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Ambient Exposure to Criteria Air Pollutants and Risk of Death from Bladder Cancer in Taiwan

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To investigate the relationship between air pollution and risk of death from bladder cancer, the authors conducted a matched case-control study using deaths that occurred in Taiwan from 1995 through 2005. Data on all eligible bladder cancer deaths were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. The control group consisted of people who died from causes other than cancer or diseases associated with genitourinary problems. The controls were pair matched to the cases by sex, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each case. Classification of exposure to municipality air pollution was based on the measured levels of nitrogen dioxide and sulfur dioxide. The results of the present study show that there is a significant positive association between the levels of air pollution and bladder cancer mortality. The adjusted odds ratios (95% confidence interval) were 1.37 (1.03–1.82) for the group with medium air pollution level and 1.98 (1.36–2.88) for the group with high air pollution level when compared to the group with the low air pollution level. Trend analyses showed statistically significant trend in risk of death from bladder cancer with increasing air pollution level. The findings of this study warrant further investigation of the role of air pollutants in the etiology of bladder 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). Air pollution is a complex mixture of different gaseous and particulate components, and it is difficult to define an exposure measure of relevance when the biological mechanisms are largely unknown (Boffetta & Nyberg, 2003). Many of the chemical compounds are formed by incomplete combustion of fossil fuels and are present in the exhaust gases from petroleum and diesel vehicles, including polycyclic aromatic hydrocarbons (PAHs) and benzo[a]pyrene (BaP) (Soll-Johanning et al., 1998). The mutagenic and carcinogenic effects of PAHs and BaP are well documented in experimental studies (IARC, 1989).

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The evidence regarding air pollution and lung cancer has been the subject of several reviews (Hemminki & Pershagen, 1994; Katsouyanni & Pershagen, 1997; Cohen, 2000; Boffetta & Nyberg, 2003; Vineis et al., 2004). However, limited results are available for bladder cancer. Excess risk of bladder cancer has been reported to be associated specifically with traffic-related air pollution among professional drivers, especially truck drivers (Silverman et al., 1986; Boffetta & Silverman, 2001). Although the specific exposure responsible for the elevation of risk among drivers has not been identified, one likely candidate is motor exhaust. An effect of vehicle exhaust on the bladder is plausible because metabolites of PAHs and nitro-PAHs present in exhaust emissions are concentrated in the urine and may interact with the urothelium of the bladder (Silverman et al., 1986). An increased risk of bladder cancer was also observed among workers in industries with high exposure to PAHs (Kogevinas et al., 2003; Boffetta et al., 1997). Furthermore, studies have shown an elevated risk for bladder cancer in urban populations compared to nonurban ones (Blot & Fraumeni, 1978; Greenberg, 1983; Muir et al., 1987). It is suspected that ambient air pollution is partly responsible for these differences, but its quantitative importance is largely unknown.

Although most of the recent epidemiological research has focused on the effects of short-term exposures, several studies suggest that long-term 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 one study has examined the risk of bladder cancer and exposure to ambient air pollution (Castano-Vinyals et al., 2008). Castano-Vinyals et al. (2008) examined the association of bladder cancer risk with air pollution (particularly industrial emissions and surrogate indices of vehicle emissions), using variables including the size of the city residence, windows facing traffic street at home, numbers of lanes and intensity of traffic that the residence faced, and having an industry with within 1 km of residence, in a large hospital-based case-control study. Living in a city with a population of more than 100,000 was associated with an increased risk for bladder cancer. A higher but not statistically significant association was found with PAH emissions or diesel from industries near the residence, as evaluated by experts, while lower or no excess risk was observed for other indices of air pollution. The study reported here was designed to explore further the possible association of bladder cancer mortality and long-term exposure to criteria air pollutants in Taiwan.

MATERIAL AND METHODS

Study Areas

Taiwan is divided into 361 administrative districts, which are referred to in this report as municipalities. They are the units that are subjected here to statistical analysis. In 1994, a network of 66 air quality monitoring stations was established in 66 municipalities by the Environmental Protection Administration (EPA) in Taiwan. Among these, two stations were excluded because they were situated in the National Park areas and served as background monitoring sites. The elimination left 64 monitoring stations situated in 64 municipalities for study. These 64 municipalities provide an opportunity to investigate the impact of air pollution on bladder cancer.

