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Ambient air pollution exposure and cancer

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Epidemiologic evidence on the relation between ambient air pollution exposure and cancer is reviewed. The well-documented urban/rural difference in lung cancer incidence and the detection of known carcinogens in the atmosphere gave rise to the hypothesis that long-term exposure to air pollution may have an effect on lung cancer risk. However, problems inherent in assessing adequately the exposure of interest led to considerable difficulties in evaluating this effect. Routinely measured air pollutants do not include, as a rule, established carcinogens, and air pollution measurements usually come from fixed-site monitors, making it difficult to estimate individual exposures, especially long-term. The nature of the exposure and associated measurement problems made ecologic comparisons a natural way to approach the study of air pollution effects on lung cancer risk. The descriptive/ecologic studies which have been undertaken after 1950 often had problems with inadequate control of confounding, but, on the whole, provided evidence compatible with the hypothesis that urban and industrial air pollution may have an effect on lung cancer risk. The results of several case-control and cohort studies are described in the present review with emphasis on the exposure metric used. These studies, which control for important potential confounders, suggest that urban air pollution may be a risk factor for lung cancer, with estimated relative risks in the order of up to about 1.5 in most situations. *Cancer Causes and Control* 1997, 8, 284-291

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Introduction

The severe, acute, adverse health effects of high air-pollution levels – first quantified around the middle of this century, following the well-known London (United Kingdom) episodes – gave rise to the hypothesis that long-term exposure to air pollution also has effects on human morbidity and mortality.[1,2] This hypothesis was strengthened further by the urban/rural differences observed in the incidence and mortality from lung cancer and chronic obstructive pulmonary disease (COPD).[3,4] The involuntary nature and the ubiquity of air pollution exposure lead to a significant public health concern.

The particular characteristics of air pollution exposure have posed considerable difficulties in the studies of its long-term effects. More specifically: (i) measurements of air pollution levels, so far, nearly always come from fixed-site monitors which are supposed to represent the air pollution situation of a whole area – *i.e.*, the data are at an aggregated (ecologic) level; (ii) even if the monitoring network is extensive and gives a good estimation of levels of air pollutants by district or neighborhood, there are sparse data to estimate inter- and intra-individual exposure variability in a population; and (iii) it is even more difficult to estimate long-term exposure, especially in retrospect.

Most studies thus far indicate relatively low effects (relative risks [RR] ranging up to about 1.5), which suggests that causal relations are difficult to determine using epidemiologic methodology, principally due to

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difficulties in controling bias, such as confounding from stronger risk factors and exposure misclassification. Different types of bias may lead to over- or underestimation of any risks related to air pollution exposure.

The present review focuses mainly on the effects of outdoor air pollution. Other types of pollution such as environmental tobacco smoke (ETS) are reviewed elsewhere in this issue and are considered here only in relation to confounding and effect modification. Regarding outcome, we focus mainly on lung cancer for which there is an *a priori* biologic hypothesis and, consequently, it has been studied more extensively in relation to air pollution.

Exposure characterization

Air pollution comprises a large number of components mostly produced by fuel combustion. On a short-term basis, fluctuations in the levels of different pollutants are determined by local meteorologic conditions, and the pollutant concentrations usually are correlated over time; thus, any pollutant may serve, to some extent, as an index of the mixture. However, over longer time periods, changes in emissions may result in substantial modifications of the air pollution mixture in both qualitative and quantitative terms, and the same is true when comparing different geographic areas.

Some pollutants have been chosen by several countries or international bodies (*e.g.*, the World Health Organization) as criteria pollutants which, on the basis of current scientific knowledge, reasonably may be anticipated to endanger public health and welfare. These usually include suspended particulate matter, sulphur dioxide, nitrogen dioxide, ozone, and carbon monoxide, and are monitored routinely by fixed-site monitoring networks. The purposes of regular monitoring are: assessing the air quality, and ensuring conformity with air quality standards set by law to protect public health from known or anticipated adverse effects associated with the presence of these specific pollutants in the air.[5] The presence of carcinogens among air pollutants supports the hypothesis that air pollution may increase the risk of lung cancer and possibly also other types of cancer.[6-10] However, such substances are not monitored routinely in most places where air pollution monitoring is established. Among these, benzo(a)pyrene concentrations have been measured sporadically as an index of air carcinogenicity but there is a lack of data on long time-trends. Diesel exhaust also has attracted attention, but studies so far have been conducted mostly on persons occupationally exposed.[10] Very few studies have been conducted providing detailed information on personal exposures, intra- and inter-person variability in exposure, and the correlation of personal exposures with levels measured at fixed-site monitors. It follows that exposure to air pollutants is not described adequately and most of the evidence linking air pollution to the risk of lung cancer cannot be attributed to a specific pollutant or mixture.

