Lung Adenocarcinoma Incidence Rates and Their Relation to Motor Vehicle Density

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Abstract

Background and Objective: The temporal trend of adenocarcinoma incidence rates of the lung (ADL) has been reported to parallel the trend of nitrogen oxide (NOx) emissions in the United States. This study explores the geographic pattern of ADL incidence and its relation to motor vehicle density, the major indicator of NOx emissions before 1970.

Methods: ADL incidence rates by counties were retrieved from the nine sites of Surveillance, Epidemiology, and End Results (SEER) Program for the period of 1973 to 1990. Motor vehicle densities by county in 1970 for these SEER sites were estimated according to the numbers of motor vehicle registration and the size of each county. Regression analysis was done with the data of motor vehicle density by counties.

Results: A dose-response pattern between motor vehicle density and ADL incidence was found. The risks are 136% and 68% higher for ADL and squamous cell carcinoma, respectively, for male residents living in areas with 937 motor vehicles per square mile, compared with those living in areas with about one motor vehicle per square mile. The R² are as high as 0.805 and 0.504 in regressions for male incidence rates of ADL and squamous cell carcinoma, respectively, with the vehicle density values. As a comparison, the prostate cancer incidence rates did not show dose-response relationship with motor vehicle density. If the effect of NOx emissions on ADL incidence rates can be proved by further studies, the current standard of allowance of NOx emissions may need to be revised.

Introduction

Many histologic types of lung cancer, including squamous cell carcinoma of the lung (SQL), have continued to decline since the 1980s following the substantial declining trend of per capita tobacco consumption, which started 16 years before the decline of SQL incidence rates. This pattern is easily explained by the change in tobacco consumption. However, continuous increases in incidence rates of adenocarcinoma of the lung (ADL) in the same period have been reported during the last several decades (1-7). ADL surpassed SQL in Connecticut in the 1980s. Devesa et al. (8) reported that through 1997, ADL incidence increased in virtually all areas of the world with increases among men exceeding 50% in many parts of Europe. Contrary to the temporal patterns of other histologic types of lung cancer, the unique pattern of ADL suggests that there may be another cause that has more impact on ADL incidence than tobacco consumption.

To explain the remarkable increasing trend in ADL incidence, it has been hypothesized that the increasing trend of adenocarcinoma is mainly due to the dissemination of low-tar filter cigarettes (9, 10). Smoke from low-yield filter-tipped cigarettes is inhaled more deeply than smoke from earlier unfiltered cigarettes and releases higher concentrations of nitrosamines. Inhalation transports tobacco-specific carcinogens more distally toward the bronchoalveolar junction where adenocarcinomas often arise. An alternative hypothesis for the increasing trend of ADL incidence may be the air pollution that stems from industrialization and urbanization. We report that the temporal trend of ADL incidence rates, including the increasing trend before 1998 and declining trend after 1998 in the United States, both parallel with the trends of nitrogen oxide (NOx) emissions; these occur 20 years after the NOx emissions trend (11). Using the same time period, we reviewed the temporal trends for particulate matter (PM-10), volatile organic compounds, sulfur dioxide (SO2), and lead emission levels, but did not find similar trends.

A determination of whether the geographic distribution pattern of ADL is associated with levels of air pollution can provide evidence to support or refute the air pollution hypothesis. Due to the remarkable difference in air pollution levels within each state, we chose to estimate air pollution at the county level. Because no historical air pollution data or NOx emission data is available at the county level and the major sources of NOx emissions is motor vehicles and power plants (12), we collected motor vehicle density data at the county level for the year 1970 as a surrogate for either NOx emission levels or air pollution levels.

