Review Article

Pollutional haze as a potential cause of lung cancer

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Abstract: Along with fast economic growth over the past few decades, the world is faced with cumulatively serious environmental pollution and now is paying increased attention to pollutional haze. In the last few years, multiple epidemiological studies and animal models have provided compelling evidences that inhalation of pollutional haze could be linked to several adverse health effects. Since the respiratory tract is the crucial passageway of entry of pollutional haze, the lung is the main affected organ. Therefore, here, we reviewed some of the important information around long-term exposure to pollutional haze and lung cancer, as well as highlight important roles of pollutional haze in human lung carcinogenesis, providing evidence for pollutional haze acting as another risk factor for lung cancer.

Keywords: Pollutional haze; lung cancer; risk factor; mortality

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Introduction

Lung cancer remains one of the most common cancers and accounts for the highest death toll of all cancer deaths among men and women (1,2). It is estimated that lung cancer accounts for more than one-quarter of all cancer in 2014 by American Cancer Society (ACS) (2). In spite of recent advances in screening and treatment, 5-year survival rate of lung cancer remains relatively low (3). Therefore, a better understanding the contribution of risk factors to lung cancer and prevention through lifestyle is needed for reducing the increasing burden of cancers worldwide (4). Results of several previous studies have already proved that smoking is a leading cause of lung cancer (5). However, it is notable that smoking cannot explain the relatively high rates of lung cancer which are observed among non-smokers and never-smokers. Therefore, some evidences suggested that other factors, such as environmental factors, family history of lung cancer and occupational exposures, also can contribute to lung tumorigenesis (6-8). More recently, the focus of scientists is shifting to one of the most serious yet ambiguous risk factor for lung cancer: air pollution, especially pollutional haze.

Along with the great economic benefits and urbanization in the world, haze weather occurred and impacted a few regions severely, for example, the Yangtze River Delta, the HuaBei Plain in Northern China and the Pearl River Delta (PRD) (9,10). The main origin of pollutional haze is form coal burning, motor vehicle exhaust, windblown soil and forest fires (10). In order to exclude the confounding influence of special weather conditions like rain, snow and fog, haze weather was defined as daily visibility <10 km with relative humidity <90% (10). In the last few decades, increasing studies have provided compelling evidences that inhalation of pollutional haze could be linked to several adverse health effects (11-13). Furthermore, among various compositions of pollutional haze, particulate matter (PM) might be most strongly linked to increased morbidity and mortality worldwide (11). Since the respiratory tract is the crucial passageway of entry of pollutional haze, the lung is the main affected organ (14). Time-series and prospective studies have demonstrated that the potential adverse effects of pollutional haze exposure on respiratory system could be divided into acute and chronic health effect. In the short term, acute exposure to pollutional haze leads to an acute condition (15-17). The APHEA project found that pollutional haze not only is associated with daily respiratory disease exacerbations but also increased daily mortality of respiratory disease, such as asthma (18,19). Although

acute respiratory effects are well established, evidence for adverse long-term effects of pollutional haze on respiratory disease in adults is more limited, in particular in Asian countries. Of late, several cohort studies have shown that lung cancer is a serious long-term effect of pollutional haze exposure and suggested an strong association mostly in never-smokers, non-smokers and in people with low fruit consumption (20-26). Therefore, in this review, we will attempt to organize some of the important information around pollutional haze and lung cancer, with discussion of open questions and future prospects. Additionally, we will highlight some functional role of pollutional haze in human lung cancer and thus provide evidence for or against pollutional haze acting as another risk factor for lung cancer.

Pollutional haze and lung cancer

As described above, the range of respiratory diseases as a result of pollutional haze exposure is wide. Given the strong correlation between tobacco and lung cancer risk, the speculation about the association between haze and lung cancer is more reasonable, particularly among never-smokers (11,23,27). Additionally, several epidemiological studies showed that in the past few decades overall incidence rates of lung cancer in developed countries was stable and that the major histological types of lung cancer shifted from squamous cell carcinomas to adenocarcinomas (28). Raaschou-Nielsen and colleagues considered that changes in tobacco blends and pollutional haze might contribute to the shifts (29-31).

Pollutional haze and lung cancer incidence

Even though it is suspected that lung cancer is a disease impacted by environmental exposure, the relationship between lung cancer and pollutional haze is very difficult to study (8-10). The main challenges are elimination of confounding factors and assessment of individual long term air pollution exposure in prospective cohort studies (32). However, there were several cohort and case-control studies showing the close relationship between the risk for lung cancer and different composition of pollutional haze exposure.