Descriptive/ecologic studies

The nature of the exposure and associated measurement problems made ecologic comparisons a natural way to approach the issue of long-term effects of air pollution. There have been comprehensive reviews on air pollution exposure and cancer which adequately present and discuss the descriptive/ecologic studies done between 1950 and 1990.[6-10] Only the main points are summarized here.

Geographic studies. Geographic studies describe urban/rural differences in lung cancer incidence and mortality. These studies may give false positive and false negative results. Adequate control for smoking and other potential confounders is difficult to achieve at the aggregate level. Further, the methodology may not be sensitive enough to detect the possible effect of air pollution exposure, given the problems of exposure misclassification.[6] Comparisons of lung cancer incidence among nonsmokers generally failed to account for exposure to passive smoking.[6]

A few studies have been performed on populations living around a point source of pollution, usually industrial. These studies suffer from the same problems concerning the use of aggregated data for exposure and confounders. In particular, there may be important uncontrolled confounding effects of occupational exposures in the industries involved as pollution sources. Studies have been done in areas with: chemical, paper and pulp, and petroleum industries; ferro-chromium alloy industries; industries with arsenic emissions; iron and steel foundries; non-ferrous smelters; and waste incinerators.[6-7]

Time trend studies. These studies also use aggregated data and evaluate time trends in incidence and mortality from lung cancer either within one area or, comparatively in several areas.[6-10] In general, such studies have the drawbacks of ecologic comparisons mentioned above. An interesting study within this group is the study by Archer[11] who compared the time trend of respiratory cancer mortality in two similar Utah (United States) counties with very low smoking rates. In one of these, a steel mill was built during World War II and substantially polluted the air. This was followed by an increase in lung cancer which was evident within 15 years of the start of operations. However, also in this study, all data concerning exposure, covariates, and outcome were at the aggregate level, which casts doubts on the interpretation of the results.[9,10]

A recent study by Tango[12] investigated the time trends of female mortality from lung cancer and two control

diseases (ischemic heart and cerebrovascular disease, hypothesized to be associated with tobacco smoking but not with air pollution exposure) in 23 wards in the metropolitan Tokyo (Japan) area. Air pollution levels from SO_2 and NO_2 were available for each ward, but not smoking prevalence. The analysis supported an effect of air pollution on lung cancer. However, the effect of smoking on the three causes under study differs in magnitude of the RR and this may explain the results if areas with higher air pollution levels also had higher prevalence of smoking.

Migrant studies. These studies have shown that migrant populations have risks of lung cancer intermediate between those of the population of their origin and those of the place to which they migrated.[6-8] This observation suggests an effect of air pollution exposure early in life.

In conclusion, descriptive/ecologic studies provided evidence compatible with the hypothesis that urban and industrial air pollution may have an effect on lung cancer risk. However, problems with the use of information on the aggregate level for exposure and confounders make it difficult to use the evidence for assessment of causal relationships.

Analytic epidemiologic studies

In analytic epidemiologic studies (cohort or case-control), the unit of data collection and analysis is the individual.[13] In analytic studies where the exposure of interest is air pollution, typically the data on the outcome (incidence or mortality form lung cancer) and potential confounders are measured at the level of the individuals, but the exposure assessment very often is assessed at the aggregated level and – especially in case-control studies – it is complemented by proxy measures of individual exposure assessment such as urban residence, distance from a point source, *etc*. It should be noted, therefore, that the exposure of interest either is not measured at all at the individual level or is a relatively crude proxy-measure in most cases.