This study aims to determine if a geographic distribution pattern of ADL showed a dose-response relationship with variations in motor vehicle density. In comparison, we determined whether a dose-response relationship exists between motor vehicle density and SQL incidence rates or prostate cancer incidence rates.
Materials and Methods

Cancer incidence data were estimated based on data from the Surveillance, Epidemiology, and End Results (SEER) Program of the U.S. National Cancer Institute. The SEER database provides information on persons diagnosed with cancer in diverse geographic areas and constitutes 10% of the U.S. population. The year 1973 is the first year for which SEER registry cancer data is available for nine sites. The nine standard SEER regions include 200 counties in the states of Connecticut; Hawaii; Iowa; New Mexico; and Utah; as well as the metropolitan areas of Atlanta, GA; Detroit, MI; San Francisco/Oakland, CA; and Seattle/Puget Sound, WA. Taking the induction period of cancer into consideration, we did not compare the motor vehicle density in 1970 with the cancer incidence data in the same year but to the cancer incidence data for the period from 1973 to 1990. If the median induction period is 15 years, the reasonable year of incidence data for this comparison should be the years around 1985. Because the population in the majority of involved counties is small and ADL is a rare disease, we merged 17 years of incidence data together, trying to obtain a relatively stable incidence rate for each county. This study uses incidence data rather than mortality data because incidence data is more closely related to the cause and is not influenced by different effects due to the progress of treatment in different places and different times. Incidence rates of ADL (ICD-O codes 8140, 8211, 8230-8231, 8250-8260, 8323, 8480-8490, 8550-8560, 8570-8572) and SQL (ICD-O codes 8050-8076) were adjusted to the 2000 U.S. standard population. To make a comparison, we also estimated prostate cancer incidence rates. We selected cancer incidence rates in white men only because the incidence estimations of black men at the county level were not stable due to the small population sizes.

For those counties in SEER sites that have ADL incidence available, we requested data from each of the state depository libraries on the number of motor vehicle registrations at the county level for 1970. Among the 200 counties we contacted, the motor vehicle registration data for the year 1970 were not available in Kalawao County, HI; Cibola County, NM; nor in any county in Utah. Therefore, we have only 168 counties with motor vehicle registration data available. The analysis of this study is based on these 168 counties. Motor vehicle density was calculated using the collected motor vehicle registration data and land area.

Although we obtained incidence data for the period from 1973 to 1990, we found that the populations in many counties were still too small to obtain stable incidence data for ADL; therefore, we further merged them to 28 county groups. We sorted the 168 counties in ascending order based on motor vehicle density. We then merged every six counties based on their similar level of motor vehicle density data, forming 28 county groups. The median motor vehicle density of each group was considered the exposure level of the residents in the six counties of that group. The incidence data we used is also based on the population of six counties for the period 1973 to 1990. Consequently, the number of cancer cases of each county group is always greater than 20 for all the incidence estimation in this study.

Results

The median motor vehicle density for the 28 county groups varied from 0.9 to 937 per square mile. A log transformation was computed for these numbers and then a linear regression was done with age-adjusted incidence rates of ADL, SQL, and prostate cancers as dependent variable, respectively, in the 28 county groups. The total person-years observed for the 28 county groups ranged from 256,824 to 43 million. Median motor vehicle densities of all county groups were used as the independent variable.

Table 1 shows that the significantly higher relative risks were found in those 14 county groups with the highest motor vehicle densities compared with the one that has the smallest motor vehicle density. Although there are 14 groups that show significantly higher relative risks for SQL also, the relative risk for SQL in the group with the highest motor vehicle density is only 1.68, whereas the relative risk for ADL in this group is 2.36. In comparison, the county groups with significantly higher relative risks for prostate cancer are not specifically for groups with high motor vehicle densities but vary widely regardless of the motor vehicle density levels. Figures 1, 2 and 3 show these different patterns.

Figures 1, 2, and 3 show the linear regression plots. The $R^2$ values are 0.805 and 0.430 for the regression of vehicle density with male and female ADL incidence rate, respectively. The $R^2$ values are 0.503 and 0.301 for the regression of vehicle density with male and female SQL incidence rate, respectively. However, the $R^2$ value is only 0.056 for regression with prostate cancer incidence rates. There is a stronger association between motor vehicle density and ADL than with SQL in both males and females, and no association were found between motor vehicle density and prostate cancer incidence rates.

