Review

Impact of fine particles in ambient air on lung cancer

Gerard Hoek[1] and Ole Raaschou-Nielsen[2]

Abstract

Recently, the International Agency for Research on Cancer (IARC) has classified outdoor air pollution and the particulate matter component of outdoor air pollution as class I carcinogen. Air pollution is consistently associated with lung cancer in epidemiologic and experimental studies. The IARC assessment is specifically designed as hazard identification, and it does not quantify the magnitude of the cancer risk. This article addresses the magnitude of the lung cancer risk in the population due to ambient air pollution exposure.

Key words Air pollution, particulate matter, $PM_{2.5}$, lung cancer

The relative risks (RRs) from ambient air pollution are much smaller than those from active smoking; however, air pollution affects the entire population. Reduction of fine particulate ($PM_{2.5}$, i.e., the mass of particles smaller than 2.5 μm) air pollution concentrations will result in substantial reduction of lung cancer cases in the population. The magnitude of the population attributable risk fraction (PAF) is uncertain because of uncertainties in the magnitude of RRs, shape of the concentration-response function, especially at high $PM_{2.5}$ concentrations, and particle composition. New epidemiologic studies, especially in high pollution settings, are therefore very useful. To fully assess the cancer burden of exposure to ambient air pollution, other cancer sites should be investigated.

Background

Cancer is a growing global public health problem, and modifiable environmental and life style factors play important roles in various cancers[1]. An association between outdoor air pollution and lung cancer has been suspected for more than a half century[2]. Early studies used ecologic designs to compare the incidence of lung cancer, e.g., in rural versus urban areas, without individual data on confounders such as smoking. Since the early 1990's, well-designed, prospective cohort and case-control studies with detailed, individual-level information on important confounders such as smoking have documented associations between ambient air pollution and lung cancer incidence or mortality[3].

Recently, the International Agency for Research on Cancer

(IARC) has classified outdoor air pollution as a class I carcinogen[4]. This assessment was based upon sufficient evidence for carcinogenicity of outdoor air pollution in human and animal studies and strong mechanistic support[4]; however, the evidence was considered sufficient for lung cancer, but not for other cancer sites. The IARC further classified particulate matter (PM) in outdoor air as a class I carcinogen based mainly upon consistent evidence for an association between the long-term average concentration of $PM_{2.5}$ in outdoor air and lung cancer incidence or mortality. In the IARC assessment, it was specifically stated that the assignment of particles as a human carcinogen does not imply that gaseous pollutants may not have an additional effect on cancer.

The IARC assessment is specifically designed as hazard identification, and it does not quantify the magnitude of the cancer risk. This article addresses the magnitude of the lung cancer risk related to ambient air pollution exposure. Assessments of the impact of ambient air pollution on lung cancer incidence and mortality in populations[5,6] have often been based upon the large American Cancer Society (ACS) study[7]. In the ACS study, significant associations between long-term exposure to $PM_{2.5}$ and all-cause, cardiovascular, and lung cancer mortalities were reported[7]. Since the publication of the ACS study, more large, prospective cohort studies have been published[8]. We will especially discuss a recently published study on 17 European cohorts[9]. In this European Study on Cohorts for Air Pollution Effects (ESCAPE), we reported significant associations between long-term exposure to PM air pollution and lung cancer incidence in over 300,000 European subjects[9]. The discussion will draw on the international literature because other papers in this special issue of the Chinese Journal of Cancer focus more specifically on Chinese studies. Using the RR estimates from different epidemiologic studies, we will calculate the PAF due to ambient air pollution and investigate the uncertainty of these estimates with emphasis on Chinese settings with high air pollution concentrations. The PAF describes the fraction of the disease

incidence in the population that can be prevented by removing a factor. Uncertainty in the cancer burden due to ambient air pollution exposure includes uncertainty about the magnitude of RRs, the shape of the concentration-response function (linear, sublinear, supralinear, and/or a lower threshold), the effect of PM composition, and the potential effects on cancer sites other than the lung. We will discuss the impact of these factors on cancer burden.