Subject Selection

Data on all deaths of residents living in the study areas from 1995 through 2005 were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health, which is in charge of the death registration system in Taiwan. For each death, detailed demographic information, including sex, occupation, marital status, year of birth, year of death, cause of death, place of death (municipality), and residential district (municipality), were recorded on computer tapes. The case group consisted of all eligible bladder cancer deaths occurring in people between 50 and 69 yr of age (International Classification of Diseases 9th rev. [ICD-9], code 188). We excluded patients younger than age 50 because the characteristics of early-onset bladder cancer are thought to be different from the more prevalent later-onset bladder cancer (Schottenfeld & Fraumeni, 1996). We excluded bladder cancer cases older than age 70 because of the difficulty in obtaining matched control subjects for them. Controls were drawn from all other deaths excluding deaths due to neoplasms and diseases which were associated with genitourinary diseases (ICD9 codes 170–189 and 580–598). Control subjects were pair matched to the cases by sex, year of birth, and year of death. Each matched control was selected randomly from the set of possible controls for each case.

Air Pollution Exposure Estimates

We obtained air quality data on measured concentrations of five "criteria" pollutants (PM_{10}, O_3, CO, NO_2, and SO_2) for study municipalities from the EPA's air quality monitoring stations for 1995–2005. The monitoring stations were fully automated and provided daily readings of levels of sulfur dioxide (SO_2) (by ultraviolet fluorescence), particulate matter (PM_{10}) (by beta-ray absorption), nitrogen dioxide (NO_2) (by ultraviolet fluorescence), carbon monoxide (CO) (by nondispersive infrared photometry), and ozone (O_3) (by ultraviolet photometry).

We used the following measures for each of the pollutants: (a) PM_{10}, SO_2, and NO_2—annual mean of the average daily 24-h values; (b) ozone—annual mean of the maximum 1h value per day; (c) CO—annual mean of the maximum 8h value for each day.

The municipality of residence for all cases and controls was identified from their death certificates. For study subjects, their municipality of residence formed the only basis for estimating their air pollution exposure.

Socioeconomic Factor

It has been found that mortality from cancer is associated with urbanization gradients (Greenberg, 1983; Swoboda & Friedl,

1991; Miller et al., 1987). In this study, an urbanization index (Tzeng & Wu, 1986) was used to adjust for possible confounding resulting from the different urbanizational levels among the municipalities. 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 has been used in our previous studies (Yang et al., 1999; Yang & Hsieh, 1998; Yang, 2004; Chiu et al., 2006; Liu et al., 2008). For the analyses, we further divided the urban-rural classification into two levels: I, urban areas (categories 1–4); and II, rural areas (categories 5–8).

Statistical Analysis

In the analysis, the subjects were divided into tertiles according to the levels of the five criteria air pollutants. Multiple logistic regression was used to estimate the relative risk in relation to air pollutants levels (Breslow & Day, 1980). We calculated odds ratios (ORs) and their 95% confidence intervals (95% CI) using the group with the lowest exposure as the reference group. All ORs 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 cases and controls by selected demographic and residential characteristics is shown in Table 1. Subjects who lived in urban municipalities had a significant excess risk of death from bladder cancer compared with those lived in rural municipalities. Cases and controls did not differ significantly in marital status.

Table 2 shows the distribution of the five criteria air pollutants and their associated crude ORs for the study subjects. There was no significant association between the risk of death from bladder cancer and O_3 and CO levels. SO_2 was positively associated with the risk of death from bladder cancer. Compared with the lowest tertile category, the OR of the risk of death from bladder cancer was 1.42 (1.10–1.85) for the middle tertile category, and 1.73 (1.32–2.27) for the highest tertile category, and the trend of increasing risk with increasing SO_2 levels was highly significant (p for trend $< .001$). There was also a trend for increased risk of death from bladder cancer associated with NO_2 levels (p for trend $= .002$), with an OR of 1.41 (1.08–1.84) in the middle tertile category and 1.73 (1.32–2.34) in the highest tertile category. A significant increase in risk of death from bladder cancer was seen in the highest tertile category of PM_{10} (OR = 1.39, 95% CI = 1.06–1.83) but not in the middle tertile category (OR = 1.08, 95% CI = 0.83–1.41). The test of trend for these associations were statistically significant ($p = .02$).