Discussion

Our results suggest that motor vehicle density is a powerful risk factor for ADL and SQL. The risks are 136% and 68% higher for ADL and SQL, respectively, for residents living in areas with ~937 motor vehicles per square mile, compared with those living in areas with about one motor vehicle per square mile. We may underestimate the risks due to the study design. In ecological studies, none of the populations compared is homogeneous but contains people with different exposure levels and even unexposed people. The observed effect associated with difference in exposure levels in different populations is diluted by large numbers of potentially unexposed people who do not have contribution on the effect.

The $R^2$ values are as high as 0.805 and 0.635 in regressions for ADL and SQL in males, respectively, with the log transformation of vehicle density values. These geographic dose-response patterns, as well as a similar pattern in females, add additional support to the air pollution–NOx hypothesis in explanation of the increase in ADL incidence in the past several decades. In contrast, we found no relationship between prostate cancer incidence and motor vehicle density in this study. We have previously reported that the temporal trend of...
ADL incidence rates, including the increasing trend before 1998 and the declining trend after 1998 in the United States, both parallel similar temporal trends of NO\textsubscript{x} emissions and occur 20 years after the NO\textsubscript{x} emissions trend (11). The geographic dose-response pattern of ADL found in this study, together with the temporal trend pattern found previously, may strongly support the air pollution–NO\textsubscript{x} hypothesis for ADL incidence changes.

We choose motor vehicle density as an indicator of NO\textsubscript{x} exposure because the emission from motor vehicles is the major source of NO\textsubscript{x} emissions and accounts for more than a half of the total NO\textsubscript{x} emissions nationwide (12). In fact, a positive relationship is true for the period from 1940 to 1970. According to our estimation, the correlation coefficient is 0.9361 for the total NO\textsubscript{x} emissions with the total number of motor vehicles during the period 1940 to 1970. Considering the induction period, the ADL in the 1980s should be compared with NO\textsubscript{x} emissions in 1970 or before 1970. In 1970, the Clear Air Act was enacted in the United States and a strict restriction on NO\textsubscript{x} emissions and five other components were instituted. This resulted in abatement in late years of NO\textsubscript{x} emissions through the gradual application of new technologies in different states. We cannot estimate the correlation of vehicle density and total NO\textsubscript{x} emissions in the United States between 1970 to 1990 because a continuous reduction of NO\textsubscript{x} emissions per motor vehicle manufactured after 1970 (changes in design of vehicles required by the law in Clean Air Act Extension of 1970, and Clean Air Act Amendments in 1977 and 1990) and further increases of emissions trend (11).

<table>
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<th>Group</th>
<th>Motor vehicle density*</th>
<th>Adenocarcinoma</th>
<th>Squamous cell carcinoma</th>
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<td>No. cases</td>
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*Number of motor vehicles/square mile.

**P < 0.05.

![Figure 1. Lung adenocarcinoma incidence rate in 1973 to 1990 by motor vehicle density in 28 county groups, SEER sites, United States.](image-url)

Model

\[
\text{Rate(ADL)} = 2.166 \ln(\text{density}) + 11.11
\]

\[
R^2 = 0.805, \quad P < 0.0001
\]

\[
\text{Rate(SQL)} = 3.745 \ln(\text{density}) + 16.59
\]

\[
R^2 = 0.504, \quad P < 0.0001
\]
vehicle density do not have the same meaning in terms of NOx emissions.

We did not use data on vehicle miles traveled, or traffic density on roadways as a surrogate for NOx because they are not available at the county level. We used the incidence data for the period 1973 to 1990 rather than select one year in midpoint of this period because ADL is rare and there are not enough cases at the level of some county groups.

Wu-Williams and Samet (15) reported that the relative risk of smoking cigarettes for SQL and ADL are 18.9 and 4.8, respectively. Apparently, smoking cigarettes is a much stronger risk factor for explaining the variation of SQL incidence rates than for ADL. This fact explains the remarkable decline in incidence rates of SQL observed since 1980, 16 years after the declining trend of tobacco consumption. However, this does not explain the continued increase in incidence rates of ADL after 1985. The temporal trend of ADL followed the trend of NOx emissions, which may indicate that NOx is a stronger factor in determining the incidence rates for ADL than cigarette smoking.

