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Air pollution as a risk factor for lung cancer

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ABSTRACT

Over the past decade, an increasing body of scientific evidence has accrued associating outdoor air pollution with certain types of cancer. Ambient air, particularly in densely populated urban environments, contains a variety of known human carcinogens such as benzo[α]pyrene and benzene, inorganic compounds (e.g., arsenic and chromium), and radionuclides. Now, it is well recognized that urbanization and lung cancer mortality are linked. This association could arise from differences in the distributions of other lung cancer risk factors, such as smoking and occupational exposures, by degree of urbanization, etc. Air pollution has positively been associated with lung cancer mortality and cardiopulmonary disease mortality, but not with mortality from other causes combined. New studies will need to develop and apply improved epidemiologic methods and to compare the effect of exposure to the pollutant mixtures on lung cancer in different cities while effectively controlling confounding factors including cigarette smoking and diet.

KEY WORDS: *Lung Neoplasms; Risk Factors; Air Pollutants; Epidemiology*

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INTRODUCTION

Air pollution is often suggested as being partly accountable for an increased incidence of lung cancer in cities. Over the past decade, an increasing body of scientific evidence has accrued associating outdoor air pollution with certain types of cancer. In many researching scientists have found out that exposure to air pollution, even at low levels, can lead to a wide range of adverse health effects including lung cancer. The consistency of the findings of epidemiologic studies regarding the effects of air pollution across a wide range of nonmalignant health end points suggests the toxic properties of this pollution. In addition, experimental toxicology studies have documented the mutagenic and carcinogenic properties of combustion-source air pollution such as diesel exhaust. A problem with epidemiological studies is that the comparatively small effect of air pollution is difficult to identify in the presence of larger and variable effects of cigarette smoking and other factors.

Several attempts have been made to clearly evaluate the role of air pollution on lung cancer etiology during the 1960s and 1970s. In 1976, in the International Agency for Research on Cancer (IARC) review Higgins concluded that the existing studies "give support for the view that air pollution is a factor in this disease. But the effect of pollution cannot be large. It is likely to be a small fraction (possibly a tenth) of the effect of cigarette smoking." (1). Almost five decades have gone since the effect of the so-called urban factor on lung cancer has been suggested (2). Considering the various estimates made over the last 35 years, it is likely that the effect of air pollution on lung cancer is something greater than zero and it is unlikely that the estimate exceeds 2% of all lung cancers. Thus, the effect on all cancers is likely to be less than 1% of all cases (3,4).

European data on the link between air pollution and lung cancer have a great advantage of providing information on confounders and exposure to traffic derived pollutants at individual rather than at community levels (5-8). When interpreting the findings regarding the impact of air pollution on the general population, it should not be forgotten that the greatest exposures to vehicular fuels and exhausts occur occupationally.

During a typical day, the average adult inhales about 10,000 liters of air. The carcinogens that are present in the air at low concentrations may be of concern as a risk factor for cancer and unavoidably affects the whole population and can interact with other carcinogenic factors, potentiating their effects. The World Health Organization reports that 3 million people now die each year from the effects of air pollution. Thus, when considering cancer as well as other diseases, there is a reason to control air pollution and keep it at a minimum (9).

Ambient air, particularly in densely populated urban environments, contains a variety of known human carcinogens such as benzo[α]pyrene and benzene; inorganic compounds for example arsenic and chromium, and radionuclides. These substances are present as components of complex mixtures, which may include carbon-based particles that absorb organic compounds, oxidants such as ozone, and sulfuric acid in aerosol form. The combustion of fossil fuels for power generation or transportation is the primary source of many organic and inorganic compounds, oxidants, and acids, and contributes a lot to particulate air pollution in most urban settings. About half of air pollution health effects can be traced to air pollution from vehicle emissions (10).

An individual's total exposure to air pollution depends on indoor as well as outdoor exposures. Indoor air quality has large potential health implications because people may spend considerable amounts of time indoors. Indoor air pollution may stem from incoming outdoor air or may originate indoors from tobacco smoking, building materials, soil gases, household products, and combustion from heating and cooking. The exposure of human populations to carcinogens in outdoor air may be the result of proximity to more localized sources such as industrial facilities, small businesses, municipal facilities, or areas with high vehicular traffic.

