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TRAFFIC AIR POLLUTION AND RISK OF DEATH FROM GASTRIC CANCER IN TAIWAN: PETROL STATION DENSITY AS AN INDICATOR OF AIR POLLUTANT EXPOSURE

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To investigate the relationship between air pollution and risk of death attributed to gastric cancer, a matched cancer case-control study was conducted using deaths that occurred in Taiwan from 2004 through 2008. Data for all eligible gastric cancer deaths were obtained and compared to a control group consisting of individuals who died from causes other than neoplasms and diseases that were associated with gastrointestinal (GIT) disorders. The controls were pair-matched to the cancer cases by gender, year of birth, and year of death. Each matched control was randomly selected from the set of possible controls for each cancer case. Data for the number of petrol stations in study municipalities were collected from two major petroleum supply companies. The petrol station density (per square kilometer) (PSD) for study municipalities was used as an indicator of a subject's exposure to benzene and other hydrocarbons present in ambient evaporative losses of petrol or to air emissions from motor vehicles. The exposed individuals were subdivided into three categories (≤ 25 th percentile; 25th–75th percentile; > 75 th percentile) according to PSD in the residential municipality. Results showed that individuals who resided in municipalities with the highest PSD were at an increased risk of death attributed to gastric cancer compared to those subjects living in municipalities with the lowest PSD. The findings of this study warrant further investigation of the role of traffic air pollution exposure in the etiology of gastric cancer.

Ambient outdoor air pollution has been implicated as a cause of various health problems including cancer (Tomatis 1990; Boffetta 2006; Curtis et al. 2006; Dominici et al. 2005; Samet and Krewski 2007). Air pollution is a complex mixture of different gaseous and particulate components; thus, it is difficult to define an exposure measure of relevance

when the biological mechanisms are largely unknown (Boffetta and Nyberg 2003). Air pollution from motor vehicle exhaust has been one of the most studied environmental factors (Craig et al. 2008). Exhaust from traffic is a complex mixture of many chemical compounds, including benzene, polycyclic aromatic hydrocarbons (PAH), and benzo[a]pyrene (BaP). The

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International Agency for Research on Cancer (IARC) classified the emission of diesel exhaust engine compounds as probably carcinogenic (Group 2A) and gas engine exhaust compounds as possibly (Group 2B) carcinogenic to humans (IARC 1989; Krewski and Rainham 2007).

The evidence regarding air pollution and lung cancer has been the subject of several reviews (Katsouyanni and Pershagen 1997; Cohen 2000; Boffetta and Nyberg 2003; Vineis et al. 2004; Dominici et al. 2005). However, limited data are available for an association between air pollution exposure and development of gastric cancer.

Occupational studies serve to formulate hypotheses and guide research into risk factors for carcinogenesis (Garcia-Perez et al. 2010). According to occupational epidemiologic studies, excess risks of gastric cancer were reported to be associated with highway maintenance workers (Maizlish et al. 1988), transport workers (Parent et al. 1998), gas station workers (Aragones et al. 2002), and professional drivers (Guberan et al. 1992; Balarajan and McDowall 1988). Recent studies also indicated positive associations between exposure to diesel engine emissions and enhanced risk of stomach cancer development (Boffetta et al. 2001; Sjordahl et al. 2007). Nevertheless, workers in other occupations likely to encounter gasoline vapors exposure do not appear to experience a particularly higher risk of gastric cancer occurrence (Lagorio et al. 1994; Lynge et al. 1997). Although potentially carcinogenic PAH and combustion particles might be involved in gastric carcinoma, the causality remains uncertain.

Recent epidemiological research predominantly focused on the effects of short-term exposures. However, several studies suggest that chronic exposure may be more important in terms of overall public health (Holgate et al. 1999; Pope et al. 2002; Vineis et al. 2004). To date, only ecologic studies examined the risk of gastric cancer occurrence and exposure to ambient air pollution (Hagstrom et al. 1967; Gardner et al. 1969; Winkelstein and Kantor 1969; Lave and Seskin 1970; Chinn et al. 1981). With respect to ambient air pollution

exposure an increase in stomach cancer incidence was related to higher SO₂, particulates, or fuel consumption in several studies (Hagstrom et al. 1967; Gardner et al. 1969; Winkelstein and Kantor 1969; Lave and Seskin 1970) but was not found by Chinn et al. (1981).