Magnitude of the Relative Risk

In the ESCAPE study, we reported a hazard ratio (HR) for lung cancer incidence of 1.40 for a 10-$\mu g/m^3$ increase in the long-term average concentration of $PM_{2.5}$[9]. In ESCAPE, 14 cohorts distributed throughout Europe were studied with highly standardized exposure assessment, confounder selection, and statistical analysis procedures. Air pollution was assessed at the individual address level using land use regression models, which were based upon standardized measurements of ambient particles and nitrogen oxides and geographic information systems[10]. Associations between air pollution exposure and lung cancer were first calculated per cohort, and then pooled estimates were calculated using meta-analysis techniques. One finding of the ESCAPE study was that no significant heterogeneity was found across the PM effect estimates of the 14 cohorts, which was remarkable because the cohorts differed markedly in air pollution exposure (e.g., mean $PM_{2.5}$ varied between 7 and 33 $\mu g/m^3$) and population characteristics (e.g., age and sex). The

magnitude of the risk was at the high end of the range of the $PM_{2.5}$ RRs observed in selected large cohort studies in other locations (**Table 1**). The RR estimate in the ESCAPE study was substantially higher than that in the ACS study (1.40 vs. 1.14). Various potential explanations for the higher estimate in the ESCAPE study compared to that in the ACS study include the following: 1) Random error (95% CI of the ESCAPE estimate includes the ACS estimate); 2) a more detailed individual exposure estimation in the ESCAPE study versus the city average exposure assignment in the ACS study that potentially resulted in less exposure measurement error in the ESCAPE study; 3) a different composition of PM; 4) differences in population sensitivity; and 5) differences between within-community (ESCAPE) versus between-community (ACS) exposure contrast. **Table 1** illustrates that some studies, such as the Rome longitudinal study[13], showed effect estimates that were smaller than those in the ACS study. A statistical test for the heterogeneity of the effect estimates in **Table 1** showed high statistical significance ($P < 0.01$).

Nearly all studies have been conducted at $PM_{2.5}$ concentrations that are low to moderate on a global scale[18]. For the Global Burden of Disease (GBD) project, global estimates of $PM_{2.5}$ were made using a consistent methodology based upon a combination of satellite data, modeling, and surface monitoring[18]. The highest annual average $PM_{2.5}$ concentration was found in East Asia, with an overall average of 55 $\mu g/m^3$ in 2005. In substantial areas within China, annual average $PM_{2.5}$ concentrations exceeded 80 $\mu g/m^3$. Because of the spatial scale of the GBD assessment (0.1 degree, approximately at 10 km

Table 1. Summary of the effect estimates from cohort studies on $PM_{2.5}$ and lung cancer incidence or mortality

Reference	Study	Study population	Follow-up period	$PM_{2.5}$ concentration ($\mu g/m^3$)	RR for $PM_{2.5}$ (per 10 $\mu g/m^3$)
Raaschou-Nielsen et al., 2013 [9]	ESCAPE study	312,944 adults in 17 European cohorts	Recruitment in 1990's. Mean follow-up of 13 years.	7–31[a]	1.40 (0.92–2.13)
Lepeule et al., 2012 [11]	Harvard Six Cities study	8,096 adults in 6 US cities	1974–2009	16 (11–24)	1.37 (1.07–1.75)
Pope et al., 2002 [7]	ACS study	500,000 adults from 51 US cities	1982–1998	18 ± 4	1.14 (1.04–1.23)
Beelen et al., 2008 [12]	Netherlands cohort study	120,852 subjects from Netherlands	1987–1996	28 (23–37)	0.81 (0.63–1.04)
Cesaroni et al., 2013 [13]	Rome longitudinal study	1,265,058 adults from Rome	2001–2010	23 (7–32)	1.05 (1.01–1.10)
Carey et al., 2013 [14]	UK national cohort study	830,842 adult GP patients from UK	2003–2007	13 (9–20)	1.11 (0.86–1.43)
Katanoda et al., 2011 [15]	Three-prefecture cohort study	63,520 adults in 6 Japanese areas	1983–1995	17–42	1.24 (1.12–1.37)
Lipsett et al., 2011 [16]	California teachers study	101,784 female teachers from California	1997–2005	16 (3–28)	0.95 (0.70–1.28)
Cao et al., 2011 [17]	China national hypertension survey	70,497 men and women in China	1991–2000	289 (113–499)[b]	1.03 (1.00–1.07)

