Research Article

Cancer Epidemiology, Biomarkers & Prevention

Air Pollution from Traffic and Risk for Lung Cancer in Three Danish Cohorts

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Abstract

Background: Air pollution is suspected to cause lung cancer. The purpose was to investigate whether the concentration of nitrogen oxides (NO_x) at the residence, used as an indicator of air pollution from traffic, is associated with risk for lung cancer.

Methods: We identified 679 lung cancer cases in the Danish Cancer Registry from the members of three prospective cohorts and selected a comparison group of 3,481 persons from the same cohorts in a case-cohort design. Residential addresses from January 1, 1971, were traced in the Central Population Registry. The NO_x concentration at each address was calculated by dispersion models, and the time-weighted average concentration for all addresses was calculated for each person. We used Cox models to estimate incidence rate ratios after adjustment for smoking (status, duration, and intensity), educational level, body mass index, and alcohol consumption.

Results: The incidence rate ratios for lung cancer were 1.30 [95% confidence interval (95% CI), 1.07-1.57] and 1.45 (95% CI, 1.12-1.88) for NO_x concentrations of 30 to 72 and >72 $\mu g/m^3$, respectively, when compared with <30 $\mu g/m^3$. This corresponds to a 37% (95% CI, 6-76%) increase in incidence rate ratio per 100 $\mu g/m^3$ NO_x. The results showed no significant heterogeneity in the incidence rate ratio for lung cancer between cohorts or between strata defined by gender, educational level, or smoking status.

Conclusion: The study showed a modest association between air pollution from traffic and the risk for lung cancer.

Impact: This study points at traffic as a source of carcinogenic air pollution and stresses the importance of strategies for reduction of population exposure to traffic-related air pollution. *Cancer Epidemiol Biomarkers Prev; 19(5); 1284–91. ©2010 AACR.*

Introduction

Lung cancer is one of the most frequent cancers and has a dismal prognosis. Active tobacco smoking is the major cause, but certain occupational exposures, residential radon, environmental tobacco smoke, and lower socioeconomic status are also established risk factors. For more than half a century, long-term exposure to ambient air pollution and, in particular, particulate matter with absorbed polycyclic aromatic hydrocarbons and other genotoxic chemicals has been suspected to increase the risk for lung cancer.

Early ecological studies, many with inadequate adjustment for smoking and other potential confounders, typically showed about 50% higher lung cancer incidence rates in urban areas and in communities polluted by industrial sources than in more rural, less polluted areas. Several case-control and cohort studies with adequate adjustment for smoking and other potential confounding factors similarly indicated higher risks for lung cancer in association with different measures of air pollution (1-8). Not all the previous studies showed significant associations and not all showed associations for the same pollutants (or proxies); furthermore, the magnitude of the risk estimates differed. Nevertheless, the overall picture is a modestly increased risk for lung cancer in association with various measures of exposure to air pollution. Furthermore, several studies have indicated that the effects of air pollution on the risk for lung cancer might be modified by smoking status, such that an effect is strongest or detectable only among nonsmokers or never smokers (3, 4, 7, 8). Other factors have also been suggested to modify the effect of air pollution, for example, fruit consumption (7), gender, and educational level (3). Thus, effect estimates for heterogeneous populations might be

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doi: 10.1158/1055-9965.EPI-10-0036

underestimates of the true effect of air pollution in susceptible subpopulations. Furthermore, imprecise assessment of exposure to air pollution might bias effect estimates, for instance, if a centrally monitored concentration is assigned to all persons living within a wide area around a central monitoring station (9) or if only a short period (or a moment in time) is used as the basis for assessing exposure.

In the study reported here, we tested the hypothesis that exposure to air pollution from traffic increases the risk for lung cancer. We pooled data for three Danish cohorts of populations in the two major cities of Denmark and used detailed data on traffic and a dispersion model with high spatial resolution to calculate the concentrations of air pollution at the actual residential addresses of lung cancer patients and a comparison group selected within the cohorts over a 30-year period.

Materials and Methods

Design and study participants. Three Danish cohort studies formed the base of the present study. (*a*) During 1993 to 1997, 57,053 men and women with the age of 50 to 64 years living in Copenhagen and Aarhus counties were recruited into the Diet Cancer Health cohort study (10). (*b*) The Copenhagen City Heart Study was initiated in 1976 and included 19,698 men and women with the age of 20 to 93 years living in Copenhagen (11); we used data for 17,597 participants enrolled at one of the first three examinations, in 1976 to 1978, 1981 to 1983, or 1991 to 1994. (*c*) Between 1970 and 1971, 5,249 men with the age of 40 to 59 years were enrolled into the Copenhagen Male Study from 14 large workplaces in Copenhagen (12). In all three population studies, the baseline examination included a self-administered questionnaire on smoking habits (status, intensity, and duration), alcohol consumption, educational level, and a number of other health-related items. Smoking intensity was calculated by equating a cigarette to 1 g, a cheroot or a pipe to 3 g, and a cigar to 5 g of tobacco.