EPIDEMIOLOGICAL EVIDENCE

Researches start to study the role of air pollution in lung cancer motivated with epidemic of lung cancer rising in the 1950s. Air pollution has been assessed as a risk factor for lung cancer in both case-control and cohort studies, but exposure to outdoor air pollution has been associated with small relative increases in lung cancer in studies conducted over the past five decades compared with role of cigarette smoking. Also, extrapolation of the risks associated with occupational exposures to the lower concentration of carcinogens in polluted ambient air leads to the conclusion that a small proportion of lung cancer cases could be due to air pollution (11-13). Therefore, interest about links between air pollution and cancer had fallen off for a few decades.

Now, it is well recognized that urbanization and lung cancer mortality are linked (14-16). This association could arise from differences in the distribution of other lung cancer risk factors, such as smoking and occupational exposures, degree of urbanization, etc. Modification for these factors may considerably intensify the effect of urban location (17,18), but an urban effect persists in a number of studies (19). Recent prospective cohort and case-control studies, which have taken into account tobacco smoking, occupational and other risk factors, have continued to report increases in lung cancer connected with air pollution.

The American Cancer Society prospective mortality study (20), which included 10 749 lung cancer deaths and the risk factor data for approximately 500 000 adults, has linked air pollution data for metropolitan areas throughout the United States and combined them with vital status and cause of death data. They conclude that long-term exposure to combustion-related fine particulate air pollution is an important environmental risk factor for lung cancer mortality and that coarse particle fraction and total suspended particles were not consistently associated with mortality. They found out that each 10 $\mu g/m^3$ raise of fine particles ($PM_{2.5}$) was associated with an 8%-14% increase in lung cancer. Detected range of $PM_{2.5}$ in the study was 9 to 34 $\mu g/m^3$.

In a cohort studies, Dockery and colleagues (21) reported the results of a 14 to 16-year prospective follow-up of 8 111 adults living in six US cities. They evaluated associations between air pollution and mortality. Mortality was ascertained through 1989. They also were monitored levels of TSP, PM_{10}, $PM_{2.5}$, SO_4, H^+, SO_2, NO_2, and O_3. Mortality risk was estimated by Cox proportional hazards regression model, directly controlling for individual differences in age, sex, cigarette smoking, BMI, education, and occupational exposure. It is recognized that in the city with the highest fine particulate concentration adjusted risk of lung cancer mortality was 1.4 times higher than that in the least polluted city. The range of PM_{10} was 18 to 47 $\mu g/m^3$ and the range of $PM_{2.5}$ was 11 to 30$\mu g/m^3$.

Associations between mortality risk and air pollution were strongest for respirable particles and sulfates. Air pollution was positively associated with lung cancer mortality and cardiopulmonary disease mortality-but not with mortality from other causes combined. After adjustment for the other risk factors, a 37% excess lung cancer risk was observed for a difference in fine particle pollution equal to that of the most polluted versus the least polluted city.

Pope and colleagues (22) in their study observed that residence in areas with high sulfate concentrations was associated with an increased risk of lung cancer (95% confidence interval, 1.1 to 1.7) after adjustment for occupational exposures. However, unlike the Six-Cities study, (20) fine particulate concentration was not associated with lung cancer risk.

Some case-control studies (23-25) have reported that air pollution is moderately associated with elevated risks of lung cancer, but others (26,27) have reported no association. This also complicates efforts to estimate the numbers of cases in which both air pollution and smoking play a role. A study that includes large numbers of well documented never smokers may be the only approach that could address these concerns, if feasible. Past approaches to exposure measurement also contribute to uncertainty in risk estimates. Doll and Peto (11) in their old review of the causes of cancer estimated that probably about 1% to 2% of lung cancer cases were related to air pollution. Recent findings remind us that it was a realistic estimate. Tango (28) use Poisson regression model based on vital statistic for time trends of mortality to detect the long-term effects of common levels of air pollution on lung cancer in Tokyo metropolitan area from 1972 to 1988. Analysis supported the existence of long-term effects of air pollution on lung cancer.

