The International Agency for Research on Cancer (IARC) evaluation of the carcinogenicity of outdoor air pollution: focus on China

Dana Loomis¹, Wei Huang² and Guosheng Chen³

Abstract

The International Agency for Research on Cancer (IARC) has classified outdoor air pollution and the particulate matter (PM) in outdoor air pollution as carcinogenic to humans, as based on sufficient evidence of carcinogenicity in humans and experimental animals and strong support by mechanistic studies. The data with important contributions to the evaluation are reviewed, highlighting the data with particular relevance to China, and implications of the evaluation with respect to China are discussed. The air pollution levels in Chinese cities are among the highest observed in the world today and frequently exceed health-based national and international guidelines. Data from high-quality epidemiologic studies in Asia, Europe, and North America consistently show positive associations between lung cancer and PM exposure and other indicators of air pollution, which persist after adjustment for important lung cancer risk factors, such as tobacco smoking. Epidemiologic data from China are limited but nevertheless indicate an increased risk of lung cancer associated with several air pollutants. Excess cancer risk is also observed in experimental animals exposed to polluted outdoor air or extracted PM. The exposure of several species to outdoor air pollution is associated with markers of genetic damage that have been linked to increased cancer risk in humans. Numerous studies from China, especially genetic biomarker studies in exposed populations, support that the polluted air in China is genotoxic and carcinogenic to humans. The evaluation by IARC indicates both the need for further research into the cancer risks associated with exposure to air pollution in China and the urgent need to act to reduce exposure to the population.

Key words. Air pollution, particulate matter, lung cancer, China
studies of cancer in experimental animals, and diverse studies of mechanisms related to cancer.

**Air Pollution Exposure in China**

Some high outdoor air pollution concentrations are currently observed in China. Resulting from the unprecedented rapid development in industrialization and urbanization in the past decades, the air pollution levels in many cities are well above health-based standards\[^{5,6}\], and air pollution-associated health impacts have become a growing concern\[^{7}\]. Coal has been the major energy source in China and will remain so in the near future. Coal combustion-type air pollution was predominant in most Chinese cities in the last century, and the air pollution was severe. The average annual levels of primary air pollutants PM\(_{10}\), SO\(_2\), and NO\(_2\) in 31 provincial capital cities in China (2003–2012) are summarized in Figure 1\[^{8}\].

Along with the concentration reductions of PM\(_{10}\), SO\(_2\), and NO\(_2\) in China, the concentrations of PM\(_{2.5}\) and O\(_3\) in some city cluster areas have increased, suggesting the degradation of regional air quality. As air pollution from transportation and industrial combustion and the overall emissions from these sources increase in China, yet become more dispersed, regional and transboundary air quality issues are likely to become increasingly important for China. The average annual levels of PM\(_{10}\), SO\(_2\), and NO\(_2\) in 31 provincial capital cities in China (2003–2012) are summarized in Figure 1\[^{8}\].

Evidence of Carcinogenicity in Humans

The IARC Working Group reviewed over 200 epidemiologic studies, including several large cohort studies collectively enrolling millions of subjects in Europe, North America, and Asia. A number of studies included estimates of quantitative levels of outdoor air pollutants. The association between an increased risk of lung cancer and exposure to polluted air measured by several indicators, including the concentrations of PM and NO\(_2\) and measures of potential exposure to traffic emissions, was consistently observed in both cohort and case-control studies after adjustment for important potential confounders, including tobacco smoking. Positive exposure-response relationships were observed in studies that reported quantitative exposure data. Among the most influential studies evaluated for the IARC monograph were a pooled analysis of lung cancer in 10 countries in Europe\[^{13}\] and a large nationwide cohort study of lung cancer in the United States\[^{14}\].