An elegant study published in Thorax by Nafstad *et al*. have combined the information about residential ambient air pollution from 1974 to 1998 for a cohort of 16,209 40- to 49-year-old men living in Oslo with the information on cancer development from the Norwegian cancer register (32). During the follow up period, they found that 418 men developed lung cancer. And after adjustment for age, tobacco smoke exposure, and length of education, the incidence rate ratios for lung cancer between 1974 and 1978 was 1.08 [95% confidence interval (CI), 1.02-1.15] for a 10 μg/m^3 increase in nitrogen oxide (NO_X) exposure and 1.01 (95% CI, 0.94-1.08) for sulphur dioxide (SO_2) exposure. This result was consistent with the result of another cohorts study conducted by Raaschou-Nielsen *et al*. They identified 679 lung cancer cases in the Danish Cancer Registry from the members of three prospective cohorts and selected 3,481 persons from the same cohorts for a comparison group according to the principle of the case-cohort design (20). When compared with NO_X concentrations of <30 μg/m^3, the risk ratio for developing lung cancer were 1.30 (95% CI, 1.07-1.57) and 1.45 (95% CI, 1.12-1.88) for 30-72 and >72 μg/m^3, respectively. Moreover, through the dose-response analysis, this study showed a 37% increase in lung cancer rate per 100 μg/m^3 NO_X. These data suggested that urban air pollution might have an effect on lung cancer but much weaker than the effect caused by smoking. However, it is notably that much stronger associations are observed in non-smokers and those with a longer school attendance or with relatively low dietary intake of fruit (26). Moreover, considering the different frequency distributions of subtypes of lung cancer throughout the world and a significant association between tobacco and squamous/small cell carcinoma in both genders (33-35), inhalation of pollutional haze might be a critical factor contributing to the shift in frequency of lung cancer types. Data from Taiwan showed the significant correlation coefficients between the mean concentrations of NO_X (r=0.41, P=0.04) and CO (r=0.47, P=0.02) and the ratio of adenocarcinoma/squamous cell carcinoma in females (36). This might mean that the worse the pollutional haze, the higher the adenocarcinoma rate, regardless of gender. Nonetheless, a stronger relationship between concentrations of NO_X and risk for lung squamous cell and small-cell carcinomas than for adenocarcinoma was reported in cohorts study in Danish which was mentioned above (20). Hence, to confirm the hypothesis, future assessments of the correlation between pollutional haze and specific types of lung cancer are urgent needed.

Besides NO_X, the relationship between ambient concentrations of other composition of pollutional haze particulate and lung cancer incidence was also investigated. In 1998, based on the data form a cohort study conducted by Beeson *et al*., the correlationship between PM with an aerodynamic diameter ≤10 μm (PM_{10}) or sulfur dioxide and the risks of lung cancer incident in nonsmoking California adults was clarified (37). Meanwhile, the role of fine PM with

an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) in lung cancer was showed in 17 European cohorts, adding substantially to the weight of the epidemiological evidence (29). Yorifuji and colleagues integrated effect estimates from 17 cohorts with standardized protocols and undertook a meta-analysis to reduce the sampling bias and systemic or random errors reported previously (38). They showed that exposure to PM significantly increased the risk of lung cancer, particularly adenocarcinoma, with hazard ratio (HR) 1.51 (1.10-2.08) for PM_{10} (per 10 μg/m^3) and 1.55 (1.05-2.29) for $PM_{2.5}$ (per 5 μg/m^3). However, in view of wide distribution of pollutional haze, future collaborative studies in other continents are more necessary in providing further insights into the risk of lung cancer caused by air pollution exposure.

Pollutional haze and lung cancer mortality

In addition to the established role of pollutional haze in increasing lung cancer morbidity, long-term epidemiological studies also provide evidences that exposure to pollutional haze has been linked to increased mortality, including all-cause, lung cancer and cardiopulmonary mortality (21,23,39-42). In 2002, the study conducted by Pope has provided "the best evidence yet" for the association between long-term exposure to pollutional haze and deaths from lung cancer and heart disease in USA (42). They indicated that each raise in long-term average $PM_{2.5}$ concentrations (10 μg/m^3) was associated with an approximately 8% increase in lung cancer mortality. Although the various factors affecting death rates were controlled for by using questionnaire results in the study, smoking status was still a potential residual confounding factor. To address this issue, the subsequent large prospective study surveyed associations between $PM_{2.5}$ exposure and lung cancer mortality in a 26-year follow-up of 188,699 lifelong never-smokers (23). In accordance with the previous the study, it also showed positive associations, with a 15-27% increase in the relative risk of lung cancer death for each 10 μg/m^3 increase in $PM_{2.5}$ concentrations. What's more, the association was stronger in those with a history of asthma, a normal body mass index (BMI) or any chronic lung disease (CLD) at enrollment but was similar in other participant characteristics, such as sex, attained age and educational attainment. Taken together, these results of epidemiological studies conducted in North America or Europe clearly showed positive associations between pollutional haze and lung cancer mortality.