A study of the association of urban air pollution and lung cancer in Stockholm, Sweden estimated exposures to motor vehicle-related air pollution (NO_x/NO_2) and heating-related air pollution (SO_2) for more than 3 000 men aged 40 to 75 years (5). Approximately 1 000 of the men were diagnosed with lung cancer from 1985 to1990, and more than 2000 men served as controls. Average traffic-related NO_2 exposure over a 30-year period was associated with a 20 % increase in the risk of lung cancer for the maximum exposed men. The study reported increase of lung cancer incidence for 40% in the group of people who were exposed to the highest average value of traffic-related NO_2 during the last 20 years. This suggests a long latency period from exposure to disease, which is consistent with the latency of lung cancer from smoking and other environmental causes. Little association was observed between SO_2 and lung cancer. Authors concluded that urban air pollution increases lung cancer risk and that vehicle emissions may be particularly significant.

In Copenhagen, Denmark (29), an analysis of air pollution found out that traffic sources contributed 90% of the organic hydrocarbon levels on working days and 60% during weekends. The study concluded that the direct effect of exposure to these organic compounds and other mutagens in the urban air was a maximum of five lung cancer cases each year per one million persons.

In Hamburg, Germany, a study of the link between traffic-related air pollution and cancer was conducted. Cancer frequency for almost 62 000 people living in street with high levels of traffic (>30 000 cars/day) were related to about 12 000 cancer cases for the period 1970-1972. The study found an excess risk of 6 % for all cancers, with a 12% overall excess cancer risk for men (30).

In the early 20th century, many studies compare lung cancer rates between urban and rural environments and generally have found facts of increased lung cancer in urban dwellers. Moreover, cancer incidence data collected by IARC continue to show evidence of urban-rural differences in lung cancer rates with urban to rural rate ratios between 1.0-1.9 (31-33).

Studies of population migration from high-exposure countries to lower-exposure countries imply that migrants have permanent risk related to their country of origin and previous exposures. Several studies have compared lung cancer rates between areas with differing levels of air pollution. Most of these studies suffer from the lack of a direct measure of the air pollution burden experienced by the study population (6,34-37).

The association between incidence of lung cancer and long-term air pollution exposure was investigated in a cohort of Oslo men from 1972/73 to 1998. Data from a follow up study on cardiovascular risk factors among 16 209, 40 to 49 year old Oslo men in 1972/73 were linked to data from the Norwegian cancer register, the Norwegian death Register, and estimates of average yearly air pollution levels at the participants' home address from 1974 to 1998. During the follow up period, 418 men developed lung cancer. Controlling for age, smoking habits, and length of education, the adjusted risk ratio for developing lung cancer was 1.08 (95% CI = 1.02 to 1.15) for a 10 $\mu g/m^3$ increase in average home address nitrogen oxide exposure. Corresponding figures for a 10 $\mu g/m^3$ increase in sulfur dioxide were 1.01 (95% CI = 0.94 to 1.08). They conclude that urban air pollution may increase the risk of developing lung cancer and therefore favor the view that traffic related air pollution increases the risk of developing lung cancer. The lack of an association between SO_2 and lung cancer could have been caused by low SO_2 concentrations. Particulate and sulfate pollution has also been found to be associated with lung cancer in some cohort studies (20) and some studies have found positive associations between nitrogen oxides and lung cancer too (38-41). The study followed a cohort of Seventh Day Adventists with extremely low prevalence of smoking and relatively uniform and healthy dietary patterns found out excess lung cancer in relation to both particle and ozone exposure (42).

Recent knowledge about ambient air pollution and lung cancer is based mostly on the experience of populations of industrialized nations. The populations of the developing countries, on the other hand, are exposed to levels of air pollution from combustion sources in both ambient and indoor environments that equal or exceed those commonly observed in the industrialized West. Within the developing countries, the highest exposures, particularly among women, have been to indoor air pollution from the combustion of coal and biomass fuels for cooking and heating. In rural Chinese homes, for example, typical concentrations of coal smoke exceeded 500 $\mu g/m^3$ and frequently exceeded 1 mg/m^3. Smith and Liu (41) have recently reviewed the epidemiologic literature on indoor air pollution and lung cancer in the developing countries and found consistent evidence of increased rates of lung cancer associated with indoor cooking and heating with coal mainly in studies done in China. A much smaller group of studies revealed no consistent association of lung cancer with indoor use of biomass fuels.

