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Review

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

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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

Outdoor air pollution consists of a mixture of constituents arising from many natural and anthropogenic sources. The composition and relative levels of pollutants are quite variable, reflecting both the diversity of the sources and the influence of atmospheric processes. However, in much of the world, transportation, power generation, industry, biomass burning, and domestic heating and cooking are the predominant anthropogenic sources[1].

A number of countries have established monitoring networks that record the levels of regulated pollutants, such as respirable particulate matter (PM_{10}), fine particulate matter ($PM_{2.5}$), and the gases nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). $PM_{2.5}$ is often used as a general indicator for the level of anthropogenic air pollution: the average annual concentrations of $PM_{2.5}$ currently range from below 10 μg/m^3 to over 100 μg/m^3 around the world. Although air pollution levels have generally declined in West Europe and North America since the middle of the 20th century, they are increasing in certain other regions, especially those undergoing rapid economic growth[2]. Indeed, international and national air quality guidelines are routinely exceeded in many areas[3].

In October 2013, a Working Group of invited experts from 11 countries, including China, met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of outdoor air pollution. The Working Group unanimously classified outdoor air pollution and PM from outdoor air pollution as carcinogenic to humans (IARC Group 1) based on sufficient evidence of carcinogenicity in humans and experimental animals and strong mechanistic evidence[4]. The findings regarding the carcinogenicity of both the overall mixture of outdoor air pollution and PM specifically were notably consistent in epidemiologic studies,

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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. At present, limited data are available on the annual levels of ambient $PM_{2.5}$ and O_3, which have been newly included in the revised Chinese National Ambient Air Quality Standards (NAAQS) released in March 2012[9]. In several studies assessing the mortality risk attributable to $PM_{2.5}$ and O_3 exposure, the reported average concentrations of $PM_{2.5}$ and O_3 were in the ranges of 55–177 μg/m^3 and 56–86 μg/m^3, respectively[10-12]. Brauer *et al*.[3] also estimated that the population-weighted annual average levels of $PM_{2.5}$ had increased from 44 to 55 μg/m^3 between 1990 and 2005 in East Asia; the highest annual average concentration of $PM_{2.5}$ measured in 2005 was 58 μg/m^3 in Beijing, and the highest derived $PM_{2.5}$ concentration (estimated from PM_{10} measurements) was 121 μg/m^3 in Datong, a coal mining center in Shanxi Province. The estimated levels of $PM_{2.5}$ in 2010 ranged above 80 μg/m^3 in North China (**Figure 2**)[2,3], which were well above the WHO air quality guideline of 10 μg/m^3 annual average and the Chinese NAAQS of 35 μg/m^3 (equivalent to the WHO interim target).

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 μg/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 μg/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.

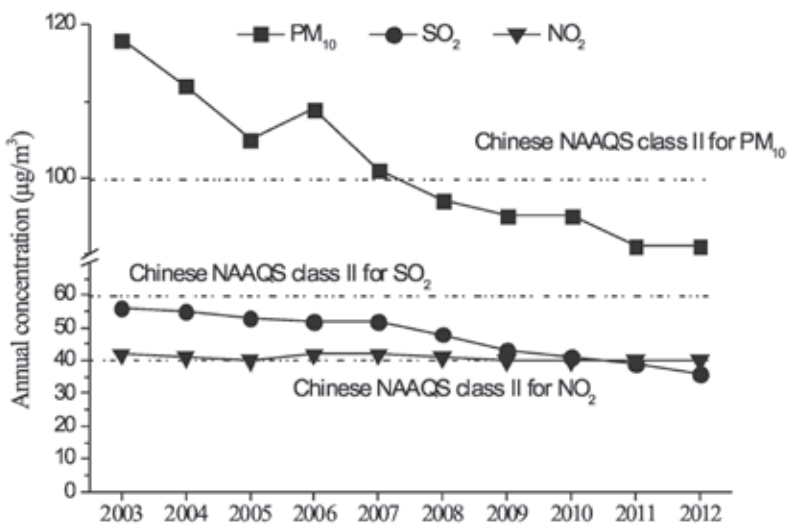

Figure 1. **The national annual levels of respirable particulate matter (PM_{10}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) in China, 2003–2012.** Data source: China Statistic Yearbook 2004–2013. The national levels are averaged from the annual levels of 31 provincial cities in China. The dotted line indicates the annual level of the Chinese National Ambient Air Quality Standard (NAAQS) Class II.