Each cohort member was followed up for cancer occurrence until February 16, 2001, in the Danish Cancer Registry (13) by use of the personal identification number, which is unique for each Danish citizen. From among the cohort members, we selected a comparison group according to the principle of the case-cohort design (14). The numbers in the subcohort were weighted to ensure a similar distribution to that of the identified lung cancer cases within strata defined by combinations of cohort, gender, smoking duration (never, <10, 10-19, 20-29, 30-39, 40-49, 50-59, ≥60 y), and year of birth (<1900, 1900-1909, 1910-1919, 1920-1929, 1930-1939, 1940-1949, 1950-1959, ≥1960; but ≤1934, 1935-1939, and ≥1940 for the Diet Cancer Health cohort). We traced the date of death, emigration, or disappearance of patients with lung cancer and subcohort members in the Central Population Registry by use of the personal identification number and retrieved the addresses of each patient and subcohort member from January 1, 1971, until February 16, 2001, from the same registry. The dates of moving in and leaving each address were noted, and the addresses were linked to the Danish address database to obtain geographic coordinates (denoted in the following as "geocodes").

Exposure assessment. The concentration of NO_x in the air was calculated for each year at each residential address at which the cohort members had lived by use of the Danish AirGIS modeling system (15), which is based on a geographic information system and is used for estimating traffic-related air pollution with high temporal and spatial resolution. AirGIS can be used for a large number of addresses and to calculate air pollution at a location as the sum of three contributors: (*a*) local air pollution from street traffic calculated with the Operational Street Pollution Model from input data on traffic (intensity and type), emission factors for the car fleet, street and building geometry, and meteorology when modeling dispersion of tail pipe emissions in the street (16); (*b*) urban background calculated from a simplified area source dispersion formula that takes into account urban vehicle emission density, city dimensions (transport distance), and building height (initial dispersion height) (17); and (*c*) regional background estimated from trends at rural monitoring stations and from national vehicle emissions (18).

Input data for the AirGIS system were established from various sources and were integrated into the model. A geographic information system road network including construction year and traffic data for the period 1960 to 2005 was developed (19), and a database on emission factors for the Danish car fleet, with data on light- and heavy-duty vehicles back to 1960, was built and entered into the emission module of the Operational Street Pollution Model. A national geographic information system database with building footprints was supplemented with the construction year and building height from the National Building and Dwelling Register, which provided the correct street and building geometry for a given year at a given address. The geocode of an address refers to the location of the front door with a precision within 5 m for most addresses. The geocode of the front door and the geographic information system road network combined with the geographic information system database with building footprints provided data on street width, distances between buildings (street canyons), the distance between the address geocode and the street, and the height of surrounding buildings. With the geocode of an address and a specified year as the starting point, the AirGIS system automatically generates street configuration data for the Operational Street Pollution Model, including street orientation, street width, building heights in wind sectors, and traffic amount, speed, and type, as well as other data required as input for the modeling system. Air pollution is calculated in 2-m height at the façade of the address building. The AirGIS system has been validated in several studies (15, 17, 20, 21).

Table 1. Characteristics of study participants

Characteristic	Subcohort		Cases	
	n (%)	Mean/median (5-95 percentile)	*n* (%)	Mean/median (5-95 percentile)
All participants	3,481 (100)		679 (100)	
Cohort				
DCH	1,325 (38.1)		254 (37.4)	
CCHS	1,488 (42.8)		295 (43.5)	
CMS	668 (19.2)		130 (19.2)	
Gender				
Male	2,275 (65.4)		441 (65.0)	
Female	1,206 (34.7)		238 (35.1)	
Smoking				
Never	109 (3.1)		16 (2.4)	
Former	537 (15.4)		43 (6.3)	
Present	2,835 (81.4)		620 (91.3)	
Missing	0 (0.0)		0 (0.0)	
Intensity (g/d)		17.3/15.0 (3-35)		20.1/20.0 (5-37)
Missing	79 (2.3)		6 (0.9)	
Duration (y)		33.0/34.7 (10-48)		33.8/35.0 (15-49)
Missing	0 (0.0)		0 (0.0)	
Length of education (y)				
<8	1,630 (46.8)		359 (52.9)	
8-10	1,288 (37.0)		240 (35.4)	
>10	439 (12.6)		58 (8.5)	
Missing	124 (3.6)		22 (3.2)	
Body mass index (kg/m^2)		25.5/25.1 (20-32)		25.2/24.9 (19-32)
Missing	12 (0.3)		5 (0.7)	
Alcohol intake (g/d)		24.1/24.0 (3-63)		25.1/24.0 (2-66)
Missing	9 (0.3)		1 (0.2)	
NO_x* (μg/m^3)		37.6/29.5 (16-96)		41.7/31.9 (17-111)
Missing	0 (0.0)		0 (0.0)	