Most recently, positive exposure response relations were consistently observed in a longitudinal study in New Zealand conducted by Dr. Hales (39). Based on the national census, they found substantially strong effects of PM_{10} on respiratory deaths (including lung cancers), 14% (5-23%) and lung cancer, 16% (4-29%). However, there was a major limitation in this study, which might probably underestimate the strength of association due to the probable misclassification of the PM_{10} exposure. Beyond that, another cohort study in Shizuoke, Japan indicated a stronger adverse effect of air pollution on lung cancer mortality among non-smokers compared to ex- and current smokers (40). Moreover, in consequence of extensive industrial development, substantial energy consumption, China now produced a larger number of major pollutants which cause serious pollutional haze (43). With the emphasis on effects of air pollution on human health, the relationship between long-term exposure to pollutional haze and mortality has also been extensively examined in Chinese cities (44-47) and these studies provided further evidence supporting plausibility and coherence of the adverse effects of pollutional haze on mortality worldwide.

The carcinogenicity of pollutional haze in vivo

The findings of epidemiological studies strongly confirmed the hypothesis that pollutional haze contribute to lung tumorigenesis in humans. Nevertheless, there are only a few studies assessing the occurrence of lung cancer in animals due to directly exposure to pollutional haze. Several studies showed that injecting subcutaneously with organic solvent extracted material from particles into mice increased the incidence of injection-site tumors (48-50). Not only that, but in 1997, an animal model was performed to investigate the association between air pollution and lung neoplasia (51). Increases in the risk of lung adenocarcinoma and in incidence of urethane-induced adenomas were observed in the mice which were chronically exposed to traffic-related outdoor air pollution in Brazil.

Taken together, both epidemiological studies and animal model indicated carcinogenicity of pollutional haze and significant associations of pollutional haze with morbidity and mortality. Even though smoking duration appeared to have a much larger impact on lung cancer mortality than pollutional haze, the public health effect of haze is quite large because everybody is daily or long-term exposed. It was reported an adverse effect on health even below the current European Union air pollution limit values (40 μg/m^3 for PM_{10} and 25 μg/m^3 for $PM_{2.5}$). Thus, our better understanding of the relationship between pollutants and lung cancer will provide further insights into safe thresholds for health effects caused by long-term exposure to pollutional haze.

The underlying molecular mechanism responsible for human lung cancer

In spite that the overall picture is that evidence for an association between different composition of pollutional haze exposure and lung cancer is accumulating, underlying molecular mechanism responsible for the impact cause by pollutional haze is only the tip of the iceberg. Given the complexity of composition of pollutional, changes in the expression of genes which are involved in oxidative stress response, DNA damage and repair, inflammation, immune and epigenetic effects are observed during exposure to pollutional haze (50,52). Of the plausible biological mechanisms explaining pollutional haze health effects, oxidative burden, especially PM-oxidative burden, have a meaningful impact on haze induced adverse health outcomes (53). This suggested the reason why fruit intake can modify the effect of air pollution on the risk for lung cancer (54,55). Thus, fruit consumption could also be a marker of confounding factors, which might have contributed to the results. Now that the extracts of PM form pollutional haze can induce mutations in bacteria, the International Agency for Research on Cancer (IARC) Working Group concluded that it is reliable that cytogenetic abnormalities and mutations, as a consequence of exposures to outdoor air pollution in real-world, might also play a critical role in respiratory diseases (52,56,57).

Concluding remarks

In general, an increasing number studies provided strong evidence for an association between pollutional haze exposure and lung cancer. Based on sufficient evidence form epidemiological or mechanistic studies and animal models, the IARC Working Group unanimously decided to classify outdoor pollutional haze, in particular PM, as carcinogenic to humans (IARC Group 1) (50). Moreover, now that the negative impact of air pollution on health is now becoming clear, both the public and authorities are getting increasingly aware of pollutional haze. And many strategies, such as changes in engineering control equipment, recycling, and air cleaning systems, have been applied to address pollutional haze and minimise its health risks (17,58). However, there are still significant gaps in our current efforts to prevent and control air pollution. According to the WHO's recommendations, the USA and Europe should lower their regulatory limits for PM concentrations (59). Indeed, studies clearly supported a possibility that even small reductions in these could confer substantial population health benefits (60). Thus, setting out safe thresholds for health effects which are caused by exposure to different composition of pollutional haze is more urgent, at this stage. In addition, with unsustainable development over the past three decades, China is faced with difficulties in addressing the challenges of environmental pollution and, at the same time, suffering from serious public health effects caused by haze weather (43). Compared with Europe and North America, limited studies have been conducted in China on the association between fine particulate concentration and lung cancer mainly due to a lack of monitoring data. Therefore, China has been equipped with 496 monitoring stations and started to monitor and releasing real-time air monitoring data, since the beginning of 2013 (43,61). Besides, China has unveiled new measures and strict targets to help control its notoriously pollutional haze. Hopefully, these tough measures should lead to an improvement in China's air quality and remarkable public health benefits.

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Footnote

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