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Air pollution: a potentially modifiable risk factor for lung cancer

Laís Fajersztajn, Mariana Veras, Ligia Vizeu Barrozo and Paulo Saldiva

Abstract | Economic growth and increased urbanization pose a new risk for cancer development: the exposure of high numbers of people to ambient air pollution. Epidemiological evidence that links air pollution to mortality from lung cancer is robust. An ability to produce high-quality scientific research that addresses these risks and the ability of local health authorities to understand and respond to these risks are basic requirements to solve the conflict between economic development and the preservation of human health. However, this is currently far from being achieved. Thus, this Science and Society article addresses the possibilities of expanding scientific networking to increase awareness of the risk of lung cancer that is promoted by air pollution.

Determining the contribution of potentially modifiable risk factors (also known as cause-specific analysis for cancer) is crucial to implement cancer-preventive health policies[1]. Air pollution — household air pollution from burning solid fuels (for heating and cooking) and ambient particulate matter — was listed as one of the ten leading risk factors for the global burden of disease in 2010 (REF. 1). Most of these diseases are due to respiratory and cardiovascular events[2–5], but cancer is also an important outcome[1,3,5–11]. Lung cancer has the most robust association with prolonged exposure to air pollution, particularly when pollution is expressed in terms of particulate matter or gaseous components of air pollution. In fact, as exposure to higher concentrations of particulate matter increases, lung cancer becomes proportionally more important than cardiovascular events to the burden of disease[11]. For lung cancer mortality, excess risks rose nearly linearly throughout the full range of exposure to particulate matter, with a median aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$; fine particulate matter), whereas the slope of the curve for cardiovascular mortality was less steep. Currently, 8% of global lung cancer deaths can be attributed to exposure to fine particulate matter alone[3], although this estimate can be much higher (12.8%; confidence interval (CI) 95% = 5.9–18.5) if fine particles that are generated from human activity (as determined from satellite-derived assessments) are taken into account[12]. The dose–response relationship relating lung cancer and ambient particulate matter might be

higher then previously estimated, particularly if only adenocarcinomas of the lung are considered. A recent European report that combined 17 long-term cohort studies in nine European countries identified a risk of 1.55 per 5 μg per m^3 of $PM_{2.5}$ (hazard ratio 1.55; 95% CI = 1.05–2.29)[51]. There is also a growing body of evidence that associates air pollution exposure to an increased risk of cancer in other tissues, such as the breast[13–16], haematopoietic tissues[17,18] and the urinary tract[7,19–22].

Air pollution and global burden of disease

Exposure to outdoor air pollution is expected to become the top environmental cause of premature mortality globally by 2050, overtaking malaria and water quality, which are traditional environmental risks for premature deaths, and the numbers of deaths from both of these are expected to fall over the same period[23]. The effect will be greater in developing countries that are not members of the Organization for Economic Cooperation and Development (OECD): these countries include Brazil, Russia, India, Indonesia, China and South Africa (BRIICS), as well as developing countries in the rest of the world[23]. There are densely populated regions in the world that have high air pollution concentrations (FIG. 1), especially megacities of developing nations. Fast urban and industrial development in these countries has resulted in growing demands for energy and rising expectations of material goods[24]. Therefore, megacities combine both concentrated emissions of air pollutants and large numbers of exposed people[25].

On a minor scale, hot spots of vulnerability can even occur in developed urban settings[26]. It is important to note that most of the epidemiological evidence relating air pollution to lung cancer has reported a linear dose–response effect[3,9,10,27–35,51] (TABLE 1). However, these studies were carried out in the United States[3,9,10,31,32] or Europe[27–30,51], which are areas with substantially lower levels of air pollution than those of developing countries. Studies in areas with higher pollution levels and high population levels are scarce[33–35] (TABLE 1) and are badly needed. Thus, this Science and Society article addresses the possibility of expanding scientific networking to increase awareness of the risk of lung cancer that is promoted by air pollution, especially in areas of the world where pollution is likely to be a substantial risk factor for lung cancer development and death.