$PM_{2.5}$, the mass of particles smaller than 2.5 μm; HR, Hazard ratio; ACS, the American Cancer Society; GP, general practioner. Most data of $PM_{2.5}$ concentration are presented as mean with minimum-maximum in parentheses or mean ± standard deviation. [a]Range of the 14 cohort-specific average concentrations. [b]Reported is the concentration of total suspended particles (TSP). Assumed conversion from TSP to $PM_{2.5}$ is multiplied by 0.325.

× 10 km), even higher concentrations will be present at individual stations.

Studies conducted at high ambient concentrations, which are relevant for East-Asian areas, including China, are largely lacking. One prospective cohort study conducted in China reported a significant association between lung cancer and long-term PM exposure[17]. PM was assessed as total suspended particles (TSP), which includes $PM_{2.5}$ and coarse particles, e.g., wind-blown dust. The annual average TSP concentrations for the 1991–2000 study period at individual measurement stations varied between 113 and 499 μg/m^3. The paper reports a conversion factor of 0.325 to convert TSP to $PM_{2.5}$, which translates into annual average $PM_{2.5}$ concentrations between 37 and 162 (average 94) μg/m^3. Overall, these concentrations have increased within China between 1990 and 2005[18]. The RR in the Chinese cohort study was smaller than those in the American ACS and ESCAPE studies and was similar to that of the Rome longitudinal study (Table 1). More studies are needed in settings with high ambient air pollution concentrations, such as in China, to be able to properly interpret the lower RR in the Chinese study. Factors that could play a role include the use of TSP as an exposure metric, potentially non-linear association between air pollution and lung cancer (lower slope at higher concentrations), different particle composition, and differences in population susceptibility. The conversion to $PM_{2.5}$ assumes one universal conversion factor, which may not exist[19]. Limited evidence suggests that the exposure of the general population to coarse particles in ambient air is not associated with long-term health effects (see section **Particle Composition**); thus, if the correlation between $PM_{2.5}$ and TSP is not high, an underestimation of RR may occur when using TSP as an exposure metric. The next section discusses evidence for the shape of the concentration-response function.

The RRs for air pollution, expressed per 10 μg/m^3, are much smaller than those reported for active smoking. In a review of studies published prior to 2000, the combined RR for current active smokers compared to that for never-smokers was 8.3 (95% CI = 7.6–9.3)[20]. In the ACS study, the RRs for active smoking increased from 8 for subjects smoking < 7 cigarettes per day to 39 for those smoking > 42 cigarettes per day[21].

Risk at Low and High $PM_{2.5}$ Concentrations (Concentration-Response Function)

Consistent evidence now exits for the association between lung cancer and $PM_{2.5}$ concentrations between approximately 10 and 30 μg/m^3[4]. However, open questions about the shape of the concentration-response function at low and high concentrations still exist. The World Health Organization (WHO) has recently evaluated the evidence on the shape of the concentration-response function for long-term effects of air pollution[8], and the review concluded that no evidence for a lower threshold for overall mortality exists. Several major cohort studies have evaluated the concentration-response functions for $PM_{2.5}$ and lung cancer within the concentration range in their cohorts[7,9,11,13,22]. In the ESCAPE study, associations

between $PM_{2.5}$ and lung cancer incidence did not deviate significantly from linear, as judged from non-parametric spline models[9]. Subset analyses further demonstrated that $PM_{2.5}$ associations with lung cancer remained after excluding concentrations above 10 μg/m^3. Across all cohorts, average $PM_{2.5}$ concentrations at individual addresses ranged between approximately 3 and 37 μg/m^3. Within individual cohorts, the contrasts were smaller, e.g., between approximately 20 and 35 μg/m^3 for the high exposure Italian Turin cohort and between approximately 5 and 15 μg/m^3 for the Swedish cohorts[9].