Abbreviations: DCH, Diet Cancer Health study; CCHS, Copenhagen City Heart Study; CMS, Copenhagen Male Study.
*Time-weighted average for the period January 1, 1971, to the censoring date.

The AirGIS system calculates air pollution hour by hour, which, in the present study, was summarized as the yearly average concentration at each residential address. We used the concentration of NO_x as the indicator for air pollution from traffic because NO_x correlates strongly with other traffic-related pollutants such as particulate matter: $r = 0.93$ for total particle number concentration (size, 10-700 nm) and $r = 0.70$ for PM_{10} (22, 23). We calculated the time-weighted average NO_x concentrations at all addresses from January 1, 1971, and entered it as a time-dependent variable into the statistical model. If NO_x could not be calculated because of failed geocoding of an address, we imputed the concentration calculated at the preceding address. If the NO_x concentration was missing for the first address, we imputed the value at the subsequent address.

Statistical methods. The endpoint for the risk analyses was primary lung cancer. Incidence rate ratios for lung cancer were estimated by a Cox proportional hazards model stratified for cohort, gender, smoking duration, and birth year, respecting the sampling strata. The unweighted case-cohort approach was used for the analyses (14), and we calculated two-sided 95% confidence intervals (95% CI) and *P*s on the basis of the robust estimates of the variance-covariance matrix (24) and the Wald test statistical for regression parameters in Cox regression models. All statistical tests were two sided. Age was the time scale, which ensured that the risk estimate was based on comparisons of individuals at exactly the same age, and analyses were corrected for delayed entry at the time of enrolment or January 1, 1990, whichever came last. People with a cancer diagnosis before entry were excluded from the analyses. Censoring occurred at the time of death, emigration, or disappearance; the time of a cancer diagnosis; or February 16, 2001 (end of follow-up), whichever came first. The average length of follow-up was 6.7 years.

The analyses included adjustment for smoking status (never, former, present), smoking intensity (grams per day tobacco; linear), duration of smoking (years, linear) within the 10-year sampling strata, length of education (<8, 8-10, and >10 y), body mass index (kilogram per square meter; linear), and alcohol intake (grams per day; linear). These lifestyle characteristics were for the time of enrolment into the cohorts.

We formed three intervals for exposure to NO_x using the 50th and 90th percentiles of the time-weighted average concentration of NO_x for all participants as the cutoff points and estimated the incidence rate ratio for lung cancer for the intermediate and high exposure ranges compared with the lower exposure range. The incidence rate ratio was also estimated as a linear trend per 100 $\mu g/m^3$ increment in NO_x concentration, which corresponded to the difference between low and relatively highly exposed people in the study. We controlled for heterogeneity of the incidence rate ratios between the three cohorts, and we analyzed possible effect modification by gender, educational level, and smoking status. We tested the sensitivity of the results by (*a*) repeating the analyses after taking into account a 10-year lag in the exposure calculation, that is, disregarding the last 10 years of exposure, and (*b*) repeating the analyses only with data on participants for whom the residential addresses were known for ≥80% of the time from January 1, 1971, until censoring. The proportion of lung cancer cases attributable to NO_x concentration, given the observed association, was calculated by standard methods (25).

Results

We identified 679 cases of lung cancer (92% with histologic confirmation) in the three cohorts and selected 3,481 subcohort members as comparison group (Table 1). Two thirds of the participants were men, and most patients (91%) and subcohort members (81%) were present smokers at the time of enrolment. People with lung cancer smoked on average 20 g/day of tobacco, and subcohort members smoked 17 g/day. The people with lung cancer and subcohort members had smoked for almost identical durations, 34 and 33 years (match criterion). Patients had a slightly lower body mass index and slightly higher alcohol intake than subcohort members.