Air pollution and cancer risk

Although the relative risk of developing cancer as a result of exposure to air pollution is generally small, the attributable risk (relative risk multiplied by the number of exposed people) is high, transforming ambient air pollution into the most significant environmental risk factor for lung cancer[1]. Indeed, lung cancer burden from air pollution is probably underestimated. Most of the long-term exposure studies for this pollutant have been carried out in areas where annual average concentrations range between 5 μg and 35 μg per m^3; however, the average concentrations of particulate matter in the major population centres of China, India and other developing countries are often much higher, and can exceed 100 μg per m^3 according to recent estimates[25].

Specific pollutants or complex mixtures?

Particulate matter can be considered as a mixture of air pollution sources that are present in the urban atmosphere rather than as a single pollutant. Particulate matter represents a complex mixture of solid and liquid components, which can vary substantially in composition and size depending on the emission source and prevailing weather conditions[36]. The composition and size of these particles determine the potential for deposition in the respiratory tract and the health effects that are associated with exposure[37]. Particles are classified according to their size, which can range from 0.005 μm to 100 μm in diameter. The smaller the size of the particle the greater its potential to penetrate deep into the respiratory tract[36].
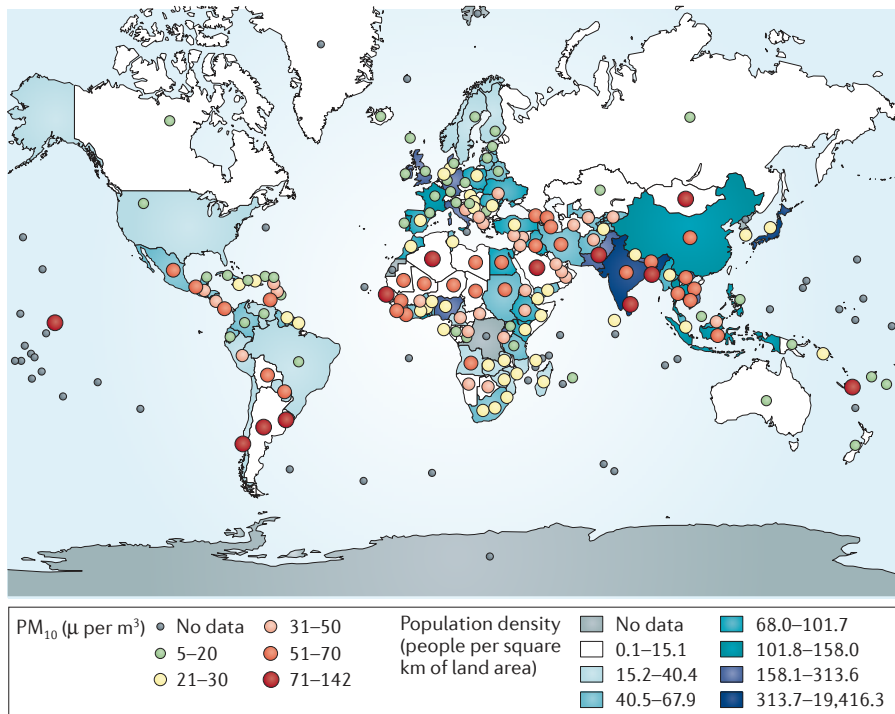
Figure 1 | **Global annual mean PM$_{10}$ concentrations in 2009 by population density.** The map compares the population density in 2009 (data from the World Bank[49]) with the annual mean concentration of particulate matter of 100 μm or less (PM$_{10}$) in 2009 (data from the World Bank[50]).

The composition of these particles includes different classes of organic and inorganic chemicals, such as heavy and transition metals, organic compounds, hydrocarbons, ions, condensed reactive gas products and microorganisms. At higher concentrations the particles can also include microorganismal products (such as endotoxins), nitrates, sulphates and elemental carbon. Some of these particulates, such as polycyclic aromatic hydrocarbons, are known carcinogens[37,38]. Recently, diesel emissions, a substantial contributor to urban particles, were considered to be class I carcinogens by the International Agency of Research on Cancer[38], meaning that there is scientific evidence of carcinogenicity in humans.