In the Six-city study, associations between $PM_{2.5}$ and lung cancer mortality did not deviate from linear and did not show a threshold, and associations were observed between 11 and 24 μg/m^{3}[11]. In the ACS study, associations between $PM_{2.5}$ and lung cancer mortality were supra-linear with a steeper slope of a non-parametric function in the concentration range of approximately 8 to 15 μg/m^3 compared with the slope in the 15 to 25 μg/m^3 range[7]. In a recent evaluation of the never-smoker population in the ACS study, a categorical analysis showed significantly increased HRs for all $PM_{2.5}$ concentration categories compared to the lowest category; the cutpoints of evaluated categories were 11.8 (reference), 14.3, 16.0, and 17.9 μg/m^{3}[22]. The Rome longitudinal cohort study reported no deviation from linear for the association between $PM_{2.5}$ and lung cancer mortality compared to non-parametric splines in a concentration range of 7 to 31 μg/m^3 [13]. Hystad et al.[23] reported increased HRs in a case-control study comparing all exposure categories to the reference category, but the HRs did not show a trend in the concentration range between 4 and 20 μg/m^3, in contrast to the findings of Turner's study[22], Overall, there is no evidence for a lower threshold being present in the associations of $PM_{2.5}$ with lung cancer. Studies have generally found linear associations or functions with a steeper slope at low concentrations. However, the demonstration of a linear association within a study does not imply that the association remains linear beyond the studied range of exposure. No solid evidence on the shape of the concentration-response function above approximately 30 μg/m^3 exists, which is a limitation for calculating the burden of disease in countries with high concentrations[5]. In a previous risk assessment, various alternatives have been evaluated for linear extrapolation, including truncation of the RR at concentrations of 30 or 50 μg/m^3 (assuming a linear function at up to 30 μg/m^3 with no further risk increase at concentrations beyond 30 μg/m^3) and a log concentration model[5].

To address this limitation, the epidemiologic literature of associations of lung cancer mortality with ambient air pollution, passive smoking, and active smoking was combined with the assumption that risks can be combined using the $PM_{2.5}$ concentration as the exposure metric[21]. The analysis, including $PM_{2.5}$ from outdoor air and passive and active smoking data from the ACS study, suggested a linear association with lung cancer across a wide range of concentrations that exceeded those observed in highly polluted areas in China[21]. Recently, Burnett et al.[19] updated this analysis in the framework of the GBD assessment by including more epidemiologic studies on ambient air pollution, more studies on passive smoking (assumed average $PM_{2.5}$ concentration of 35 μg/

m^3), and studies on household solid fuel combustion. An integrated concentration-response function fitted to all data provided a better fit to the range of concentrations than other previously used models[19]. For lung cancer, the linear model fitted the data much better than the truncated risk models, suggesting that risk did increase with increasing concentrations. The linear model fitted only modestly worse for lung cancer than the log concentration model. Because the coefficients of the integrated function were not provided, we could not use this function to calculate the RR for high concentrations. As discussed by Burnett *et al.*[19], combining data from different exposure sources requires substantial assumptions, which stresses the need for more studies in high exposure regions such as China to better establish the risk magnitude. When calculating PAF, we used linear extrapolation for approximation, which was consistent with a recent global assessment using satellite PM$_{2.5}$ data[6].

Population Attributable Risk Fraction

Using the reported RR, we can calculate PAF, which is the fraction of incident lung cancer cases that can be prevented if the PM$_{2.5}$ concentration is reduced for the entire population. To provide a realistic context, it is not useful to calculate the impact of reducing pollution to 0. In the GBD calculations, counterfactual concentrations of 7.5 µg/m^3 [5] and 5.8–8.8 µg/m^3 [19] were used based upon the lowest concentration observed in the ACS study.

We calculated the impact of changes in the annual average concentrations of 10, 20, 30, and 60 µg/m^3. The last change is approximately equivalent to reducing the PM$_{2.5}$ concentration from the average concentration of 94 µg/m^3 calculated in Cao's study[17] to the least stringent interim target value of 35 µg/m^3 set by the WHO[8]. A 10-µg/m^3 reduction is approximately equivalent to reducing the current daily PM$_{2.5}$ concentrations in large European areas to the counterfactual level, which would represent a major change. To achieve all of these reductions would require major policy efforts.