Illustrative data for the association of the risk of lung cancer with exposure to PM\(_{2.5}\) are shown in Figure 3. The relative risks (RRs) ranged from approximately 1.0 to 1.4 per 10 \(\mu g/m^3\) of PM\(_{2.5}\). A meta-analysis of 18 studies estimated a meta-RR of 1.09 [95% confidence interval (CI), 1.04–1.14] per 10 \(\mu g/m^3\) of PM\(_{2.5}\)\[^{15}\]. Associations of similar magnitude were also obtained for PM\(_{10}\) and NO\(_2\), although the data were less consistent for the latter. In contrast, most studies did not find an association of lung cancer with SO\(_2\).
Increased risk of lung cancer with exposure to outdoor air pollution was also observed in analyses restricted to non-smokers\(^1\), and the magnitude of association was not appreciably affected by adjustment for indicators of socioeconomic status\(^2\).

In addition to the extensive data available for lung cancer, there was limited epidemiologic evidence that bladder cancer is associated with various metrics of exposure to outdoor air pollution, including occupational and residential exposure to traffic emissions. Although these studies typically adjusted for tobacco smoking, most used surrogate measures of exposure based on occupational titles; thus, the results did not weigh heavily in the evaluation. Studies of several other cancers, including female breast cancer, leukemia, and childhood cancers, were also evaluated, but the evidence was judged inadequate for the purposes of determining carcinogenicity.

Only one epidemiologic study from China was available for review by IARC: a prospective cohort study of mortality in approximately 71,000 adults living in 31 Chinese cities\(^3\). Average concentrations of total suspended particles (TSP), \(\text{SO}_2\), and nitrogen oxides (\(\text{NO}_x\)) were determined directly from local air monitoring data, and the concentration of \(\text{PM}_{2.5}\) was estimated from TSP using a conversion factor. After adjusting for potential confounders, including smoking and socioeconomic status, the RRs for lung cancer in relation to \(\text{SO}_2\) and \(\text{NO}_x\) were 1.04 (95% CI, 1.02–1.06) and 1.03 (95% CI, 0.99–1.07) per 10 \(\mu\text{g/m}^3\), respectively. The RR for lung cancer in relation to the estimated concentration of \(\text{PM}_{2.5}\) was 1.03 (95% CI, 1.00–1.07) per 10 \(\mu\text{g/m}^3\).

Other studies on the cancer risks associated with exposure to outdoor air pollution in China, including those published in the Chinese language, were considered for inclusion in the monograph. However, most were aggregate association analyses of lung cancer mortality and air pollution or urban residence, and none of them met the inclusion criteria related to study design and reporting. The contribution of indoor air pollution from coal combustion to the occurrence of cancer in China has been more extensively studied: IARC has classified indoor emissions from household coal combustion as carcinogenic to humans based largely on studies of lung cancer in China\(^4\).

**Evidence of Carcinogenicity in Experimental Animals**

The IARC Working Group also reviewed evidence regarding the carcinogenicity of outdoor air pollution in experimental animals. As part of this process, IARC’s previous evaluations of animal bioassay evidence for the carcinogenicity of diesel engine exhaust and emissions from the combustion of coal and wood were updated and confirmed. All of these agents can be present in outdoor air and were shown previously to cause benign and malignant lung tumors in mice or rats.

Only a few studies have assessed the occurrence of cancer in...
animals exposed directly to outdoor air pollution by inhalation, and none of them were conducted in China. Mice exposed to outdoor air pollution in São Paulo, Brazil, showed an increase in the incidence of lung adenomas and a dose-dependent increase in the incidence and multiplicity of adenomas after treatment with urethane[19]. Several other studies in which mice were injected subcutaneously with organic solvent-extracted material from particles collected from outdoor air pollution showed increased incidence of injection site tumors, hepatoma, and lung adenoma or adenocarcinoma[20,21]. Two Chinese studies indicated that organic extracts of suspended particulates were carcinogenic in two-stage skin carcinogenicity test[22,23]. However, insufficient experimental details were reported in these studies.