Since the results for SO_2 and NO_2 were more suggestive of a positive association with the risk of death from bladder cancer, a combined index of exposure to community air pollution based on SO_2 and NO_2 concentrations was developed subsequently using three levels: low = $NO_2 \leq 20.99$ ppb (the lowest tertile) and $SO_2 \leq 4.32$ ppb (the lowest tertile); high = $NO_2 \geq 27.33$ ppb (the highest tertile) and $SO_2 \geq 6.49$ ppb (the highest tertile); medium = others.

Table 3 shows the distribution of the resulting variable. The ORs for the risk of death from bladder cancer were significantly higher for the two groups with high levels of air pollution. The

TABLE 1
Characteristics of study population enrolled in the study

Characteristics	Cases ($n = 680$)	Controls ($n = 680$)	Crude OR (95% CI)
Enrollment municipality	64	64	
Age (yr)			
50–54	74 (10.9%)	74 (10.9%)	
55–59	118 (17.3%)	118 (17.3%)	
60–64	191 (28.1%)	191 (28.1%)	
65–69	297 (43.7%)	297 (43.7%)	
Gender			
Male	461 (67.8%)	461 (67.8%)	
Female	219 (32.2%)	219 (32.2%)	
Marital status			
Single	31 (4.5%)	47 (6.9%)	1.00
Married	518 (76.2%)	509 (74.9%)	1.07(0.82–1.40)
Ever married	131 (19.3%)	124 (18.2%)	0.90(0.39–2.08)
Urbanization level of residence			
Rural	85 (12.5%)	111 (16.3%)	1.00
Urban	595 (87.5%)	569 (83.7%)	1.43(1.03–1.99)

TABLE 2
Distribution of five criteria air pollutants and unadjusted odds ratio (OR) for study subjects

Pollutants	Cases ($n = 680$)	Controls ($n = 680$)	Crude OR (95% CI)
NO_2 (ppb) (median)			
≤20.99	200 (29.4%)	253 (37.2%)	1.00
21.19–26.87 (24.09)	238 (35.0%)	226 (32.1%)	1.41 (1.08–1.84)
27.33–44.85 (29.54)	242 (35.6%)	201 (29.6%)	1.73 (1.27–2.34)
			p for trend = .002
SO_2 (ppb) (median)			
≤4.32	196 (28.8%)	261 (38.4%)	1.00
4.39–6.09 (5.05)	240 (35.3%)	227 (33.4%)	1.42 (1.10–1.85)
6.49–17.87 (9.98)	244 (35.9%)	192 (28.2%)	1.73 (1.32–2.27)
			p for trend < .001
PM_{10} ($\mu g/m^3$) (median)			
≤52.80	213 (31.3%)	241 (35.4%)	1.00
53.04–71.72 (57.46)	221 (32.5%)	235 (34.6%)	1.08 (0.83–1.41)
72.24–90.29 (80.62)	246 (36.2%)	204 (30.0%)	1.39 (1.06–1.83)
			p for trend = .020
CO (ppm) (median)			
≤0.64 (0.52)	216 (31.7%)	238 (35.0%)	1.00
0.63–0.79 (0.72)	231 (34.0%)	230 (33.8%)	1.11 (0.86–1.43)
0.81–2.99 (0.94)	233 (34.3%)	212 (31.2%)	1.24 (0.94–1.63)
			p for trend = .152
O_3 (ppb)(median)			
≤22.41 (20.71)	229 (33.7%)	225 (33.1%)	1.00
22.42–25.06 (23.71)	216 (31.7%)	238 (35.0%)	0.88 (0.68–1.16)
25.11–35.70 (27.03)	235 (34.6%)	217 (31.9%)	1.07 (0.82–1.39)
			p for trend = .642

TABLE 3
Odds ratios (ORs) and 95% confidence interval (CI) for bladder cancer associated with air pollution exposure index based on multiple logistic regression model