When we consider whether our finding is confounded by cigarette smoking, we have no data on whether the dose gradient pattern of cigarette smoking is similar to, opposite of, or unrelated to the dose gradient pattern of motor vehicle density in these 28 county groups. Nevertheless, if it was similar to the gradient pattern of motor vehicle density, we could see much higher relative risk for SQL than that for ADL in this study, because of the much higher relative risk of smoking for SQL than ADL. Apparently, this is not the case. This fact indicates that the dose gradient pattern in cigarette smoking is not similar to that of motor vehicle density pattern in these 28 county groups; therefore, the relative risk we found in this study is less likely caused by cigarette smoking.

To determine whether the relationship we found is due purely to urbanization, and if vehicle density is only a marker of urbanization but not a cause of ADL, we used a similar method to determine whether there is a strong relationship between ADL incidence and population density. The $R^2$ of the regression between ADL incidence and the log transformation of population density is 0.206. Although it indicates a weak statistical relationship between ADL incidence and population density, it is remarkably smaller than the $R^2$ for the relationship between ADL and vehicle density. Most likely, vehicle density, not population density, could be a driving force of the increase in ADL in the last several decades.

It has been reported by Vineis et al. (16) that long-term exposure to NOx is a risk factor of lung cancer. They conducted a nested case-control study in 10 European countries and found a 30% increase in the risk of developing lung cancer (relative risk, 1.30; 95% confidence interval, 1.02-1.66) for those who were exposed to NO2 at levels >30 μg/m² compared with those who were exposed to NO2 at levels <30 μg/m². There were no histologic types of these lung cancers mentioned in this study.

The limitations of this study are as follows: As an ecological study, the data of motor vehicle density was obtained from populations that cannot be linked to exposure in individuals; that is, the ecological fallacy could not be eliminated. All the estimations are based on the assumption that all people in the same county group have the same level of exposure. Although we have reasons to speculate, we do not have data on smoking prevalence rates for the counties studied; therefore, we could not actually adjust for the influence of cigarette smoking or discuss possible interaction. Moreover, there are many factors that may be associated with degree of urbanization or vehicle density. These include occupational factors associated with economic activities that we could not adjust in our current study. Although we use the air pollution–NOx hypothesis to explain the finding in our study, we do not have reasons to exclude

Figure 2. Lung squamous cell carcinoma incidence rate in 1973 to 1990 by motor vehicle density in 1970 in 28 county groups, SEER sites, US.

Figure 3. Prostate cancer incidence rate in 1973 to 1990 by motor vehicle density in 1970 in 28 county groups, SEER sites, US.
the possible effect of particulate matter (PM$_{2.5}$) and polycyclic aromatic hydrocarbons, which are also associated with vehicle density. We did not discuss these matters in detail because the temporal patterns of ADL incidence rates had been shown to parallel the patterns of NO$_x$, but not to PM$_{10}$, SO$_2$, volatile organic component, or lead emissions (11). We were unable to obtain data for emission trends of PM$_{2.5}$; therefore, we could not exclude the possible effect of PM$_{2.5}$ in the relationship of motor vehicle density and ADL incidence.

Nevertheless, NO$_x$ emission patterns can simultaneously explain the temporal trend, including the increase before 1998 and the decline after that and the geographic pattern in the SEER sites of the United States. The distribution by time and place points out the same factor, which is a much stronger evidence than finding a correlation between two factors like the routine ecological study do. The results of this study warrant the necessity for further studies on this issue.

In conclusion, long-term exposure to some components of polluted air, especially NO$_x$, may play a major role in the increase of ADL over the last 50 years. There is an urgent need to conduct further studies to determine whether there is a causal relation between long-term low-dose exposure to NO$_x$ and ADL occurrence. Both the current standard of 21 ppb (40 g/m$^3$) proposed by the WHO (17) and the National Ambient Air Quality Standards of 53 ppb (100 g/m$^3$; ref. 18) proposed in the United States are far above the level proposed in a study by Vineis et al. (16), which suggested a great increase in risk of lung cancer when exposed to NO$_2$ for a long time at a level above 16 ppb (30 g/m$^3$). Although cigarette smoking is a cause of ADL, it may play a lesser role in causing the substantial change in ADL incidence rates over the last several decades than does air pollution.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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References