In European and some Asian studies, significant associations were obtained relating lung cancer risk to gaseous components of air pollution, such as NO$_2$ and SO$_2$ (REFS 28–30,34,35). NO$_2$ has been shown to be a good indicator of traffic-related pollution[39], and SO$_2$ can be used to estimate diesel and industrial emissions. It is important to note that large cohort studies on lung cancer and air pollution rely on measures of specific pollutants. However, the atmosphere contains many compounds with known carcinogenic potential, such as polycyclic aromatic hydrocarbons and heavy metals, levels of which are not

routinely measured. Thus, in such a complex mixture, it is difficult to ascribe the responsibility of causing lung cancer to a single component. Until a clear pathogenetic mechanism is defined, it would be prudent to consider the pollutants mentioned above as possible substitute markers of sources of air pollution, such as traffic or industrial pollution.

Air pollution control
The National Ambient Air Quality Standards (NAAQS), set up in the United States as part of the Clean Air Act, has been effective in controlling air quality[40], and it is a policy that has been recommended by the World Health Organization since 1987 (REF. 41). The stringency of air pollution control procedures varies substantially worldwide[42]. Indeed, a comprehensive global analysis that reviewed the 24-hour NAAQS for PM$_{10}$ (particulate matter with a median aerodynamic diameter of less than 10 μm) revealed a positive correlation between the stringency of the NAAQS and the average annual exposure to PM$_{10}$, meaning that less stringent air quality standards lead to higher air pollution concentrations[42]. Efforts to control the sources of ambient air pollution should be considered a public health strategy to reduce lung cancer incidence, similar to the strategies that apply to tobacco and asbestos.

The process of reducing the use of asbestos and tobacco raised considerable public health controversies, which were driven by political, economic and individual liberty arguments. In the case of air pollution, the adoption of effective policies to control emission levels will be conceivably more challenging, as these policies will call into question our present use of energy and our apparently unbreakable dependence on personal motorized vehicles. Energy production — including oil and thermoelectric power — and the automobile industry represent enormous economic interests, and 'modern life' is based on increased energy use, which has become incorporated into our culture. Thus, a reduction in particulate matter levels will demand a considerable behavioural change. Traffic is one of the major sources of particulate matter[39]. Substantial technological advances have improved the efficiency of the nineteenth century internal combustion engine, leading to a reduction of air pollution concentrations. However, although air pollution from motorized vehicles has decreased in cities in Europe and North America as a result of more efficient petrol and diesel engines, it has not decreased as much as was hoped[25]. This is because the increase in road traffic and the resulting decrease in vehicle velocity are offsetting the gains that have been made by better car technology. In São Paulo, Brazil, particulate matter concentrations were decreasing progressively from 1996 to 2004, but they have remained unchanged since 2004 (REF. 43), indicating that technology alone will not be a solution if the numbers of vehicles and their intensity of use continue to increase. The same is true for the generation of electricity based on fossil fuels (coal, petroleum and gas); 40% of the electricity produced worldwide is currently generated from the combustion of coal, and this percentage is expected to rise in the next few decades as worldwide energy demands increase[44]. Thus, this will offset any improvements to levels of particular matter that have been gained through the use of modern thermoelectric power plants[45,46]. Moreover, the technological benefits of more advanced combustion engines and energy generation processes are not evenly distributed across the globe. One particularly difficult challenge is to tackle the lack of access to clean energy and the dependence of many people in low-income settings on inefficient and inadequately ventilated burning of biomass for household energy needs[44,47,48]. In this scenario, there are links between indoor and outdoor sources