We identified 13,685 addresses at which the patients and subcohort members had lived from January 1, 1971, and geocoded and calculated yearly average concentrations of NO_x for 12,810 (94%) of these addresses. Geocoding of residential addresses and, therefore, exposure assessment failed >20% of the time of 4% of patients and subcohort members. Figure 1 shows a substantial variability in the time-weighted average concentrations of NO_x among the study participants, calculated for the addresses from January 1, 1971, to the censoring date. The mean concentration was 41.7 $\mu g/m^3$ for patients and 37.6 $\mu g/m^3$ for the subcohort (Table 1).

Table 2 shows the incidence rate ratios for lung cancer, which were 1.30 (95% CI, 1.07-1.57; $P = 0.008$) for the intermediate exposure interval and 1.45 (95% CI, 1.12-1.88; $P = 0.005$) for the highest exposure interval when compared with the lowest exposure category, corresponding to a 37% increase in incidence rate ratio for lung cancer per 100 $\mu g/m^3$ NO_x (linear trend) after adjustment for smoking status, smoking intensity, smoking duration, educational level, body mass index, and intake of alcohol. Figure 2 shows a tendency to higher lung cancer rates in association with higher exposure to NO_x when evaluated for five exposure groups.

There was no significant heterogeneity between the three cohorts; the incidence rate ratios for lung cancer per 100 $\mu g/m^3$ increase in NO_x concentration were

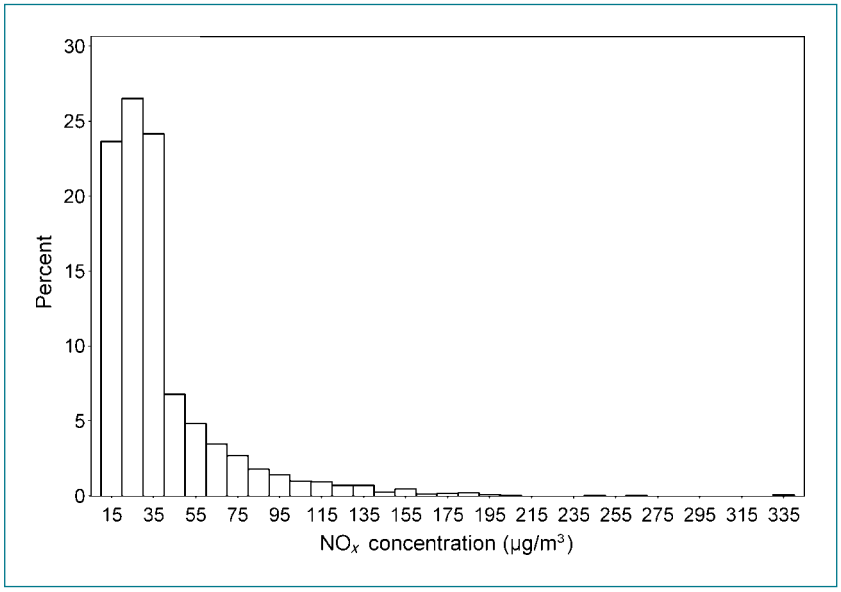

Figure 1. Distribution of time-weighted average concentration of NO_x at the residences of the study participants.

Table 2. Incidence rate ratios for lung cancer associated with the time-weighted average concentration of NO_x at residences from January 1, 1971

NO_x concentration (μg/m^3)*	n_{cases}	IRR	95% CI
≤29.8	294	1.00	—
29.8-72.4	298	1.30	1.07-1.57
≥72.4	87	1.45	1.12-1.88
Linear trend per 100 μg/m^3	679	1.37	1.06-1.76

NOTE: The analyses were stratified for cohort, gender, duration of smoking, and period of birth (sampling strata) and further adjusted for smoking status (never, former, present), smoking intensity (linear), duration of smoking (linear; to adjust within the 10-y sampling strata), length of education (<8, 8-10, >10 y), body mass index (linear), and alcohol intake (linear).
Abbreviation: IRR, incidence rate ratio.
*The cutoff points between exposure groups were the 50th and 90th percentiles for all participants.

1.28 (95% CI, 0.84-1.95), 1.51 (95% CI, 1.07-2.11), and 1.05 (95% CI, 0.51-2.17) for the Diet Cancer Health, Copenhagen City Heart Study, and Copenhagen Male Study cohorts, respectively, and the *P* for no difference between the cohorts was 0.63. Table 3 shows similar incidence rate ratios for men and women and tendencies for higher incidence rate ratios with higher educational level and among never smokers, but none of the incidence rate ratios differed significantly (all *P* for interaction > 0.46).

Table 4 shows that exposure to NO_x was associated with small-cell and, in particular, squamous cell carcinomas of the lung, whereas no clear association was present for adenocarcinomas or the mixed group of other or unknown histologic subtypes of lung cancer.