We used the formula PAF = P_e × (RR − 1) / (P_e × (RR − 1) +

1), with P_e being the prevalence of exposure in the population[24]. For a discussion on the calculation and interpretation of PAF, we refer to a commentary in the *American Journal of Public Health*[24]. A specific feature of air pollution exposure is that the entire population is exposed, i.e., P_e = 1. Our formula is then reduced to PAF = (RR−1) / RR. This formula was also used in the GBD calculation[6,19]. Once emitted, PM$_{2.5}$ can travel long distances in the atmosphere, leading to widespread exposure. Furthermore, PM$_{2.5}$ infiltrate readily into homes and offices, which offer little protection. However, this does not imply that air pollution exposure is homogenous within a population. PM$_{2.5}$ concentrations vary significantly within and between countries[18]. The variability of concentrations does not affect our calculations because we calculated the PAF for specific reductions and we assume linear concentration-response functions.

Table 2 presents the calculated PAFs for the four reduction scenarios and various RR estimates from the literature. For a 10-µg/m^3 reduction in the PM$_{2.5}$ concentration, we calculated PAFs of between 3% and 29%. Note that the PAF changed less than linearly with the value of the PM reduction. For the largest reduction, PAFs between 16% and 86% were calculated. These calculations illustrate that reduction of pollution may result in substantial reductions in lung cancer mortality and significant uncertainty regarding the magnitude of the reduction related to the RR estimate. The uncertainty illustrated in **Table 2** does not incorporate the uncertainty about the shape of the concentration-response function at high concentrations. To reduce this uncertainty, more studies in countries with high air pollution concentrations are needed.

Although a possible interaction between smoking and air pollution in the causation of lung cancer may imply that the sum of the PAFs may exceed 100%[25], the highest estimated PAF seemed unrealistically high compared to the known major contribution of smoking to lung cancer cases. In a study using satellite PM$_{2.5}$ data from 132 countries, the RR estimate of 1.14 from the ACS study, and linear extrapolation, the PAF for lung cancer was estimated as 13% (95% CI = 6%–19%)[6]. Applying a model with the logarithm

Table 2. Reduction in lung cancer mortality for specified reductions in the PM$_{2.5}$ concentration, depending on the assumed RR

Assumed RR per 10 µg/m^3	Reduction in PM$_{2.5}$ concentration (µg/m^3)	RR for reduction	PAF (%)
1.40	10	1.40	28.6
	20	1.96	49.0
	30	2.74	63.6
	60	7.53	86.7
1.14	10	1.14	12.3
	20	1.30	23.1
	30	1.48	32.5
	60	2.19	54.4
1.03	10	1.03	2.9
	20	1.06	5.7
	30	1.09	8.5
	60	1.19	16.3

RR, relative risk; PAF, population attributable risk fraction.

of the concentration as the exposure metric resulted in 6% lower estimates compared with the linear model. The difference between the estimates based upon the linear and log models increased for average concentrations above approximately 40 μg/m^3. Burnett *et al.*[19] reported country average PAFs for lung cancer between 0 and 25% based upon estimated average PM$_{2.5}$ concentrations between 2 and 70 μg/m^3 and a non-linear integrated concentration-response function based upon combining evidence from ambient air pollution and smoking. Furthermore, a substantial number of PAF estimates were between 10% and 20%. Our estimates and the recent global estimates are substantially higher than earlier estimates of, at most, a few percent[25]. In the recent decade, new studies have significantly strengthened the evidence for an association between ambient air pollution and lung cancer.

In the current assessment, we have assumed that the RR estimates associated with air pollution are equal for smokers and non-smokers. Because the incidence of lung cancer is much higher in smokers, this assumption implies that a large proportion of the calculated absolute population burden of lung cancer is related to air pollution effects in smokers.