Benzene, total suspended particles (TSP), and NO₂ are commonly used markers for traffic-related air pollution (Raaschou-Nielsen et al. 2001; Van Wijnen and Van der Zee 1998; Bedeschi et al. 2007; Muzykl et al. 1998). Measurements of the spatial distribution of benzene in the atmosphere showed that the highest outdoor concentrations within urban areas tended to occur adjacent to main roads (Leung and Harrison 1999). However, benzene levels were not recorded in fixed, outdoor monitoring stations in Taiwan. Previously Weng et al. (2008) used NO₂ as a marker for traffic-related air pollution in 64 municipalities. Traffic counts and proximity to roads have commonly served as surrogates for exposure to traffic-related potential carcinogens (Reynolds et al. 2004). Concentrations of these compounds are higher within 500 to 1000 feet of busy roads and freeways, based on measured traffic-related air pollutant levels (Dubowsky et al. 1999; Raaschou-Nielsen et al. 2000; 2001). To our knowledge, it is not known which exposure assessment approach best reflects chronic personal exposure to traffic-related air pollution (Raaschou-Nielsen and Reynolds 2006; Bedeschi et al. 2007).

Data reported here were designed as a cancer case-control study to explore further whether the risk of death attributed to gastric cancer is associated with exposure to vehicle exhaust emissions using petrol station density (PSD) as an indicator of traffic-related air pollution in Taiwan.

MATERIAL AND METHODS

Study Areas

Taiwan is divided into 359 administrative districts, which are designated in this report as municipalities and are the units subjected to statistical analysis.

Subject Selection

Data on all deaths of residents living in the study areas from 2004 through 2008 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health, which is responsible for the death registration system in Taiwan. For each death, detailed demographic information, including gender, occupation, marital status, year of birth, year of death, cause of death, place of death (municipality), and residential district (municipality), were recorded. The cancer case group consisted of all eligible deaths due to gastric cancer occurring in individuals between 50 and 69 yr of age ([ICD-9], code 151). Patients younger than age 50 yr were excluded because the characteristics of early-onset gastric cancer are postulated to differ from the more prevalent later-onset gastric carcinoma (Schottenfeld and Fraumeni 1996). Gastric cancer cases older than age 70 yr were excluded because of the difficulty in obtaining matched control subjects. Controls were drawn from all other deaths excluding deaths due to neoplasms and diseases which were associated with GIT disorders ([ICD-9] codes 140–239, 531–534, 578). Control subjects were pair-matched to cancer cases by gender, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each case. For controls, the most frequent causes of death were diabetes mellitus (13.9%), chronic liver disease and cirrhosis (8.8%), acute myocardial infarction (5.4%), motor vehicle traffic accidents of unspecified nature (5.4%), and intracerebral hemorrhage (4.5%).

Petrol Station Density (PSD)

Data on the number of petrol (gas) stations in study municipalities were collected from two major petroleum supply corporations, Chinese Petroleum Corporation (CPC 2008) and Formosa Petrochemical Corporation (FPCC 2008). Total number of petrol stations in each of the two corporations were then summed and divided by the municipality's land area (km²). This proportion (petrol station density) (PSD) was used as an indicator of a subject's exposure

to benzene and other PAH present in ambient evaporative losses of petrol and/or air emissions from motor vehicles. The municipality of residence for all cancer cases and controls was identified from death certificates. The municipality of residence formed the only basis for defining exposure to traffic air pollution. This index was used in previous studies (Weng et al. 2009; Chang et al. 2009; Ho et al. 2010).