Pollutants	Cases ($n = 680$)	Controls ($n = 680$)	Crude OR (95% CI)	Adjusted OR (95% CI)
Air pollution level[a]				
Low	125 (18.4%)	172 (25.3%)	1.00	1.00
Medium	400 (58.8%)	396 (58.2%)	1.44 (1.10–1.90)	1.37 (1.03–1.82)
High	155 (22.8%)	112 (16.5%)	2.09 (1.46–3.01)	1.98 (1.36–2.88)
Marital status				
Single	31 (4.5%)	47 (6.9%)	1.00	1.00
Married	518 (76.2%)	509 (74.9%)	1.07(0.82–1.40)	1.05 (0.80–1.38)
Ever married	131 (19.3%)	124 (18.2%)	0.90(0.39–2.08)	0.89 (0.38–2.10)
Urbanization level of residence				
Rural	85 (12.5%)	111 (16.3%)	1.00	1.00
Urban	595 (87.5%)	569 (83.7%)	1.43(1.03–1.99)	1.23 (0.87–1.75)

[a]Low, $NO_2 \leq 20.99$ ppb (the lowest tertile) and $SO_2 \leq 4.32$ ppb (the lowest tertile); high, $NO_2 \geq 27.33$ ppb (the highest tertile) and $SO_2 \geq 6.49$ ppb (the highest tertile); medium, others.

urbanization level of residence was correlated with air pollution categories (data not shown) but was controlled for in the multivariate analyses. Adjustments for the urbanization level of residence and marital status only slightly altered the ORs. Therefore, the adjusted ORs presented in Table 3 can be interpreted as free from confounding by the earlier mentioned variables. The adjusted OR (95% CI) was 1.37 (1.03–1.82) for the group with medium air pollution level and 1.98 (1.36–2.88) for the group with high air pollution level when compared to the group with the low air pollution level. Trend analyses showed statistically significant trend in risk of death from bladder cancer with increasing air pollution level (p for trend $<.001$).

DISCUSSION

This study used a death-certificate-based case-control study to examine the relationship between the risk of death from bladder cancer and outdoor air pollution in Taiwan. The results of the present study show that people who lived in the group of municipalities with high levels of air pollution (based on measured levels of NO_2 and SO_2) were at a statistically significant increased risk of death from bladder cancer compared to the group living in municipalities with the low air pollution level after controlling for possible confounders.

There have been a number of epidemiological studies that have assessed the increased risk of bladder cancer from living in an urban rather than a rural area. In general, bladder cancer mortality had been considerably higher in urban populations than nonurban ones (Blot & Fraumeni, 1978; Greenberg, 1983; Muir et al., 1987). The only "urban factor" consistently mentioned in the literature is air pollution, suggesting that living in an urban area is a surrogate for increased air pollution exposure (Greenberg, 1983).

The five pollutants identified as being of greatest concern from a health perspective, known as "criteria" pollutants, are O_3, PM_{10}, SO_2, NO_2, and CO. Our study found that NO_2 and SO_2 were more likely to be responsible for the increased risk of death from bladder cancer. To the authors' knowledge, no studies have investigated the association between ambient criteria air pollutants and the risk of death from bladder cancer.

Our previous study found that death from lung cancer for females is significantly associated with residential petrochemical air pollution (Yang et al., 1999). The average levels of air pollutants in the municipalities with higher petrochemical air pollution exposure index were higher than in those municipalities with lower petrochemical air pollution exposure index (Yang et al., 1999). Levels of traffic intensity were not available to validate the traffic-related exposure to air pollutants. It is possible that our finding of a positive association between air pollution and the risk of death from bladder cancer may be at least partially related to air pollution from petrochemical industries. 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 PAHs but also large quantities of criteria pollutants, particularly SO_2 and NO_2 (EPA/Taiwan, 2002; Suess et al., 1985). To our knowledge there is only one epidemiologic study examining the relationship between risk of bladder cancer and living near specific sources of industrial air pollution (Castano-Vinyals et al., 2008). A higher but not statistically significant risk was observed among subjects with residence within 1 km of an industry with either PAH or diesel emissions.

Despite their inherent limitations (Morgenstern, 1982), studies of ecological correlation between mortality and environmental exposures are widely used to generate or discredit epidemiological hypotheses. Before any conclusion based on such a mortality analysis is made, however, the completeness and accuracy of the death registration system needs to be evaluated. In Taiwan, any birth, death, marriage/divorce, and migration is mandatory to register in the household registration offices. Demographic and vital statistics data derived from the household registration system are quite complete 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 bladder cancer, were found to be among the most unambiguously classified causes of death in Taiwan (Chen & Wang, 1990). Because of the potentially fatal outcome for this disease, it is believed that all bladder cancer cases exposed to either high or low levels of air pollution have had access to medical care regardless of geographical location.