Table 1 | **Key studies relating air pollution to lung cancer**

Study	Setting	N (follow-up period)	Pollutant considered	Estimated risk	Adjustments
Europe					
Beelen et al.[27]	Netherlands	111,378 (1986–1997)	Black smoke concentration	RR (95% CI) = 1.47 (1.01–2.16) for never smokers; 0.91 (0.68–1.23) for ex-smokers; and 0.85 (0.70–1.03) for current smokers	Age, sex, smoking status and SES
			Black smoke (10 μg per m^3)	RR (95% CI) = 1.03 (0.78–1.34)	
			NO$_2$ (30 μg per m^3)	RR (95% CI) = 0.86 (0.57–1.29)	
			PM$_{2.5}$ (10 μg per m^3)	RR (95% CI) = 0.65 (0.41–1.04)	
			SO$_2$ (20 μg per m^3)	RR (95% CI) = 1.01 (0.67–1.54)	
Brunekreef et al.[28]	Netherlands	120,000 (1987–1996)	Black smoke (10 μg per m^3)	RR (95% CI) = 1.03 (0.88–1.20)	Age, sex, smoking status and SES
			NO$_2$ (30 μg per m^3)	RR (95% CI) = 0.91 (0.72–1.15)	
			PM$_{2.5}$ (10 μg per m^3)	RR (95% CI) = 1.06 (0.82–1.38)	
			SO$_2$ (20 μg per m^3)	RR (95% CI) = 1.00 (0.79–1.26)	
Cesaroni et al.[29]	Italy	1,265,058 (2001–2010)	NO$_2$ (10 μg per m^3)	HR (95% CI) = 1.04 (1.02–1.07)	Age, sex, marital status, place of birth, education, occupation and area-based socioeconomic position
Heinrich et al.[30]	Germany	4,800 (1980–2008)	NO$_2$ (16 μg per m^3)	HR (95% CI) = 1.25 (0.72–2.17)	Age, smoking status and education
			PM$_{10}$ (7 μg per m^3)	HR (95% CI) = 1.97 (0.59–6.57)	
Raaschou-Nielsen et al.[51]	Nine European countries	312.944 (mean of 12.8 years)	PM$_{10}$ (10 μg per m^3)	HR (95% CI) = 1.22 (1.03–1.45) for all lung cancers; 1.51 (1.10–2.08) for adenocarcinomas of the lung	Age, sex, smoking status and SES
			PM$_{2.5}$ (5 μg per m^3)	HR (95% CI) = 1.18 (0.96–1.46) for all lung cancers; 1.55 (1.05–2.29) for adenocarcinomas of the lung	
North America					
Dockery et al.[31]	United States	8,111 (1974–1991)	PM$_{2.5}$ (18.6 μg per m^3)	AMR (95% CI) = 1.37 (0.81–2.31)	Age, sex, smoking status, education, occupational exposure and medical history
Jerrett et al.[32]	United States	22,905 (1982–2000)	PM$_{2.5}$ (10 μg per m^3)	HR (95% CI) = 1.44 (0.98–2.11)	Forty-four individual level covariates, including income, race and SES
Krewski et al.[9]	United States	1,200,000 (1999–2000)	PM$_{2.5}$ (10 μg per m^3)	HR (95% CI) = 1.142 (1.057–1.234)	Forty-four individual level covariates, including income, race and social factors
Pope et al.[3]	United States	1,200,000 (1979–1983)	PM$_{2.5}$ (10 μg per m^3)	RR (95% CI) = 1.08 (1.01–1.16)	Age, sex, smoking status, marital status, education, occupational exposure, race, BMI, alcohol consumption and diet
		1,200,000 (1999–2000)	PM$_{2.5}$ (10 μg per m^3)	RR (95% CI) = 1.13 (1.04–1.22)	
		1,200,000 (1982–1998)	PM$_{2.5}$ (10 μg per m^3)	RR (95% CI) = 1.14 (1.04–1.23)	
Turner et al.[10]	United States	188,699 (1979–1983)	PM$_{2.5}$ (10 μg per m^3)	HR (95% CI) = 1.15 (0.99–1.35)	Age, sex, passive smoking, marital status, education, occupational exposure, race, BMI, diet, prevalent lung disease and radon exposure
		188,699 (1999–2000)	PM$_{2.5}$ (10 μg per m^3)	HR (95% CI) = 1.27 (1.03–1.56)	
		188,699 (1982–2008)	PM$_{2.5}$ (10 μg per m^3)	HR (95% CI) = 1.19 (0.97–1.47)	
Asia					
Cao et al.[33]	China	70,947 (1991–2000)	SO$_2$ (10 μg per m^3)	ΔM (95% CI) = 4.2 (2.3–6.2)	Age, sex, smoking status, education, BMI, alcohol consumption, physical activity and hypertension
Kantanoda et al.[34]	Japan	63,520 (1974–1983)	PM$_{2.5}$ (10 μg per m^3)	HR (95% CI) = 1.23 (1.09–1.38)	Age, sex, smoking status, diet and indoor charcoal or briquette braziers used for heating
			SO$_2$ (10 μg per m^3)	HR (95% CI) = 1.19 (0.97–1.45)	
			NO$_2$ (10 μg per m^3)	HR (95% CI) = 1.15 (1.06–1.24)	
Yorifuji et al.[35]	Japan	14,001 (1999–2009)	NO$_2$ (10 μg per m^3)	HR (95% CI) = 1.20 (1.03–1.40)	Age, sex, smoking status, BMI, hypertension, diabetes, financial capability and area mean income