Particle Composition

In the ESCAPE study, we evaluated a large set of air pollutants. The most significant associations were found with the mass-based concentrations of PM$_{2.5}$ and PM$_{10}$[9]. The gaseous pollutant nitrogen dioxide (NO$_2$) and the absorbance of PM$_{2.5}$ (a marker for black carbon) were less significantly associated with lung cancer risk. In the ESCAPE study setting, motorized traffic was the dominant source of NO$_2$ and black carbon in particles. The concentrations of PM$_{2.5}$ and PM$_{10}$ were affected by a wider range of sources, including motorized traffic. Collectively, these observations suggest that the ESCAPE findings are explained by more than just pollutants emitted from motorized traffic. A similar conclusion was drawn in the ESCAPE paper on natural cause mortality in which associations were also most significant with PM$_{2.5}$[26]. In China, coal combustion is more prevalent than in Europe, and a recent paper illustrated the importance of smoky coal in explaining high lung cancer incidence in Xuanwei, China[27]. Because PM$_{2.5}$ is a significant fraction of PM$_{10}$ and was highly correlated with PM$_{10}$ in the ESCAPE study, we could not study the effects of PM$_{2.5}$ independent from PM$_{10}$. However, we did study the independent effects of fine (PM$_{2.5}$) and coarse (PM$_{10}$ – PM$_{2.5}$) particles. In single-pollutant models, the RR for PM$_{2.5}$ was higher than that for coarse particles (1.18 vs. 1.09 per 5 μg/m^3). When PM$_{2.5}$ and coarse particles were added in one model, the RR for PM$_{2.5}$ remained essentially unchanged (RR = 1.25, 95% CI = 0.97–1.61), whereas the effect for coarse particles was further reduced, which suggests that especially PM$_{2.5}$ determines the lung cancer risk. This interpretation could be explained by combustion particles from various sources contributing to cancer. In the ACS study, lung cancer was associated with PM$_{2.5}$, but not with coarse particles[7]. Effect estimates for coarse particles were essentially null. Although the number of studies that evaluated the effects of long-

term exposure to coarse particles on lung cancer is still limited, and we should not draw strong conclusions, the lack of clear associations between coarse particles and lung cancer is consistent with the lack of an association with natural cause and cardiovascular mortality[28]. In contrast, short-term exposure to coarse particles has been associated with increased incidence and mortality[29].

The use of PM$_{2.5}$ and PM$_{10}$ as particle metrics in studies of health effects relies on an assumption that the composition of the particles does not play an important role, which seems unlikely and may especially be problematic when associations are compared across settings with different sources contributing to PMs. Further work on the components of PMs that determine lung cancer risk is important for guiding effective air quality policies. Candidates for causal agents in the development of lung cancer, including polycyclic aromatic hydrocarbons (PAH), N-nitroso compounds[9], and transition metals that have been linked to oxidative stress, should be further investigated.

Other Cancer Sites

From the beginning of this research field, diseases of the respiratory system have been a natural focus for studies on air pollution and health. However, during the last decades, associations of air pollution with adverse effects related to the cardiovascular system have been established, and other types of diseases are now being investigated for possible associations with air pollution[30,31]. Because the postulated mechanism of air pollutants involves systemic oxidative stress and inflammation, systemic effects are plausible. It is, therefore, possible that air pollution is affecting cancers other than lung cancer. Although an insufficient number of studies using state-of-the-art exposure assessment have evaluated cancers other than lung cancer, some evidence from epidemiologic studies assessing occupational and residential exposure suggests an association between air pollution and bladder cancer[32,33]. Other cancers in adults for which associations have been suggested, but with less evidence, include brain tumors[33,34], liver cancer[33], breast cancer[33,35,36], gastric cancer[37], and hematologic cancers[38]. Studies on childhood cancer are inconsistent, although some large studies indicate a slightly increased risk of acute lymphoblastic leukemia[39,40].

Histological Subtype

In the United States, a relative increase in the incidence of lung adenocarcinoma and decrease in the incidence of lung squamous cell carcinoma have been observed[25,41]. Additionally, the distribution of histological subtypes of lung cancer differs between smokers and non-smokers, with adenocarcinoma being the only of the major subtypes that also develops in a substantial number of non-smokers. These observations, combined with the apparently stronger association of air pollution with lung adenocarcinoma than with lung squamous cell carcinoma in the ESCAPE study, calls for further studies of air pollution and histological subtypes of lung cancer.