Evidence on the Mechanisms of Carcinogenesis

The findings of carcinogenicity in humans and animals are strongly supported by a large, diverse body of evidence showing genetic and related effects in exposed humans and animals and a wide range of experimental systems. Studies of people exposed occupationally to outdoor air pollution have demonstrated enhanced frequencies, relative to controls, of chromosomal aberrations (CAs) and micronuclei (MNs) in lymphocytes[24,25]. Genetic damage, including somatic and germ cell mutations, cytogenetic abnormalities, and DNA damage, were also observed in mammals, birds, and plants exposed to outdoor air pollution[26]. Genotoxic effects have also been observed in studies of human and animal cell lines in vitro.

Several studies in China show increased cytogenetic effects in humans associated with exposure to outdoor air pollution (Table 1). The CA frequencies in peripheral blood were significantly higher in traffic policemen (0.98%) than in traffic officers (0.4%) in Hebi city, Henan, China[27]. Cui et al.[28] studied the CA frequencies in the chorionic villi of 2,698 women having abortions in 3 cities with different levels of air pollution, and the results indicated that the incidences of polyploidy, trisomy, and chromosome structural abnormalities in heavily polluted Shenyang and moderately polluted Zhengzhou were significantly higher than those in Dalian, which was the least polluted. The frequencies of MNs and sister chromatid exchanges (SCEs) were significantly higher in traffic policemen than in indoor police officers in Lanzhou[29] and Tangshan[30], China. Significantly higher MN and SCE frequencies were also observed in bus drivers or bus conductors on a route that ran through heavily polluted tunnels in Shanghai compared with officers in the Shanghai Botanical Garden[31]. Moreover, higher MN frequencies were observed in urban residents than in rural residents in Shenyang, China[32]. These studies of genetic biomarkers in humans provide direct evidence that polluted outdoor air causes damage to genetic material, which may increase the risk of cancer.

A number of studies from China indicate that extracts of airborne PM cause significant dose-dependent increases in cytogenetic abnormalities in experimental animals as well as in cultured animal and human cells. Dose-dependent increases in CAs were observed in mice treated with extracts of PM from Harbin[33] and Taiyuan[34]. The increases in CA frequencies were observed in cultured human lymphocytes exposed to extracts of PM from Lanzhou[35] and Shanghai[36]. Elevated MN
frequencies were observed in the bone marrow of Kunming mice treated with organic extracts of PM collected from Shanghai[31], Taiyuan[32], and Lanzhou[33]. Increased MN and SCE frequencies were also observed in cultured human lymphocytes and animal cells. The cytogenetic effects of airborne PM extracts suggest that outdoor air pollution may cause cancer through a genotoxic mechanism. The similar genotoxic effects consistently observed in human and animal cells strongly support that the carcinogenicity observed in animals is relevant to that in humans.

Exposure to polluted outdoor air in the workplace or urban settings is associated with the altered expression of genes involved in DNA damage and repair, inflammation, and immune and oxidative stress responses as well as in altered telomere length and epigenetic effects such as DNA methylation[34]. In Chinese studies, significant increases in DNA damage were observed in human blood lymphocytes from traffic policemen, as measured by the comet assay, when compared with indoor traffic officers in Shanghai[35] and Guangzhou[36]. DNA damage was also observed in experimental animals and cultured human and animal cells exposed to extracts of airborne PM. Significantly lower serum antioxidant enzyme activities, i.e., superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), were observed in traffic policemen in Beijing compared with suburb residents, indicating that outdoor air pollution causes oxidative stress in humans[37].

In addition, PM extracts from outdoor air from diverse locations worldwide, collected at different time periods and under various atmospheric conditions, induce mutations in Salmonella. This bacterial mutagenic activity, covering more than 5 orders of magnitude per volume of air across locations, is quantitatively related to the concentration of atmospheric PM. Notably, the highest air mutagenic activity of PM extracts was observed in an industrial area in Shanghai, with a mutagenic activity of over 2,500 revertants per m$^3$ in Salmonella typhimurium TA98 strain, according to a database compiled for the IARC evaluation that contains 2,375 observations.[38]

### Discussion and Implications for China

Epidemiologic data from Asia, Europe, and North America consistently show positive associations of lung cancer with PM and other indicators of air pollution throughout the range of exposure.
These associations are observed in high-quality studies and persist after adjustment for the most important lung cancer risk factors.