Discussion

The study shows an association between NO_x concentration at the residence and risk for lung cancer. The dose-response analysis suggests a 37% increase in lung cancer rate per 100 μg/m^3 NO_x. An association was seen in all three cohorts, although weak in the Copenhagen Male Study, and within all strata of gender, length of education, and smoking status.

If we assume that the observed risk association in the categorical analyses is causal and that the population exposure corresponds to that of the subcohort, an estimated 14% of lung cancer cases are attributable to air pollution. The population in the present study lived, however, mainly in urban areas and was thus not representative of the whole population in terms of exposure to air pollution. Because approximately half the Danish population lives in urban settings (of >50,000 inhabitants), the proportion of lung cancer cases attributable to air pollution in the whole Danish population is probably substantially <14%.

Our finding of a modest association between air pollution and risk for lung cancer is in accordance with the findings of previous studies (1-3). In particular, the results are in accordance with those of most previous European studies showing effects of indicators of air pollution from traffic, such as NO_2 and proximity to traffic (4-6, 26). The only previous study in which NO_x was used as an indicator of air pollution (5), conducted in Norway, showed an incidence rate ratio for lung cancer of 1.08 (95% CI, 1.02-1.15) per 10 μg/m^3 increase in NO_x concentration at the residence. We found an incidence rate ratio of 1.37 (95% CI, 1.06-1.76) per 100 μg/m^3, corresponding to 1.03 (95% CI, 1.01-1.06)

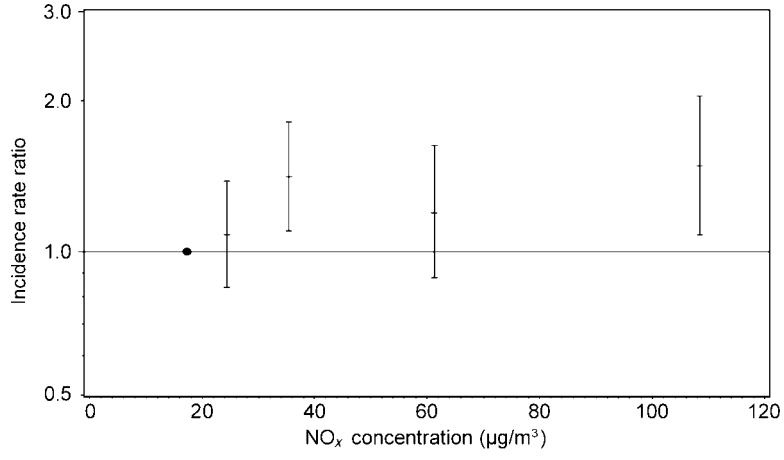

Figure 2. Dose-response relationship between NO_x exposure and rate ratio for lung cancer. The vertical whiskers show the rate ratios with 95% CIs for four exposure categories compared with the reference category of 0 to 20 μg/m^3. Owing to the skewed distribution, the exposure range of the categories increased, such that the four upper exposure categories were 20 to 30, 30 to 50, 50 to 80, and >80 μg/m^3 NO_x. The incidence rate ratios are placed on the exposure axis at the median value of each exposure category.

Table 3. Incidence rate ratios for lung cancer in association with a 100 μg/m^3 increase in NO_x concentration (linear effect); sensitivity analyses and effect modification by cohort, gender, education, and smoking

Characteristic	IRR	95% CI
All participants*	1.37	1.06-1.76
10-y Lag†	1.35	1.04-1.76
>80% Exposure time known‡	1.37	1.06-1.77
Gender		
Male	1.32	0.92-1.90
Female	1.44	1.02-2.02
Length of education (y)		
<8	1.21	0.88-1.67
8-10	1.53	1.05-2.23
>10	1.70	0.60-4.83
Smoking status		
Never	2.58	0.39-17.20
Former	1.27	0.54-2.98
Present	1.36	1.04-1.77

NOTE: The analyses were stratified for cohort, gender, duration of smoking, and period of birth (sampling strata). The analyses were further adjusted for smoking status (never, former, present), smoking intensity (linear), duration of smoking (linear; to adjust within the 10-y sampling strata), length of education (<8, 8-10, >10 y), body mass index (linear), and alcohol intake (linear).

*Identical to the linear trend estimate of Table 2 (included in this table for comparison).

†The time-weighted average concentration of NO_x was calculated for the period January 1, 1971, to 10 years before the censoring date.