Interaction with Smoking

In the ESCAPE study, we did not find significant differences in the associations between PM exposure and lung cancer risk for subgroups defined by sex, age, diet, and smoking status. However, the power to detect significant differences between subgroups was limited. Further work based on a large study would, therefore, be useful.

In particular, studies on the interaction between smoking and PM air pollution seem warranted. Several studies have shown stronger associations between PM air pollution and risk for lung cancer among non-smokers compared with smokers, and the possible mechanisms for such an interaction might include differences in lung deposition and competition for metabolic activation[42]. Furthermore, interactions with a clear distinction between RR and absolute risks for lung cancer should be studied. Even a higher RR for lung cancer in association with air pollution among never-smokers could imply fewer (absolute) cases of lung cancer than a lower (although increased) RR among smokers, simply because the basic lung cancer incidence is much higher among smokers.

Conclusions

Air pollution has been consistently associated with lung cancer in epidemiologic studies. The RRs for ambient air pollution are much smaller than those for active smoking; however, air pollution affects the entire population. A reduction in $PM_{2.5}$ air pollution concentrations will result in substantial reductions in the number of lung cancer cases in the population. The magnitude of PAF is uncertain because of uncertainties in the magnitude of RRs, the shape of the concentration-response function, especially at high concentrations, and differences in particle composition. Therefore, new epidemiologic studies, especially in high pollution settings, are useful. To fully assess the cancer burden of exposure to ambient air pollution, other cancer sites should be investigated.

Acknowledgement

References

[1] Vineis P, Wild CP. Global cancer patterns: causes and prevention. Lancet, 2014,383:549–557.

[2] Curwen MP, Kennaway EL, Kennaway NM. The incidence of cancer of the lung and larynx in urban and rural districts. Br J Cancer, 1954,8:181–198.

[3] Vineis P, Forastiere F, Hoek G, et al. Outdoor air pollution and lung cancer: recent epidemiologic evidence. Int J Cancer, 2004,20:647–652.

[4] Loomis D, Grosse Y, Lauby-Secretan B, et al. The International Agency for Research on Cancer Monograph Working Group IARC. The carcinogenicity of outdoor air pollution. Lancet Oncol, 2013,14:1262–1263.

[5] Cohen AJ, Ross Anderson H, Ostro B, et al. The global burden of disease due to outdoor air pollution. J Toxicol Environ Health A, 2005,68:1301–1307.

[6] Evans J, van Donkelaar A, Martin RV, et al. Estimates of global mortality attributable to particulate air pollution using satellite imagery. Environ Res, 2013,120:33–42.

[7] Pope CA 3rd, Burnett RT, Thun MJ, et al. Lung cancer, cardio-pulmonary mortality, and long–term exposure to fine particulate air pollution. JAMA, 2002,287:1132–1141.

[8] WHO. Review of evidence on health aspects of air pollution—REVIHAAP project: final technical report. 2013. Available at http://www.euro.who.int/en/health-topics/environment-and-health/air-qulity/publications/2013/review-of-evidence-on-health-aspects-of–air-pollution-revihaap-project-final-technical-report.

[9] Raaschou-Nielsen O, Andersen ZJ, Beelen R, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol, 2013,14:813–822.

[10] Eeftens M, Beelen R, de Hoogh K, et al. Development of Land Use Regression Models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas; results of the ESCAPE project. Environ Sci Technol, 2012,16:11195–11205.

[11] Lepeule J, Laden F, Dockery D, et al. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. Environ Health Perspect, 2012, 120:965–970.

[12] Beelen R, Hoek G, van den Brandt P, et al. Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology, 2008, 19:702–710.

[13] Cesaroni G, Badaloni C, Gariazzo C, et al. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ Health Perspect, 2013, 121:324–331.

[14] Carey IM, Atkinson RW, Kent AJ, et al. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med, 2013,187:1226–1233.

[15] Katanoda K, Sobue T, Satoh H, et al. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J Epidemiol, 2011, 21:132–143.