AMR, adjusted mortality rate ratio; BMI, body mass index; CI, confidence interval; ΔM, percentage increase in mortality; HR, hazard ratio; PM$_{2.5}$, particulate matter with a median aerodynamic diameter of less than 2.5 μm; PM$_{10}$, particulate matter with a median aerodynamic diameter of less than 10 μm; RR, relative risk; SES, socioeconomic status.
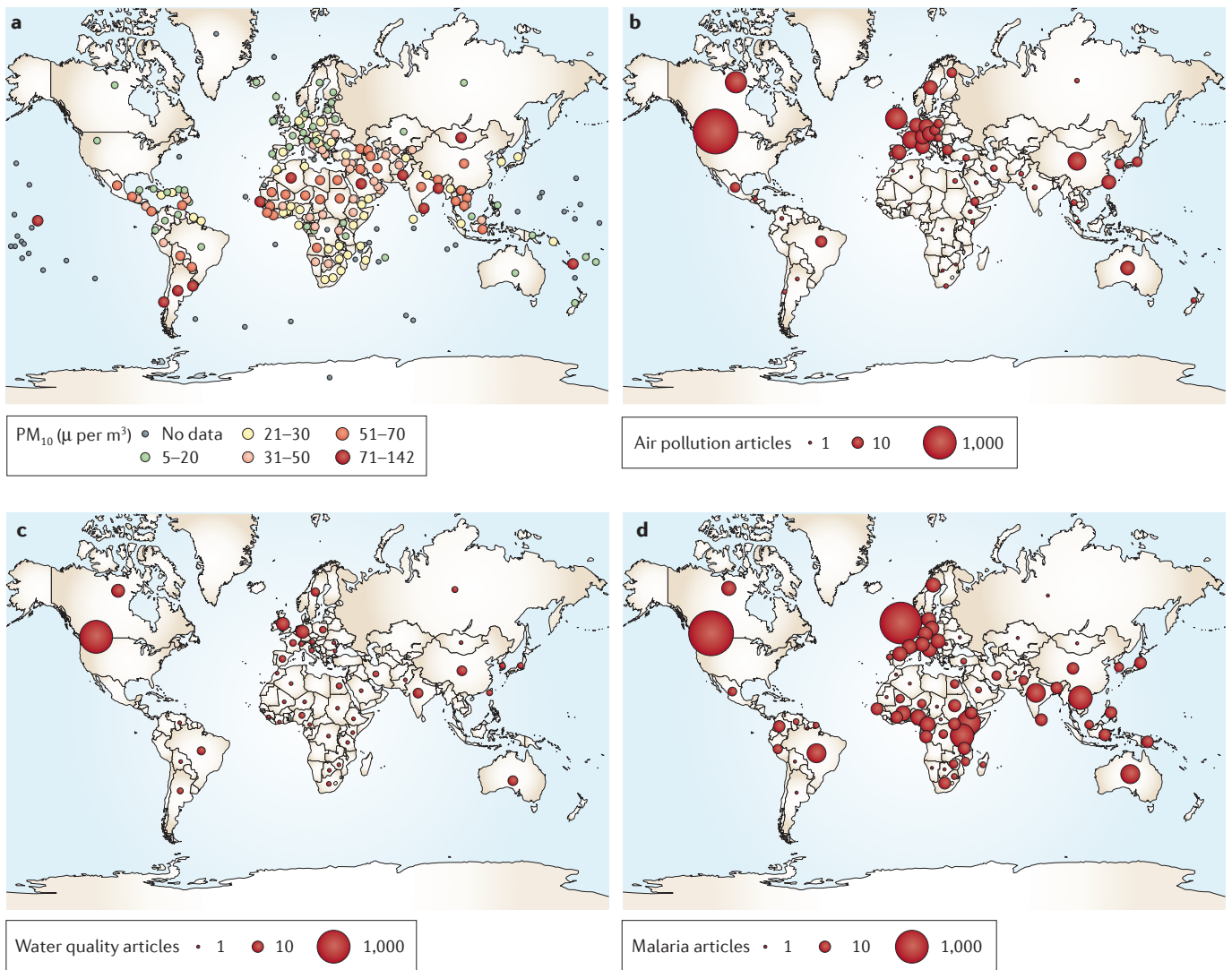
Figure 2 | **A comparison of scientific research output on various global health issues.** Global annual mean PM$_{10}$ (particulate matter with a median aerodynamic diameter of less than 10 μm) concentration (μg per m^3) in 2009 (part **a**)[49]. Number of articles in environmental public health published between March 1983 and March 2013 on air pollution (part **b**), water quality (part **c**) and malaria (part **d**), according to data from the Web of Science database. Search terms used were air pollution (part **b**), water quality (part **c**) and malaria (part **d**). The public environmental and occupational health filter was used for all searches.