‡Exclusion of 24 cases and 132 subcohort persons with unknown exposure during ≥20% of the time from January 1, 1971, to censoring date.

per 10 μg/m^3, which is lower than that in the Norwegian study. The exposure levels differed in the two studies, with 68% of the Norwegian study subjects exposed to <20 μg/m^3 NO_x and 75% of the Danish study subjects above that level. The risk estimates are, however, compatible because of the wide overlap in the confidence intervals.

Although associations have been found with NO_x and NO_2 in the present and previous studies, it seems more likely that other highly correlated pollutants from traffic, such as particulate matter with absorbed polycyclic aromatic hydrocarbons and other genotoxic substances, are responsible for a possibly higher risk for lung cancer. Engine exhausts are complex mixtures containing thousands of chemical compounds, including many carcinogenic and mutagenic chemicals, and diesel engine exhaust causes cancer in experimental animals (27). Furthermore, numerous studies show a higher risk for lung cancer among populations occupationally exposed to diesel engine exhaust (28). It is difficult to disentangle the effect of single air pollutants in epidemiologic designs because they are part of complex mixtures. Single pollutants are, however, often used as indicators of air pollution from specific sources, and NO_2 and NO_x are good markers for traffic-related air pollution; NO_x has been shown to correlate closely with particulate matter, especially the ultrafine fraction emitted from diesel engines in Danish streets (22, 23). The exposure assessment in the present study focused on vehicle traffic emissions, which is the major source of NO_x air pollution in Danish cities. Moreover, two studies from other Scandinavian countries showed effects of traffic-related nitrogen oxides but not of heating- and industry-related SO_2 on the risk for lung cancer (4, 5).

In most previous studies on air pollution and lung cancer, the address (or area or city) of residence at one moment in time, typically the time of enrolment into a cohort, was used as the basis of the exposure assessment. Exposure over a long period, perhaps over a whole life, is probably relevant for the development of lung cancer, and the present study benefited from information on residential histories from 1971 onwards as the basis for the exposure assessment providing 19 years of exposure before the beginning of follow up for cancer in 1990. One of the few previous studies with information on exposure decades back in time indicated that the effect of air pollution on the risk for lung cancer is stronger after inclusion of a lag, that is, after disregarding exposure during the period closest to the diagnosis (4). Including a 10-year lag in the exposure assessment in the present study had no effect on the incidence rate ratio for lung cancer. This coincides with the observation that the NO_x concentration calculated for the whole exposure period correlated strongly with that calculated after inclusion of a 10-year lag (r = 0.96). Thus, our material would seem not to be suitable for investigating possible effects of lag time.

We found no significant differences in the incidence rate ratios for lung cancer between cohorts or by gender or educational level; associations were found within each stratum. This consistency in the results increases our confidence that the association is true. Associations between air pollution and risk for lung cancer were found among never, former, and present smokers. The highest incidence rate ratio was found for never smokers, in accordance with the results of several previous studies (3, 4, 7). The lung cancer incidence rate is very low among never smokers; if air pollution contributes a similar absolute risk to never and ever smokers, the relative risk would be highest for never smokers. Nevertheless, the wide confidence interval around the risk estimate for never smokers indicates that the result should be interpreted with caution. We also found a tendency of a stronger risk association among those with a longer education, which is opposite of what was found by Pope et al. (3). However, the risk association did not differ

significantly between the educational levels ($P = 0.59$), and the pattern might be due to chance.

The time trends in incidence rates of lung cancer in the United States are different for different histologic subtypes. The incidence rates of squamous cell and small-cell carcinomas of the lung increased during the 1970s, peaked at the beginning of the 1980s, and decreased thereafter, whereas the incidence rate of adenocarcinoma of the lung first decreased from about 1998. An association between NO_x air pollution and adenocarcinoma of the lung has been suggested as the explanation for these different time trends, supported by ecological correlations between the incidence rates of adenocarcinomas and vehicle densities at county area level (29, 30). Use of individual exposure assessments in our study did not confirm this hypothesis because we observed stronger associations between NO_x concentrations and risk for squamous cell and small-cell carcinomas than for adenocarcinoma of the lung. Because of the wide confidence intervals, the incidence rate ratio for each histologic type of lung cancer (Table 4) is compatible with the incidence rate ratio of 1.37 per 100 $\mu g/m^3$ NO_x for all lung cancers combined (Table 2).

For case ascertainment, we took advantage of the virtually complete nationwide Danish Cancer Register (13). We used only the first cancer as the endpoint, that is, we excluded participants from the risk analyses if a cancer was diagnosed before entry and censored them at diagnosis of any cancer during follow-up, because the distinction between relapse of a previous cancer and the development of a new independent cancer becomes irrelevant, metastases will not be misclassified as primary lung cancers, and the potential influence of previous cancer treatment on the risk for a new primary cancer is excluded. Selection bias is unlikely in the present study because the subcohort was sampled within the same cohort population in which the cases occurred.