In Table 1, case-control studies on ambient air pollution and lung cancer are summarized.[14-28] The description of exposure assessment is classified in two categories: one is the individual exposure-assessment method used; and the other is the characterization of air pollution in different geographic areas (aggregate level), either by degree of urbanization or by actual measurements of air pollutant levels. These measurements usually are provided by the state monitoring networks, which are set up to monitor 'criteria' pollutants. The pollutants available are not always the same nor are they necessarily the most relevant for cancer induction. It is therefore difficult to compare the study areas on the basis of these measurements. On the other hand, it is often possible to reach useful conclusions considering the sources and emissions of pollution in each case. In some of the studies, air pollution originates mainly from industrial and heating sources, while in others, it is mostly generated from traffic. However, although the situation during the study period may be characterized adequately, there is much more uncertainty about retrospective information which may be more relevant for lung cancer etiology.

Assessment of air pollution at the aggregate level assumes that all individuals with residence in one area have the same exposure to air pollution. When the only criterion of individual air-pollution exposure is current residence, then the exposure assessment may be considered as ecological. However, in most case-control studies, some measure of individual exposure has been used, based usually on history of residence. Then, the areas of residence are ordered according to air pollution levels and a weighted average is usually taken, the weights being proportional to length of stay in each area. This approach differentiates individuals of the same population according to air pollution exposure, but it should be noted that the measurements used for classifying areas according to air pollution levels are often inadequate for this purpose, leading to substantial misclassification in the exposure assessment. Further, the studies on air pollution and lung cancer suffer from the fact that smoking is a potential confounder of the association with high RRs for the disease. The sample size requirements increase considerably with increasing RR of a confounder.[29] This means that many of the smaller studies probably have inadequate power.

If the studies which use a classification of areas based on air pollution measurements are considered,[21,23-28] then the largest RRs observed concern the most polluted area studied, *i.e.*, Shenyang in China. Four other studies[21,24,27,28] resulted in RRs of 1.2 to 1.5, while the two smallest ones in size gave rather unstable results. It should be noted that several studies suggested a combined effect of smoking and air pollution exposure exceeding an additive effect of the two factors.[17-19,21,24-25]

In Table 2, the cohort studies are summarized.[30-38] All cohort studies use exposure data at the aggregate level, and estimation of individual exposure is based on area of residence at a certain point in time, usually at the beginning of the follow up. The older studies [30-36] generally have adjusted for age and smoking, but smoking data were often rather crude. The two most recent cohort studies[37-38] have detailed information on many potential confounders and good characterization of the air pollution situation in the areas involved, as far as 'criteria' pollutants are concerned. One of the studies suggested that exposure to sulphate particulates was especially important for lung cancer. The estimated RRs for lung cancer mortality in the cohort studies are remarkably consistent and of the same order as the ones estimated by the case-control studies.