The levels of major air pollutants in Chinese cities significantly exceed national and international air quality standards that have been established to protect health. It has been estimated that approximately 223,000 deaths from lung cancer—nearly 15% of all lung cancer deaths—worldwide are attributable to particulate air pollution in 2010, with 139,000 of those deaths (9% of all lung cancer deaths) occurring in China alone. It is important to recognize, however, that virtually all of the studies currently available for such risk assessments were conducted in locations where the annual average concentrations of PM$_{2.5}$ were between 10 and 30 µg/m$^3$, which represents approximately the lower third of the exposure distribution worldwide. Conversely, areas with far higher pollution levels, such as those found in many Chinese cities, tend to be less studied.

Exposure-response coefficients derived from cohort studies of air pollution exposure are urgently needed to support future NAAQS revisions in China. The sole datum point at the upper end of the exposure scale in Figure 4 is from the Chinese cohort studied by Cao et al. Although that study is notable for finding a significant association of lung cancer with the level of SO$_2$, which is generally not observed elsewhere, the RR for PM$_{2.5}$ is low relative to other studies. The authors speculated that this might be due to a flattening of the exposure-response function at the high levels of exposure prevailing in Chinese cities, but the indirect method they used to estimate exposure to PM$_{2.5}$ may have involved considerable measurement errors, which could have attenuated the risk coefficient. In light of this inconsistency in the risk coefficients and the concerns about the quality of exposure data, this single study does not provide sufficient guidance about the risk of cancer associated with exposure to outdoor air pollution in China.

The combination of a very sparse epidemiologic database with large populations exposed to high levels of air pollution points to a significant research gap with respect to the effects of air pollution in China. There is a clear need for more large studies of cancer with high-quality measures of exposure to air pollutants, particularly PM$_{2.5}$, and the ability to control for important risk factors. The assessment of exposure for cancer studies in China is likely to be challenging because the estimates should ideally extend back 10–20 years to account for latency, though PM$_{2.5}$ was not routinely monitored in most Chinese cities until 2012. However, methods combining remote-sensing data from satellites and available ground-based monitoring data that have been used in other parts of the world are promising for future epidemiologic studies in China.

The exposure of several species to outdoor air pollution has been associated with increases in genetic damage, including cytogenetic abnormalities, mutations in both somatic and germ cells, altered gene expression, and altered telomere length, and epigenetic effects, such as DNA methylation, which have been linked to increased cancer risk in humans. The studies from China, especially the genetic biomarker studies in exposed populations, substantially support that the polluted air in China is genotoxic and carcinogenic to humans.

A number of mechanistic studies have shown that extracts of airborne PM in many cities in China are genotoxic in an array of bioassays, including bacteria, mammalian and human cell systems, and experimental animals. Genetic biomarker studies in humans lend further strong support to the proposition that air pollution in China...
may contribute to human lung cancer. The integration of molecular epidemiology and genetic biomarkers with traditional epidemiology will advance the etiologic study of human lung cancer in China. Emerging molecular biological approaches, such as toxicogenomics and epigenomics, will provide a powerful tool for investigating the adverse health effects that might be caused by outdoor air pollution.

In conclusion, there is an urgent need for research to characterize the sources, levels, and composition of air pollution in China and to quantify its contribution to adverse effects on the health of Chinese populations. Nevertheless, as demonstrated by the recent IARC evaluation, a vast body of scientific knowledge about the effects of air pollution in China and to adverse health effects that might be caused by outdoor air pollution. Emerging molecular biological approaches, such as toxicogenomics and epigenomics, will provide a powerful tool for investigating the adverse health effects that might be caused by outdoor air pollution.

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