The dispersion models we used to assess air pollution levels at the addresses of study participants have been successfully validated (17, 20) and applied in Denmark (31) and the United States (21). Nevertheless, such estimates of air pollution concentrations are inevitably associated with some degree of uncertainty. We cannot see how such uncertainty could differ for patients and the subcohort and would therefore expect the misclassification to be nondifferential. A previous comparison between NO_2 concentrations measured and calculated by the Danish dispersion models (20, 31) showed that the misclassification was primarily of the Berkson type as might be expected when exposure is predicted from a model (32, 33). Berkson error is expected not to bias the risk estimates (34, 35), although it decreases the precision (36), such that the confidence intervals reported in the present study are probably too narrow.

Confounding from smoking is a major concern in any study on air pollution and lung cancer because smoking is the major risk factor and it is more prevalent in urban areas. We matched the people in the subcohort to the patients by the smoking variable that is most important for lung cancer development, that is, duration. Thus, the risk estimate was based on comparisons of people with the same 10-year smoking duration. The analyses were further adjusted for smoking status, intensity, and duration to eliminate possible confounding from variation in smoking duration within each 10-year smoking duration stratum. Furthermore, an effect of air pollution was observed among never, former, and present smokers, making us more confident that the observed effect of air pollution on risk for lung cancer is not a result of confounding by smoking. Data on environmental tobacco smoke were not available, and this might therefore have confounded the results. Environmental tobacco smoke affects the risk for lung cancer only marginally however, and we would expect possible confounding to be minimal.

Table 4. Incidence rate ratios for different histologic subtypes of lung cancer in association with the time-weighted average concentration of NO_x at residences from January 1, 1971

NO_x concentration ($\mu g/m^3$)*	IRR (95% CI)			
	Small-cell carcinomas (*n* = 132)	Squamous cell carcinomas (*n* = 154)	Adenocarcinomas (*n* = 194)	Other/unknown (*n* = 199)
≤29.8	1.00	1.00	1.00	1.00
29.8-72.4	1.29 (0.83-2.00)	1.01 (0.65-1.56)	1.53 (1.10-2.12)	1.38 (0.96-1.98)
≥72.4	1.65 (0.96-2.85)	2.12 (1.32-3.40)	1.18 (0.70-1.99)	1.05 (0.60-1.84)
Linear trend per 100 $\mu g/m^3$	1.53 (1.02-2.28)	2.01 (1.27-3.43)	0.95 (0.57-1.58)	1.18 (0.68-2.03)

NOTE: The analyses were stratified for cohort, gender, duration of smoking, and period of birth (sampling strata) and further adjusted for smoking status (never, former, present), smoking intensity (linear), duration of smoking (linear; to adjust within the 10-y sampling strata), length of education (<8, 8-10, >10 years), body mass index (linear), and alcohol intake (linear).
*The cutoff points between exposure groups were the 50th and 90th percentiles for all participants.

In conclusion, in this study with high spatial resolution exposure assessment over three decades, we found a modest association between air pollution from traffic at the residence and risk for lung cancer, in line with the weight of the epidemiologic evidence to date.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

Research Centre for Environmental Health, Danish Ministry of the Interior and Health.

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Received 01/12/2010; revised 03/10/2010; accepted 03/11/2010; published online 05/06/2010.