of pollution, as a substantial proportion of outdoor air pollution may derive from poor household fuel combustion, particularly in Asia[44].

Science-based control of air pollution?
Theoretically, good scientific research is necessary to provide the basis for the implementation of policies that aim to control harmful environmental agents, helping society to decide a course of action once the apparent dilemma between preservation of human health and economic growth becomes more widely appreciated. In fact, governments that have a greater expenditure on health care have more stringent air quality standards, probably because of greater governmental

awareness of the adverse health effects of air pollution and the consequent establishment of air pollution control measures to avoid increased health costs[42]. In this context, it would be interesting to know whether there is enough scientific research in air pollution hot spots to drive public policies that aim to reduce the problem. FIGURE 2 depicts a comparative panel of the number of papers produced from 1983 to date on malaria, water quality and air pollution, using the Web of Science database. There is a marked imbalance between levels of air pollution and local scientific production: a more balanced scenario emerges when waterborne diseases and malaria are considered. Developing rest of the world countries contribute to almost

20% of all the research on water quality and to approximately 70% of the research on malaria, but to only 5% of all air pollution papers. A 2012 report from the World Meteorological Organization[25] about the effects of megacities on air pollution and climate identified 11 international collaborative research projects, but only 50% focused on developing regions.

Conclusions and future directions
Sources of air pollution are unequivocally linked to economic activities; therefore, it is important to devise strategies to increase the collaboration between developed and developing nations to address the health effects of air pollution. Gains in scientific

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knowledge and global partnerships were effective in reducing the cancer risks associated with other environmental health issues, such as tobacco smoke and asbestos. Is now the time to do the same for air pollution?

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