Socioeconomic Factors

It was found that mortality attributed to cancer was associated with urbanization gradients (Greenberg 1983; Miller et al. 1987; Yang and Hsieh 1998). In this study, an urbanization index (Tzeng and Wu 1986) was used to adjust for possible confounding resulting from different urbanization levels among the municipalities. The urbanization index used in this study serves as a proxy for a large number of explanatory variables such as population density, age composition, mobility, economic activity and family income, educational level, environmental factors, and health service-related facilities, which are related to the etiology of mortality. Each municipality in Taiwan was given a degree of urbanization category, 1–8. A municipality with the highest urbanization score, such as the Taipei metropolitan area, was classified in category 1, while mountainous areas with the lowest score were assigned to category 8. This index was used previously (Yang et al. 1999; Yang 2004; Chiu et al. 2006; Liu et al. 2008). For the analyses, the urban–rural classification was further subdivided into two categories: I, urban areas (categories 1–4); and II, rural areas (categories 5–8).

Statistics

In the analysis, subjects were assigned into one of the three exposure categories according to the levels of PSD in their residential municipality: low (the lowest 25th percentile; ≤ 0.094); medium (25th–75th percentile; 0.095–0.523); and high (above 75th percentile; 0.526–2.692). Conditional logistic regression was used to estimate the relative risk in relation to the levels of

PSD (Breslow and Day 1980). Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated using the group with the lowest exposure as the reference group. All OR were adjusted for marital status (single, married, ever married) and urbanization level of residence (rural, urban). Tests for trend were conducted using the method described by Mantel (1963). Values of $p < .05$ were considered statistically significant.

RESULTS

The distribution of cancer cases and controls by selected demographic and residential characteristics is shown in Table 1. In total, 3510 gastric cancer cases with complete records were selected using the study criteria for the period 2004–2008. Subjects who were married or ever married had a significant excess risk of death due to gastric cancer compared to single individuals. Cancer cases demonstrated a significantly higher rate (62.2%) of residing in urban municipalities than controls (54.4%).

The crude OR were significantly higher than 1 for the groups with high levels of PSD in their residential municipality.

After adjustments for the urbanization level of residence and marital status, the adjusted OR were lower than the crude OR. The adjusted OR (95% CI) were 1.14 (0.98–1.32) for the group with PSD levels between 0.095 and 0.523 and 1.26 (1.04–1.53) for the group with PSD levels of 0.526 or more compared to the group with the lowest PSD levels. Trend analyses showed statistically significant trend in risk of death attributed to gastric cancer with increasing PSD level (Table 2).

DISCUSSION

This investigation used a death certificate-based cancer case-control study to examine the relationship between risk of death due to gastric cancer and exposure to traffic air pollutants using PSD as an indicator of pollutant exposure in Taiwan. The results of the present study showed that individuals who

TABLE 1. Characteristics of Study Population

Characteristics	Cancer cases ($n = 3510$)	Controls ($n = 3510$)	OR (95% CI) ^a
Enrollment municipality	358	358	
Age (yr)			
50–54	733 (20.9%)	733 (20.9%)	
55–59	782 (22.3%)	782 (22.3%)	
60–64	829 (23.6%)	829 (23.6%)	
65–69	1166 (33.2%)	1166 (33.2%)	
Gender			
Male	2261 (64.4%)	2261 (64.4%)	
Female	1249 (35.6%)	1249 (35.6%)	
Marital status			
Single	152 (4.3%)	255 (7.3%)	1.00
Married	2811 (80.1%)	2555 (72.8%)	1.90 (1.53–2.36)*
Ever married	547 (15.6%)	700 (19.9%)	1.33 (1.05–1.69)*
Petrol station density (per km ²) (median)			
≤0.094 (0.042)	693 (19.7%)	879 (25.0%)	1.00
0.095–0.523 (0.242)	1823 (52.0%)	1769 (50.4%)	1.40 (1.23–1.59)*
0.526–2.692 (0.762)	994 (28.3%)	862 (24.6%)	1.69 (1.44–1.98)*
Urbanization level of residence			
Rural	1328 (37.8%)	1599 (45.6%)	1.00
Urban	2182 (62.2%)	1911 (54.4%)	1.67 (1.47–1.89)*

Note. Asterisk indicates significant difference at $p < .05$.