Table 1. Case-control studies on air pollution and lung cancer

Author (ref) Year	Study area/ time period	Number of cases	Number of controls	Exposure assessment		Results
				Aggregate level	Individual level	Relative risk (RR)
Stocks & Campell[14] 1955	North Wales 1952-54	725	12,000	Urban: BS[a]≅200-350μg/m^3; BαP[b]≅20-80ng/m^3 Rural: BS≅50μg/m^3; BαP≅10ng/m^3	Current residence: urban/rural	RR = 1.1-3.4 in different smoking categories
Haenszel *et al*[15] 1962 Haenszel & Taeuber[16] 1964	USA 1958-59	2,381 men 749 women	31,516 men 34,339 women		Current residence: urban/rural & yrs of residence	RR = 1.43 for men; RR = 1.27 for women for urban *cf* rural, adjusting for age and smoking. Positive trend with duration of urban residence
Hitosughi[17] 1968	Two cities near Osaka, Japan 1960-66	180 men 79 women	2,241 men 2,475 women	High: SPM[c] = 390μg/m^3 BαP = 79ng/m^3; Low: SPM = 190μg/m^3; BαP = 26ng/m^3	Current residence: high/low	RR = 1.8 for men RR = 1.2 for women, adjusting for age and smoking
Dean[18] 1966 Dean *et al*[19] 1977, '78	Northeastern England & Northern Ireland 1960-72	780-2,873 men 138-199 women	1,371-2,873 men 167-2,985 women	Urban: monthly average TSP[d] > 100μg/m^3	Current residence: urban/rural	RR = 1.2-1.9, adjusting for age and smoking
Pike *et al*[20] 1979	Los Angeles County (USA) 1972-75	1,425 men 576 women	445 men 186 women	BαP≅3ng/m^3 (earlier estimated ≅30-60ng/m^3)	Yrs of residence, adjusting for age, smoking and occupational exposures	No association
Vena[21] 1982	Erie County, New York (USA) 1957-65	417 men	752 men	TSP from 80 to 200μg/m^3; low to high town	Residence history, air pollution exposure quantified	RR = 1.26 for men exposed more than 50 years to high/medium air pollution, adjusting for age, smoking and occupation
Samet *et al*[22] 1987	New Mexico (USA) 1980-82	283 men 139 women	475 men and women	Urban residence (in county with > 50,000 people)	Yrs living in urban areas	No consistent association of residence with lung cancer risk
Xu *et al*[23] 1989	Shenyang, China 1985-87	729 men 520 women	788 men 557 women	BαP up to 60ng/m^3	Lifetime exposure to air pollution based on weighted average of stay in residences with degrees of 'smoky outdoor environment' and overall exposure with indoor air pollution index	RR = 2.3 in men and 2.5 in women for smoky outdoor environment, adjusting for age, education, smoking and indoor pollution. There was a dose-response

Continued

Table 1. Continued

Jedrychowski *et al*[24] 1990	Cracow, Poland 1980-85	901 men 198 women	875 men 198 women	Annual average TSP = 150μg/m^3, SO_2[e] = 100μg/m^3 in central town. Air pollution isoplets constructed on the bases of TSP and SO_2 levels	Level of outdoor pollution (3 categories) in place of last residence	RR = 1.46 in men living in high air pollution areas compared with low adjusting for age, smoking and occupation
Katsouyanni *et al*[25] 1991	Athens, Greece 1987-89	101 women	89 women	BS maximum levels above 400μg/m3 in highest pollution areas. Areas were classified into 5 pollution levels based on smoke and NO_2[f] measurements	Lifetime exposure to air pollution based on weighted average of stay in area of residence and area of occupation	RR = 0.81 for non-smokers; 1.35 for moderate smokers; 2.23 for heavy smokers, contrasting extreme quartiles of air pollution exposure, adjusting for age, education, interviewer
Holowahy *et al*[26] 1991	Niagara Region, Ontario, Canada 1983-85	51 women	45 women	Urban/rural	Lifetime exposure based on residential history	RR = 2.3 for adult residence in large town-city *cf* country-small town, adjusted for smoking
Jockel *et al*[27] 1992	5 German cities	146 men 48 women	292 men 96 women	Each German county classified according to 8 pollution categories for the period 1895-1984 (10-yr intervals)	Lifetime exposure to air pollution based on residential history	RR = 1.16 for high to low exposure to air pollution in men; allowing for latency 20 years, the RR became 1.82, both adjusting for smoking and occupation
Barbone *et al*[28] 1995	Trieste, Italy 1979-81 1985-86	755 men	755 men	Levels of particulate deposition based on 28 stations varied from < 0.175 and > 0.298 g/m^2 per day	Level of pollution in current place of residence (tertiles)	RR = 1.4 for most polluted *cf* least polluted area of last residence; 1.5 for current residence in city center; 1.4 for industrial area day residence, adjusting for age, smoking, occupation and socioeconomic status

[a] BS = black smoke.
[b] BαP = benzo(a)pyrene.
[c] SPM = suspended particulate matter.
[d] TSP = total suspended particles.
[e] SO_2 = sulphur dioxide.
[f] NO_2 = nitrogen dioxide.