There have been a few researches on ambient air pollution and lung cancer among urban residents of the rapidly rising cities of the developing countries. Levels of urban air pollution from local stationary and mobile sources are recognized as an important environmental problem in the cities of the poorest developing countries. WHO's Global Environmental Monitoring System observed average ambient concentrations of total suspended particles of 300 mg/m^3 and in places where coal is used for fuel, such as poor communities in South Africa, may exceed 1g/m^3. According to these data, it can be expected that the high levels of ambient air pollution would be associated with greater excess lung cancer occurrence than has been observed in industrialized settings. Although there are currently few reliable data, a case-control study in Shenyang, China (42) observed 2-fold increases in lung cancer risk after adjustment for age, education, and smoking, among residents in "smoky" areas of the city and 1.5-fold increases among those in "somewhat or slightly smoky" areas. Obviously, we need better data if we wish to make such estimates in the developing world.

MAGNITUDE OF CANCER RISK

Our understanding of the relation between urban air pollution and lung cancer has mostly been based on ecological or semi ecological studies (42-46), and few studies have so far tried to assess long term air pollution exposure on an individual level.

In the US, estimates of the population-attributable risk of lung cancer due to air pollution have been published recently but they have used evidently different methods and their results span an order of magnitude. For example, Doll and Peto (11) used estimates of benzo[α]pyrene in urban air and extrapolated from occupational studies of PAH-exposed workers. They estimated that less than 1% of future lung cancer would be due to air pollution from the burning of fossil fuels, although they noted that perhaps 10% of presented lung cancer in large cities might have been due to air pollution. In 1990, the US Environmental Protection Agency (EPA) estimated that 0.2% of all cancer, and probably less then 1% of lung cancer, could be attributed to the effects of air pollution (43). This estimate was obtained by applying the unit risks for more than twenty known or suspected human carcinogens found in outdoor air to estimates of the ambient concentrations and numbers of persons potentially exposed. The unit risks were derived from either animal experiments or extrapolation from studies of workers exposed to higher concentrations.

One group based their estimates on direct observation of populations exposed to ambient levels of air pollution. Karch and Schneiderman (44), using data from the American Cancer Society study and US Census data, estimated that the urban factor accounted for 12% of lung cancer in 1980. They predicted that 1980 levels of TSP (approximately 60 $\mu g/m^3$) would be associated with a lung cancer rate ratio of 1.32.

Estimation of the magnitude of the contribution of air pollution to lung cancer occurrence at existing levels of air pollution poses a major challenge. Samet (45) recently reviewed the issue of risk assessment of air pollution exposure. Usually estimates of the population-attributable risk of lung cancer due to outdoor air pollution have used diverse approaches and produced variable estimates.

Each attributable risk estimate is subject to considerable uncertainty because of a lack of knowledge about both the relative magnitude of the effect and the proportion of the population exposed. However, there seems to be no convincing evidence to prefer estimates based on extrapolation from animal experiments or occupational studies to direct epidemiologic observation of the general populations at risk if valid and reasonably precise epidemiologic results are available (46).

FUTURE RESEARCH

Better estimates of the amount of effect will need additional epidemiologic studies. Large numbers of cases will be essential to measure the effects of air pollution and to measure combined effects of air pollution and factors such as occupation and smoking and such studies will probably require pooling data from multiple locales.

New studies will need to develop and apply improved epidemiologic methods and to compare the effect of exposure to the pollutant mixtures on lung cancer in different cities while effectively controlling confounding factors including cigarette smoking and diet. Also we need methods for the retrospective estimation of lifetime exposure to air pollutants.

The air pollution mixtures in major population centers should be characterized both in terms of physical and chemical constituents and in terms of sources of major constituents. If possible, retrospective characterization of levels of certain constituents could be accomplished (47). This information would aid greatly in the interpretation of between city epidemiologic contrasts. For the epidemiology of lung cancer, urban and relatively clean areas with established population-based tumor registries should be targeted.

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