[16] Lipsett MJ, Ostro BD, Reynolds P, et al. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. Am J Respir Crit Care Med, 2011,184:828–835.

[17] Cao J, Yang C, Li J, et al. Association between long-term exposure to outdoor air pollution and mortality in China: a cohort study. J Hazard Material, 2011,186:1594–1600.

[18] Brauer M, Amann M, Burnett RT, et al. Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. Environ Sci Technol, 2012,17:652–660.

[19] Burnett RT, Pope CA 3rd, Ezzati M, et al. An integrated risk function for estimating the global burden of disease attributable to ambient

fine particulate matter exposure. Environ Health Perspect, 2014 Feb 11. [Epub ahead of print]

[20] Lee PN, Forey BA, Coombs KJ. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. BMC Cancer, 2012,12:385.

[21] Pope CA 3rd, Burnett RT, Turner MC, et al. Lung cancer and cardio-vascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. Environ Health Perspect, 2011,119:1616–1621.

[22] Turner MC, Krewski D, Pope CA, et al. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am J Respir Crit Care Med, 2011,184:1374–1381.

[23] Hystad P, Demers PA, Johnson KC, et al. Long-term residential exposure to air pollution and lung cancer risk. Epidemiology, 2013, 24:762–772.

[24] Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health, 1998,88:15–19.

[25] Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest, 2003,123:21S–49S.

[26] Beelen R, Raaschou-Nielsen O, Stafoggia M. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet, 2013,383:785–795,

[27] Kim C, Chapman RS, Hu W, et al. Smoky coal, tobacco smoking, and lung cancer risk in Xuanwei, China. Lung Cancer, 2014,84:31–35.

[28] Hoek G, Krishnan RM, Beelen R, et al. Long-term air pollution exposure and cardiorespiratory mortality: a review. Environ Health, 2013,12:43.

[29] Brunekreef B, Forsberg B. Epidemiological evidence of effects of coarse airborne particles on health. Eur Respir J, 2005,26:309–318.

[30] Rückerl R, Schneider A, Breitner S, et al. Health effects of particulate air pollution: a review of epidemiological evidence. Inhal Toxicol, 2011,23:555–592.

[31] Raaschou-Nielsen O, Sørensen M, Ketzel M, et al. Long-term exposure to traffic-related air pollution and diabetes-associated mortality: a cohort study. Diabetologia, 2013,56:36–46.

[32] Castaño-Vinyals G, Cantor KP, Malats N, et al. Air pollution and risk of urinary bladder cancer in a case-control study in Spain. Occup Environ Med, 2008,65:56–60.

[33] Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, et al. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ Health, 2011,10:67.

[34] McKean-Cowdin R, Calle EE, Peters JM, et al. Ambient air pollution and brain cancer mortality. Cancer Causes Control, 2009,20:1645–1651.

[35] Nie J, Beyea J, Bonner MR, et al. Exposure to traffic emissions throughout life and risk of breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. Cancer Causes Control, 2007,18:947–955.

[36] Crouse DL, Goldberg MS, Ross NA, et al. Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case-control study. Environ Health Perspect, 2010,118:1578–1583.

[37] Sjödahl K, Jansson C, Bergdahl IA, et al. Airborne exposures and risk of gastric cancer: a prospective cohort study. Int J Cancer, 2007,120:2013–2018.

[38] Johnson KC, Pan S, Fry R, et al. Canadian Cancer Registries Epidemiology Research Group. Residential proximity to industrial plants and non-Hodgkin lymphoma. Epidemiology, 2003,14:687–693.

[39] Ghosh JK, Heck JE, Cockburn M, et al. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. Am J Epidemiol, 2013,178:1233–1239.

[40] Heck JE, Wu J, Lombardi C, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect, 2013,121:1385–1391.

[41] Chen F, Cole P, Bina WF. Time trend and geographic patterns of lung adenocarcinoma in the United States, 1973–2002. Cancer Epidemiol Biomarkers Prev, 2007,16:2724–2729.

[42] Silverman DT, Samanic CM, Lubin JH, et al. The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. J Natl Cancer Inst, 2012,104:855–868.