^aOR (95% CI): odds ratio and 95% confidence interval.

TABLE 2. Odds Ratios for Gastric Cancer Associated With PSD Levels Based on Multiple Logistic Regression Model

	Petrol station density (PSD), (median)		
	≤0.094 (0.042)	0.095–0.523 (0.242)	0.526–2.692 (0.762)
Number of cancer cases	693 (19.7%)	1823 (52.0%)	994 (28.3%)
Number of controls	879 (25.0%)	1769 (50.4%)	862 (24.6%)
Crude OR	1.0	1.40 (1.23–1.59)	1.69 (1.44–1.98)
Adjusted OR ^a	1.0	1.14 (0.98–1.32)	1.26 (1.04–1.53)
χ^2 , trend = 29.59, $p < .001$			

^aOR adjusted for marital status and urbanization level.

resided in municipalities with the highest PSD levels were at a significantly increased risk of death attributed to gastric cancer. There was also a significant exposure-response relationship between PSD and risk of gastric cancer development. This finding is consistent with previous studies (Hagstrom et al. 1967; Gardner et al. 1969; Winkelstein and Kantor 1969; Lave and Seskin 1970).

There have been a number of epidemiological studies that assessed the elevated risk of gastric cancer development due to living in an urban compared to rural area. In general, mortality due to gastric cancer was considerably higher in urban than nonurban populations (Goldsmith 1980; Greenberg 1983; Muir et al. 1987). The only "urban factor" consistently mentioned in the literature is air pollution, suggesting that residing in an urban area may be a reliable surrogate for enhanced air pollution exposure (Greenberg 1983).

The specific exposure chemicals responsible for the elevation of gastric cancer have not been identified with certainty, but a possible candidate may be motor exhaust emissions. An effect of vehicle exhaust emissions on the GIT is plausible. Airborne particles emitted from petroleum or diesel engines contain numerous PAH and BaP. The mutagenic and carcinogenic effects of PAH and BaP are well documented in experimental studies (IARC 1989; Krewski and Rainham 2007). The postulation that a mechanism by which vehicle exhaust emissions might increase the risk of gastric cancer occurrence could be that airborne particles containing carcinogens are inhaled, then swallowed, and thus act directly as carcinogens on the gastric

mucosa (Guberan et al. 1992; Sjordahl et al. 2007).

The petrochemical industry is considered to be the main source of industrial air pollution in Taiwan (EPA/Taiwan 2002). The pollutants emitted by the petrochemical industries include not only PAH but also large quantities of criteria pollutants, particularly SO₂ and NO₂ (EPA/Taiwan 2002; Suess et al. 1985). The average levels of air pollutants in the municipalities with higher petrochemical air pollution exposure indices were higher than in those municipalities with lower petrochemical air pollution exposure indices (Yang et al. 1999). It is possible that a positive association between PSD and risk of death attributed to gastric cancer may be, at least partially, related to air pollution from petrochemical industries.

The completeness and accuracy of the death registration system needs to be evaluated before any conclusion based on mortality analysis is made. In Taiwan, it is mandatory to register any birth, death, marriage/divorce, and migration in the household registration offices. Demographic and vital statistics data derived from the household registration system are reliable and accurate in Taiwan. Although causes of death may be misdiagnosed and/or misclassified, the problem has been minimized through the improvement in the verification and classification of causes of death in Taiwan since 1972. Furthermore, malignant neoplasms, including gastric cancer, were found to be among the most unambiguously classified causes of death in Taiwan (Chen and Wang 1990). Because of the potentially fatal

outcome for this disease, it is postulated that all gastric cancer cases exposed to either high or low levels of air pollution had access to medical care regardless of geographical location in recent years.