References

1. Dockery DW, Pope CA III, Xu X, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753–9.
2. Beeson WL, Abbey DE, Knutsen SF, Adventist Health Study on Smog. Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. Environ Health Perspect 1998;106:813–23.
3. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002;287:1132–41.
4. Nyberg F, Gustavsson P, Jarup L, et al. Urban air pollution and lung cancer in Stockholm. Epidemiology 2000;11:487–95.
5. Nafstad P, Haheim LL, Oftedal B, et al. Lung cancer and air pollution: a 27 year follow up of 16 209 Norwegian men. Thorax 2003;58:1071–6.
6. Vineis P, Hoek G, Krzyzanowski M, et al. Air pollution and risk of lung cancer in a prospective study in Europe. Int J Cancer 2006;119:169–74.
7. Beelen R, Hoek G, van den Brandt PA, et al. Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology 2008;19:702–10.
8. Yorifuji T, Kashima S, Tsuda T, et al. Long-term exposure to traffic-related air pollution and mortality in Shizuoka, Japan. Occup Environ Med 2009.
9. Kim SY, Sheppard L, Kim H. Health effects of long-term air pollution: influence of exposure prediction methods. Epidemiology 2009;20:442–50.
10. Tjonneland A, Olsen A, Boll K, et al. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. Scand J Public Health 2007;35:432–41.
11. Schnohr P, Jensen G, Lange P, Scharling H, Appleyard M. The Copenhagen City Heart Study. Eur Heart J 2001;3:H1–83.
12. Hein HO, Suadicani P, Gyntelberg F. Alcohol consumption, serum low density lipoprotein cholesterol concentration, and risk of ischaemic heart disease: six year follow up in the Copenhagen male study. BMJ 1996;312:736–41.
13. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. Dan Med Bull 1997;44:535–9.
14. Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. J Clin Epidemiol 1999;52:1165–72.
15. Jensen SS, Berkowicz R, Hansen SH, Hertel O. A Danish decision-support GIS tool for management of urban air quality and human exposures. Transport Res Part D: Transport Environ 2001;6:229–41.
16. Berkowicz R. OSPM—a parameterised street pollution model. Environ Monit Assess 2000;65:323–31.
17. Berkowicz R, Ketzel M, Jensen SS, Hvidberg M, Raaschou-Nielsen O. Evaluation and application of OSMP for traffic pollution assessment for large number of street locations. Environ Model Software 2008;23:296–303.
18. Jensen SS. Background concentrations for use in the Operational Street Pollution Model (OSPM). Roskilde: National Environmental Research Institute, Aarhus University; 1998, Report No. 234.
19. Jensen SS, Hvidberg M, Pedersen J, et al. GIS-based national street and traffic data base 1960-2005 (In Danish; English summary). Roskilde: National Environmantal Research Institute, Aarhus University; 2009, Report No. 678.
20. Raaschou-Nielsen O, Hertel O, Vignati E, et al. An air pollution model for use in epidemiological studies: evaluation with measured levels of nitrogen dioxide and benzene. J Expo Anal Environ Epidemiol 2000;10:4–14.
21. Jensen SS, Larson T, Deepti KC, Kaufman J. Modeling traffic air pollution in street canyons in New York City for intra-urban exposure assessment in the US Multi-Ethnic Study of atherosclerosis and air pollution. Atmos Environ 2009;43:4544–56.
22. Ketzel M, Wahlin P, Berkowicz R, Palmgren F. Particle and trace gas emission factors under urban driving conditions in Copenhagen based on street and roof level observations. Atmos Environ 2003;37:2735–49.
23. Hertel O, Jensen SS, Andersen HV, et al. Human exposure to traffic pollution. Experience from Danish studies. Pure Appl Chem 2001;73:137–45.
24. Barlow WE. Robust variance estimation for the case-cohort design. Biometrics 1994;50:1064–72.
25. Olsen JH. Avoidable cancers in the Nordic countries. Aims and background. APMIS Suppl 1997;76:1–8.
26. Filleul L, Rondeau V, Vandentorren S, et al. Twenty five year mortality and air pollution: results from the French PAARC survey. Occup Environ Med 2005;62:453–60.
27. International Agency for Research on Cancer (IARC). Diesel and gasoline engine exhausts and some nitroarenes. Lyon: IARC; 1989.
28. Lipsett M, Campleman S. Occupational exposure to diesel exhaust and lung cancer: a meta-analysis. Am J Public Health 1999;89:1009–17.
29. 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;16:2724–9.
30. Chen F, Jackson H, Bina WF. Lung adenocarcinoma incidence rates and their relation to motor vehicle density. Cancer Epidemiol Biomarkers Prev 2009;18:760–4.
31. Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH. Air pollution from traffic at the residence of children with cancer. Am J Epidemiol 2001;153:433–43.
32. Clayton D. Models for the longitudinal analysis of cohort and case-control studies with inaccurately measured exposure. In: Dwyer JH, Feinleib M, Lippert P, editors. Statistical model for longitudinal studies of health. Oxford: Oxford University Press; 1992.
33. Heid IM, Kuchenhoff H, Miles J, Kreienbrock L, Wichmann HE. Two dimensions of measurement error: classical and Berkson error in residential radon exposure assessment. J Expo Anal Environ Epidemiol 2004;14:365–77.
34. Prentice RL. Covariate measurement errors and parameter estimation in a failure time regression model. Biometrika 1982;69:331–42.
35. Steenland K, Deddens JA, Zhao S. Biases in estimating the effect of cumulative exposure in log-linear models when estimated exposure levels are assigned. Scand J Work Environ Health 2000;26:37–43.
36. Szpiro AA, Sheppard L, Lumley T. University of Washington: The Berkeley Electronic Press (bepress); 2009, Report No. 350.