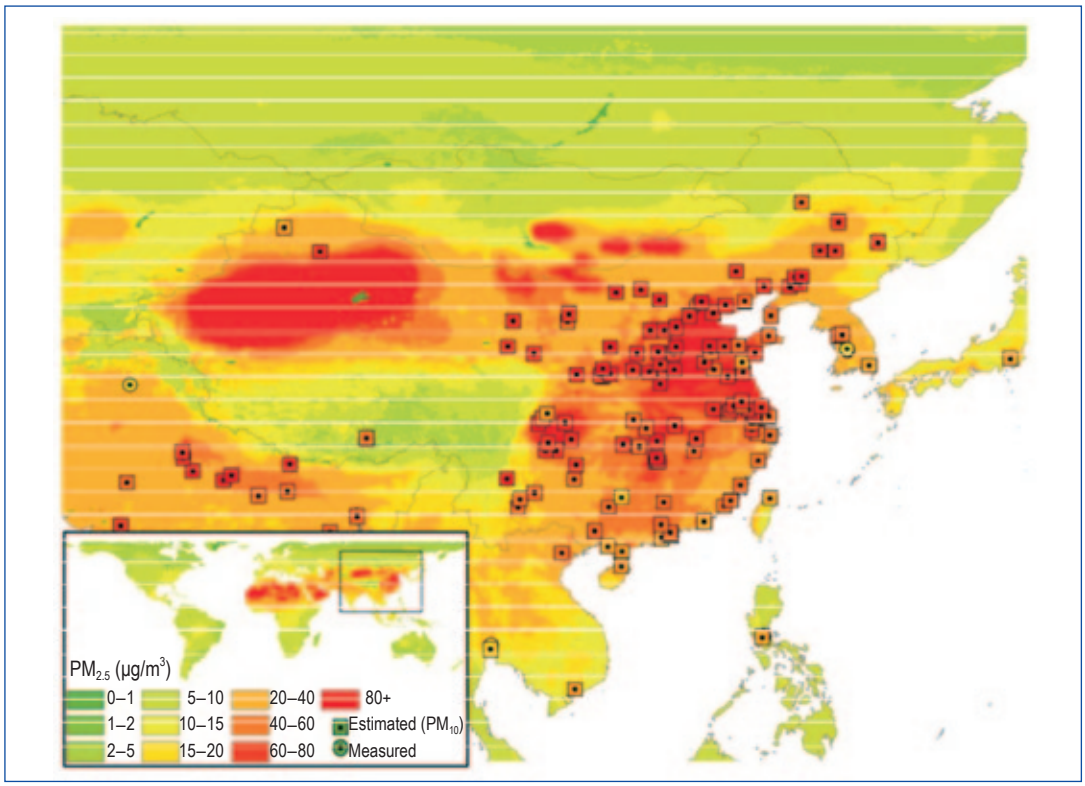

Figure 2. **Estimated levels of fine particulate matter ($PM_{2.5}$) in China, 2010 as reported in the 2014 International Agency for Research on Cancer (IARC) Monographs.**

Increased risk of lung cancer with exposure to outdoor air pollution was also observed in analyses restricted to non-smokers[16], and the magnitude of association was not appreciably affected by adjustment for indicators of socioeconomic status[15].

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[17]. Average concentrations of total suspended particles (TSP), SO_2, and nitrogen oxides (NO_x) were determined directly from local air monitoring data, and the concentration of $PM_{2.5}$ 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 SO_2 and NO_x were 1.04 (95% CI, 1.02–1.06) and 1.03 (95% CI, 0.99–1.07) per 10 μg/m^3, respectively. The RR for lung cancer in relation to the estimated concentration of $PM_{2.5}$ was 1.03 (95% CI, 1.00–1.07) per 10 μg/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[18].