Since the measure of effect in this study is mortality rather than incidence, migration during the interval between cancer diagnosis and death also needs to be considered. During this period, cancer diagnosis may influence a decision to migrate and possibly introduce bias. Data are not available for the differences in survival rates of gastric cancer patients between high and low PSD areas. If there is a trend toward migration to more urban or high PSD areas because of proximity to medical care for example, a spurious association between PSD and cancer death would result. Three aspects of this study presumably minimize this possibility. First, migration due to gastric cancer diagnosis would be less likely for married subjects (about 80% of cases and 73% of controls are married). For this cohort of decedents the subject's occupational status would weigh against a move requiring a job change late in life. Second, urbanization level was included as a control variable in the analysis. Finally, the ages for both cancer cases and controls were between 50 and 69 yr, and it was presumed that the elderly are more likely to remain in the same residence.

Of greater concern is whether the relative levels of PSD in the period around 2008 corresponded to the relative levels occurring in periods 20–30 yr earlier. This is important since it is likely that exposure to causal factors would precede cancer mortality. However, it is possible that the correlation between the current PSD levels (2008) and levels in the past of 20–30 yr ago would be high since a municipality's urban development is gradual. It was therefore assumed that levels of PSD in 2008 were a reasonable indicator of historical levels occurring over the past 20–30 yr.

Our study employed an ecologic design using group-level exposure data. It was presumed that individuals residing in the municipalities of higher levels of PSD experienced a greater exposure to benzene and other PAH

present in evaporative losses of petrol and/or to air emissions from motor vehicles. Nonetheless, significant air pollutant concentrations may differ substantially within a municipality and therefore group exposure levels may not necessarily correspond to individual exposure levels (Reynolds et al. 2003). Further, potential exposure misclassification may also have resulted from differing individual time–activity and personal exposure from indoor sources (Elliott et al. 2000). While these sources of misclassification are important, such misclassification of exposure is most likely to be nondifferential (i.e., unlikely to be associated with gastric cancer development), which would reduce the magnitude of association rather than introduce a positive bias in the association. Therefore, it is not likely that the observed positive association between PSD exposure and higher risk of death due to gastric cancer was a result of exposure misclassification. Similarly, a study of this nature can not account for variations in susceptibility among individuals with comparable exposure.

Cigarette smoking, consumption of alcohol, green tea, salted or cured meat, smoked or fried food, and fermented beans (Lee et al. 1990), and *Helicobacter pylori* (Wu et al. 2009) are documented risk factors for gastric cancer occurrence in Taiwan. There is, unfortunately, no information available on these variables for individual study subjects. These risk factors represent potential confounders that need to be taken into account when investigating the role of traffic air pollution in gastric cancer development. However, there is no reason to believe that there would be any correlation between these potential confounders and PSD levels, and therefore the estimated effects of traffic air pollution on gastric cancer are likely to be free of confounding by these variables. Data on other suspected risk factors for gastric cancer, such as occupational exposure to carcinogens acting on the GIT and socioeconomic status (such as income levels) for the study subjects were not collected (Ji and Hemminki 2006). Areas with high industrial activity have higher air pollution levels and individuals who work in those industries

tend to reside close to these sites. It is, therefore, likely that people with high occupational exposures tend to reside in areas with higher air pollution levels. However, it is difficult to predict how the distributions of these variables might have differed according to PSD and hence, acted to confound the associations observed in the present study. For these reasons, the results of this study need to be considered hypothesis driven. Even though more complete information would have been desirable, one measure of the study's internal validity is that the observed associations for PSD pointed in the direction expected based on previous investigations.

In summary, the present study showed that individuals who resided in the group of municipalities with high PSD levels were at an increased risk of death attributed to gastric cancer compared to those living in municipalities with low PSD. The findings of this study warrant further investigation into the role of air pollutants in the etiology of gastric cancer development. Future study would increase the precision of estimation of the individual's air pollution exposure and take into account indoor as well as mobile pollution sources, and control for confounding factors such as smoking, diet, and occupation.

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