Table 2. Cohort studies investigating air pollution effects on lung cancer risk

Author (ref) Year	Study area/ time period	Population	Number of cases	Exposure assessment	Results: relative risk (RR)
Hammond & Horn[30] 1958	9 US states 1952-55	183,783 men	448	Urban (> 50,000 inhabitants)/ Rural	RR = 1.3 adjusting for age and smoking
Buell *et al*[31] 1967	California (USA) 1957-62	69,868 men	304	Degree of urbanization (In most polluted cities maximum hourly oxidant concentrations exceeded 300µg/m^3 on 0.3 to 6.7% of days)	RR = 1.3 adjusting for age and smoking
Hammond[32] 1972	25 US states 1959-65	500,000 men	1,510	Degree of urbanization (population > 1,000,000; < 1,000,000 and rural)	RR = 1.23 for persons occupationally exposed to dust & fumes in large metropolitan areas; 1.14 in smaller metropolitan areas; and 0.98 in non-metropolitan areas, adjusting for age and smoking
Cederlof[33] 1975	Sweden 1963-72	25,444 men 26,467 women	166 men 28 women	Degree of urbanization (cities, towns, rural)	RR = 1.4 for smokers in cities *cf* rural areas; RR = 1.1 in towns *cf* rural, adjusting for age and smoking
Doll & Peto[34] 1981	UK 1951-71	34,400 men	430	Degree of urbanization (conurbations, large town 50,000 to 100,000 inhabitants, small towns < 50,000, rural)	RR = 0.99, 1.07, 0.99, and 0.96 according to degree of urbanization, adjusting for age and smoking
Tenkanen & Teppo[35] 1987	Finland 1964-80	4,475 men	233	Degree of urbanization (urban/rural)	RR = 1.2 among smokers for laryngeal and lung cancer in urban *cf* rural; RR = 1.86 for non- or ex-smokers (based on small number)
Mills *et al*[36] 1991	California (USA) 7th-day Adventists 1977-82	6,340	17	Mean concentration and exceedance frequencies of TSP[a] and ozone	RR = 1.72 per 1000h/y of TSP concentrations exceeding 200µg/m^3, adjusted for age, gender, and smoking
Dockery *et al*[37] 1993	Six US cities 1974-91	8,111	Total number of deaths = 1,430; Number of deaths from lung cancer not given	Mean TSP ranged 34-90 µg/m^3; inhalable particles 18-47µg/m^3; fine particles 11-30 µg/m^3; sulfates 5-13µg/m^3; SO_2[b] 4-24ppb; NO_2[c] 6-22ppb; ozone 20-28ppb. Residence at time of entry	RR = 1.37 for most *cf* least polluted city, adjusted for age, gender, smoking, education, and body mass index[d]
Pope *et al*[38]	151 metropolitan areas in 50 US states 1982-89	552,138	Total number of deaths = 38,963; Number of deaths from lung cancer not given	Mean concentration of sulfates in 1980 ranged from 3.6 to 23.5µg/m^3 Median fine particulate concentration, 1979 to 1983, ranged from 9.0 to 33.5µg/m^3. Residence at time of entry	RR = 1.36 using sulfates as the index of pollution, and 1.03 using fine particles. Adjusted for age, gender, race, passive smoking exposure, smoking, body mass index,[d] alcohol intake, education and occupational exposure

[a] TSP = total suspended particles
[b] SO_2 = Sulphur dioxide
[c] NO_2 = Nitrogen dioxide
[d] Body mass index = wt(kg)/ht(m)^2.

Conclusions and recommendations for research

Analytic epidemiologic studies, which control for important potential confounders, suggest that urban air pollution may be a risk factor for lung cancer. The RRs are in the order of up to about 1.5 in most situations, but may be higher in areas with extreme pollution levels. Some data point to an interaction between air pollution exposure and smoking exceeding an additive effect, but the evidence is not conclusive.

A major drawback in the studies has been the inadequate characterization of air pollution exposure. First, measurements of air pollution in the study areas should span the time period relevant for disease etiology and preferably should include concentrations of suspected carcinogens. Second, an estimation of individual exposure should be based on exposure studies, studies of the time-activity patterns, and the geographic distribution of pollutants in micro-scale. Exposure studies should provide data on how individual exposure is related to the levels measured at fixed monitors, considering different activities and transportation used.[39,40] Further, methods for retrospective exposure assessment covering periods of several decades should be developed. The results of such studies could be used as input in large analytic epidemiologic investigations to address the problems of measurement error and reduce uncertainties in the RR estimates.

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