, in addition to conducting more in-depth scientific studies on the biology of air pollution-associated cancers, it is highly important to also reduce air pollution, promote the practical use of clean energy in a broad sense (e.g., in transportation, cooking, etc.), and regulate the release of polluted air into the atmosphere. In the meantime, the use of indoor air-filtering systems can reduce health hazards until the outdoor air quality is improved. There are increasing efforts to adhere to WHO's guideline to clean air in European countries. There is a hope that other countries, especially heavily populated countries in Asia, can also aim for this healthy goal in the near future. These concerted efforts, if carried out successfully and cooperatively, will significantly reduce cancer incidence and the related health burdens in Asia and potentially worldwide.

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