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

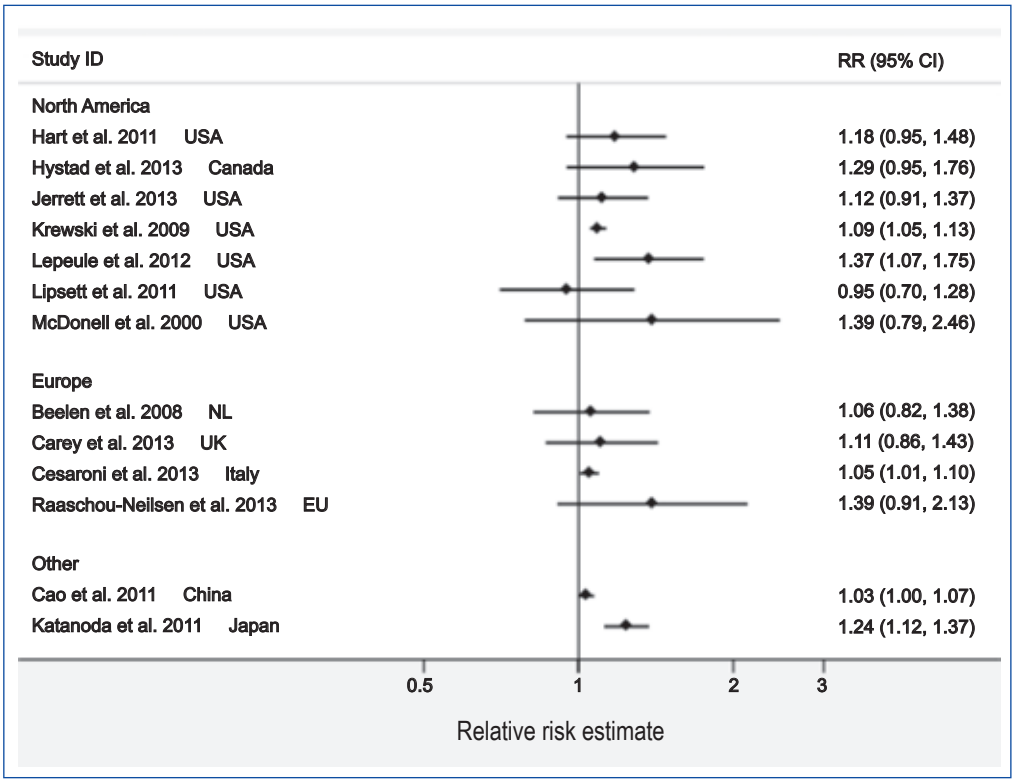

Figure 3. **Forest plot of the relative risk (RR) of lung cancer per 10 μm/m^3 of $PM_{2.5}$. CI, confidence interval. Weights are from random effects analysis.**

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 moderated 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

Table 1. Cytogenetic effects in humans associated with exposure to polluted outdoor air in China

Reference	Endpoint	Control subjects	Results	Exposed subjects	Results	*P*
Chen *et al.* 1999[27]	CA[a]	Indoor police officers in Hebi, Henan (*n* = 30)	0.40%	Traffic policemen exposed to outdoor air pollution from coal combustion and automobile exhaust in Hebi, Henan (*n* = 45)	0.98%	<0.01
Cui *et al.* 1991[28]	CA[a]	Chorionic villi in pregnant women in Dalian, Liaoning (*n* = 827)	0.11%	Chorionic villi in pregnant women in Shenyang, Liaoning (*n* = 811)	1.66%	<0.01
				Chorionic villi in pregnant women in Zhengzhou (*n* = 1,060)	0.52%	<0.01
Zhao *et al.* 1998[29]	MN[b]	Household register police officers in Lanzhou, Gansu (*n* = 34)	3.22±1.31	Traffic policemen exposed to outdoor air pollution from automobile exhaust in Lanzhou, Gansu (*n* = 67)	5.72±2.57	<0.05
	SCE[c]	Household register police officers in Lanzhou, Gansu (*n* = 34)	3.73±1.51	Traffic policemen exposed to outdoor air pollution from automobile exhaust in Lanzhou, Gansu (*n* = 67)	8.81±1.83	<0.05
Bai *et al.* 2005[30]	MN[d]	Indoor police officers in Tangshan, Hebei (n = 49)	1.97±0.21	Traffic policemen exposed to outdoor air pollution from automobile exhaust at crossroads in Tangshan, Hebei (n = 65)	4.27±0.68	<0.05
	SCE[c]	Indoor police officers in Tangshan, Hebei (*n* = 49)	2.69±0.35	Traffic policemen exposed to outdoor air pollution from automobile exhaust at crossroads in Tangshan, Hebei (*n* = 65)	4.32±0.58	<0.05
Peng *et al.* 1995[31]	MN[b]	Botanical garden officers, Shanghai (*n* = 36)	0.69±0.06	Bus drivers or bus ticket officers on route through DaPu tunnel in Shanghai (*n* = 40)	1.28±1.02	<0.01
	SCE[c]	Botanical garden officers, Shanghai (*n* = 36)	4.50±0.99	Bus drivers or bus ticket officers on route through DaPu tunnel in Shanghai (*n* = 40)	5.94±1.23	<0.01
Ishikawa *et al.* 2006[32]	MN[d]	Female residents in rural areas in Shenyang, Liaoning (*n*= 63)	1.02	Female residents in urban and industrial areas in Shenyang, Liaoning (*n* = 66)	1.56	<0.05