Since the measure of effect in this study is mortality rather than incidence, migration during the interval between cancer diagnosis and death must also 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 bladder cancer patients between high and low air pollution exposure areas. If there is a trend toward migration to more urban or high air polluted areas because of proximity to medical care for example, a spurious association between air pollution exposure and cancer death would result.

Of greater concern is whether the 11-yr (1995–2005) avarage levels of air pollution correspond to the relative levels in periods 20–30 yr previously. This is important since it is likely that exposure to causal factors would precede cancer mortality by at least 20 yr (the latency period for carcinogen exposure). The air pollution levels are not available for the study areas before 1995. However, we believe that the correlation between the current levels (1995–2005) and levels 20–30 yr ago would be high since a municipality's urbanization and industralization are gradual. We therefore assumed that average levels of air pollution in the study periods were a reasonable indicator of historical levels occurring over the past 20 to 30 yr.

Our study employed an ecologic design using group level exposure data. It was assumed that individuals living in the municipalities of higher air pollution exposure index, on average, experienced a higher exposure to hazardous air pollutants than subjects residing in municipalities with less air pollution.

Previously, Yang et al. (1999) verified this phenomenon. However, significant concentration variations might exist within a municipality and therefore group exposure levels do not necessarily correspond to individual exposure levels (Reynolds et al., 2003). Likewise, a study of this nature can not account for variations in susceptibility among individuals with comparable exposures (Reynolds et al., 2003). Additionally, potential exposure misclassification may also have resulted from differing individual time-activity and behavior patterns of each subject (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 bladder cancer), which would reduce the magnitude of association rather than introduce a positive bias into the association. Therefore, it is unlikely that the observed positive association between air pollution exposure index and the risk of death from bladder cancer was a result of exposure misclassification. To our knowledge, this is the first study to find a significant association between residential exposure to air pollution exposure index and risk of death from bladder cancer. However, because there is no evidence to date for an association between residential exposure to air pollution and risk of death from bladder cancer, the possibility that this is a chance finding needs to also be considered.

Long-term arsenic exposure from drinking water has been found to be associated with bladder cancer mortality in Taiwan (Chen et al., 1988). However, this was found only in a limited area in four municipalities, which were in the so-called blackfoot disease (BFD) endemic areas. Residents in BFD endemic areas consumed artesian well water with high arsenic content (ranged from 0.35 to 1.14 ppm) since 1910. These 4 municipalities were not included in our 64 study municipalities. All residents in the study area obtained their drinking water from public drinking water supply systems served by the Taiwan (or Taipei) Water Supply Corp. The tap water came from several water reservoirs. The arsenic concentration of water in these reservoirs was nondetectable (<0.9 ppb) (TWSC, 1997). Therefore, the potential influence from arsenic in drinking water is probably not important.

Cigarette smoking is well established as a cause of bladder cancer (Alberg et al., 2007; Zeegers et al., 2000; Schottenfeld & Fraumeni, 1996). As with active cigarette smoking, environmental tobacco smoke (ETS) contains arylamines, which are established bladder carcinogens (Vineis et al., 2004). The dose of carcinogens from ETS is relatively small compared to that from active smoking, but it has been hypothesized to make a disproportionately large contribution to bladder carcinogenesis (Vineis et al., 2004). There is, unfortunately, no information available on these variables for our individual study subjects. We also did not collect data on other suspected risk factors for bladder cancer, such as occupation exposure to bladder carcinogens and socioeconomic status (such as income levels) for the study subjects (Schottenfeld & Fraumeni, 1996). Areas with high industrial activity have higher air pollution levels and the people who work in those industries tend to live around them. It is, therefore, likely that people with high occupational exposures tend to live in areas with higher air pollution levels. However, it is difficult to predict how the distributions of these variables might have differed according to air pollution exposure and hence, acted to confound the associations observed in the present study. For these reasons, the results of this study should be considered hypothesis-generating. Even though more complete information would have been desirable, one measure of the study's internal validity is that the observed associations for air pollution exposure pointed in the direction expected based on previous research.

In summary, this study shows that under the conditions found in Taiwan, air pollution may increase the risk of death from bladder cancer. The findings of this study warrant further investigation of the role of air pollutants in the etiology of bladder cancer. Future study should increase the precision of the 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 and occupation.

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