CA, chromosomal aberration; MN, micronucleus; SCE, sister chromatid exchange. [a]The results are expressed as the percentage of cells with CA, with 100 metaphases examined for each subject. [b]The results are expressed as the number of MNs per 1,000 cells. [c]The results are expressed as the number of SCEs per cell. [d]The results are expressed as the number of MN-containing cells per 1,000 binucleated cells.

frequencies were observed in the bone marrow of Kunming mice treated with organic extracts of PM collected from Shanghai[37], Taiyuan[38], and Lanzhou[39]. 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[25]. 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[40] and Guangzhou[41]. 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[42].

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 collected from 174 scientific publications. One factor for such high mutagenic activity is due to the high concentration (up to 1.3 mg/m^3) of PM in gasworks[43]. Relatively high mutagenic activities of PM extracts are also observed in several streets in Shanghai, with mutagenic activities up to 250 revertants per m^3 in TA98[44]. In general, the Salmonella mutagenic activity of air PM extracts in rural areas is undetectable or less than 10 revertants per m^3. These studies indicate that the outdoor air in China, especially in large cities, is highly contaminated with mutagens, which may damage genetic material and cause cancer in humans.

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[45]. 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 (**Figure 4**). 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*.[17]. 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

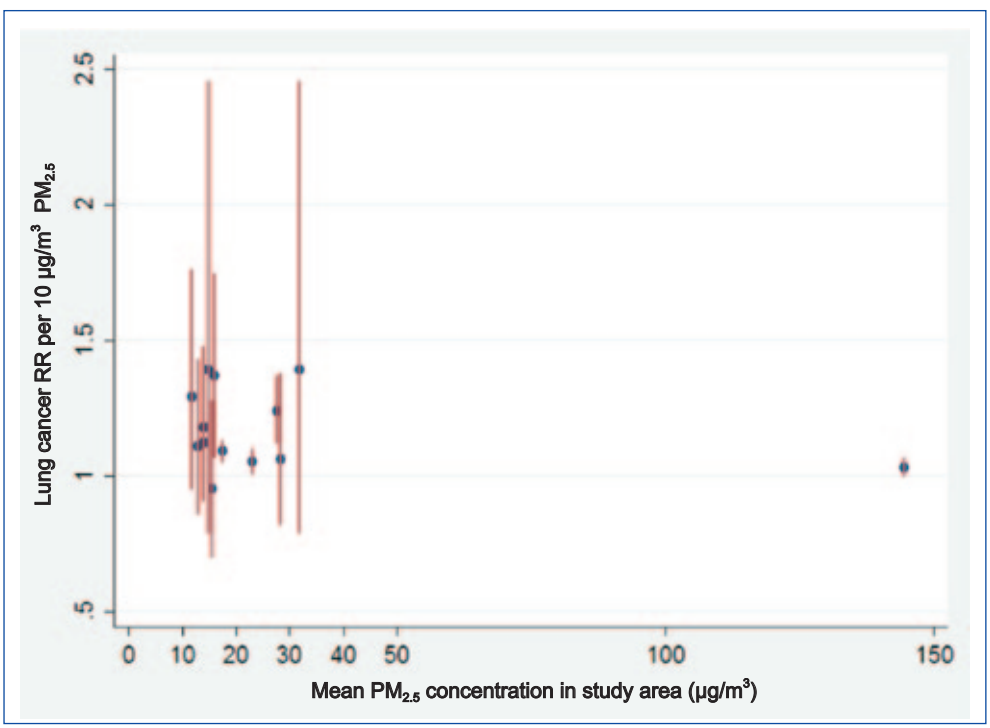

Figure 4. **Relative risk of lung cancer in relation to average exposure to $PM_{2.5}$ in studies included in the IARC evaluation.**

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 has already accumulated, and this has prompted successful efforts to reduce air pollution levels in some countries. The need for new research in China, while clearly substantial, should not delay taking appropriate action based on what is already known.

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