Aerosol and Air Quality Research, 12: 275–282, 2012

ISSN: 1680-8584 print / 2071-1409 online
doi: 10.4209/aaqr.2011.09.0155

Traffic Air Pollution and Risk of Death from Breast Cancer in Taiwan: Fine Particulate Matter ($PM_{2.5}$) as a Proxy Marker

Li-Ju Hung[1,2], Shang-Shyue Tsai[3], Pei-Shih Chen[4], Ya-Hui Yang[5], Saou-Hsing Liou[6], Trong-Neng Wu[6,7], Chun-Yuh Yang[4,6*]

[1] *Department of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan*
[2] *Department of Family Medicine, Kaohsiung Veterans General Hospital, Ksohsiung, Taiwan*
[3] *Department of Healthcare Administration, I-Shou University, Kaohsiung, Taiwan*
[4] *Department of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan*
[5] *Department of Occupational Safety and Hygiene, Fooyin University, Kaohsiung, Taiwan*
[6] *Division of Environmental Health and Occupational Medicine, National Health Research Institute, Miaoli, Taiwan*
[7] *Graduate Institute of Public Health, China Medical University, Taichung, Taiwan*

ABSTRACT

The relationship between breast cancer mortality and air pollution was examined using an ecological design. The study areas consisted of 61 municipalities in Taiwan. Air quality data for recorded concentrations of fine particulate matter ($PM_{2.5}$) from study municipalities for 2006–2009 were obtained as a marker of traffic emissions and were used as a proxy for polycyclic aromatic hydrocarbons (PAHs) exposure. Age-standardized mortality rates for breast cancer mortality were calculated for the study municipalities for the years 1999–2008. A weighted multiple regression model was used to calculate the adjusted risk ratio in relation to $PM_{2.5}$ levels. Results showed that individuals who resided in municipalities with the highest $PM_{2.5}$ were at an increased risk of death from breast cancer. This study is the first to suggest that exposure to high levels of $PM_{2.5}$, a proxy measure of PAHs, may be associated with an increased risk of death from breast cancer. The findings of this study warrant further investigation into the role of air pollutants in the risk of breast cancer.

Keywords: Traffic air pollution; Breast cancer; Fine particulate matter.

INTRODUCTION

The incidence of breast cancer varied widely internationally, with the highest rates observed in North America and Europe and the lowest rates in Asia (Schottenfeld and Frauimeni, 1996). In Taiwan, the incidence rates for breast cancer was 51.95 per 100,000 in 2008 (DOH, 2008). Breast cancer is the fourth leading cause of female cancer mortality (DOH/Taiwan, 2011). The age-adjusted mortality rate for breast cancer was 11 per 100,000 in 2010. There is substantial geographic variation in female breast cancer mortality within the country (NHRI/Taiwan, 2004), which suggests an environmental risk factor may be involved.

The known risk factors for breast cancer are primarily related to the reproductive life of women and inheritance (e.g., BRCA1 and BRCA2 gene mutations) (Coyle, 2004). Only about one-third of new cases of breast cancer are attributable to known risk factors, and much of the etiology remains unexplained (Coyle, 2004; Crouse *et al.*, 2010). Therefore it has been hypothesized that environmental exposures may also contribute to breast cancer risk (Laden and Hunter, 1998; Coyle, 2004).

Ambient outdoor air pollution has been implicated as a cause of various health problems including cancer (Dominici *et al.*, 2005; Boffetta, 2006; Curtis *et al.*, 2006; 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; Chen and Li, 2010; Chuang *et al.*, 2010a; Shen *et al.*, 2010; Tsai *et al.*, 2011). Exhaust from traffic is a complex mixture of many chemical compounds, including benzene, polycyclic aromatic hydrocarbons (PAHs) and benzo[a]pyrene (B[a]P) (Chuang *et al.*, 2010b; Wu *et al.*, 2010; Huang *et al.*, 2011a, b; Kao *et al.*, 2011). The International Agency for Research on Cancer (IARC) classified the emission of diesel exhaust engine compounds

* Corresponding author. Tel.: 886-7-3121101 ext. 2141; Fax: 886-7-3110811
E-mail address: chunyuh@kmu.edu.tw

as probably carcinogenic (Group 2A) and gas engine exhaust compounds as possibly (Group 2B) carcinogenic to humans (IARC, 1989).

According to occupational epidemiologic studies, excess risks of breast cancer were reported to be associated with occupational exposure to PAHs among pre- and postmenopausal women (Petralia *et al.*, 1999; Gammon *et al.*, 2002; Labreche *et al.*, 2010). Given that these same pollutants are present in the motor vehicle exhaust, it is plausible that traffic-related exposures may contribute to the risk of breast cancer (Crouse *et al.*, 2010). Several studies reported an increased risk for breast cancer in association with surrogate measures of exposure to vehicle exhaust, including emissions associated with heavy traffic density (Lewis-Michl *et al.*, 1996), total suspended particulates (TSP) (Bonner *et al.*, 2005), estimated exposures to B[a]P derived from a traffic emissions model (Nie *et al.*, 2007), and estimated nitrogen dioxide (NO_2) derived from a land-use regression model (Crouse *et al.*, 2010).

In Taiwan, the major source of PAHs is traffic exhaust (Chang *et al.*, 2003). PAHs can be present in particulate or gaseous phase. Gaseous PAHs usually contain more fractions of less carcinogenicity and lower molecular weights, while particulate PAHs contain more fractions of higher carcinogenicity and higher molecular weights (Chang *et al.*, 2006). PAHs with high molecular weights are often more carcinogenic than those with low molecular weights (Ravindra *et al.*, 2001). Therefore particulate phase PAHs are considered to be the most hazardous substances to human health. Most of the PAHs were in the particulate phase. Ninety to 95% of particulate phase PAHs are physically associated with particular matter (PM) < 3.3 μm (Ravinndra *et al.*, 2001; Bonner *et al.*, 2005). These small particles are thought to have biological relevance because they can be inhaled and deposited in the lower respiratory tract (Bonner *et al.*, 2005).

The study reported here was designed to explore further whether the risk of death from breast cancer is associated with exposure to PAHs, using fine particulate matter ($PM_{2.5}$), a marker of traffic-related air pollution, as a proxy for PAHs exposure in Taiwan.

METHODS

Study Areas

Taiwan is divided into 359 administrative districts, which are referred to in this study as municipalities. In 1994, a network of 66 air pollution 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. In addition, three stations were removed due to the reconstruction of the buildings where there were built during 2000–2007, and were excluded from analysis. This elimination left 61 monitoring stations situated in 61 municipalities for study (Fig. 1). These 61 municipalities provide an opportunity to investigate the impact of $PM_{2.5}$ air pollution on the risk of death from breast cancer.

Fig. 1. Locations of the monitoring stations in this study.

$PM_{2.5}$ Exposure Estimates

There is an extensive air pollution monitoring network in Taiwan, managed by Taiwan EPA as mentioned above, which routinely monitors five "criteria" pollutants (PM_{10}, O_3, CO, SO_2, NO_2). However, $PM_{2.5}$ was not regularly monitored. The monitoring stations were fully automated and provided daily readings of polutant levels.

$PM_{2.5}$ concentrations in Taiwan have been measured continuously since 2006. The monitoring stations provided data for $PM_{2.5}$ in mean daily mass concentration ($\mu g/m^3$). The availability of the monitoring network for $PM_{2.5}$ provides an opportunity to investigate the impact of fine particle air pollution on female breast cancer mortality. We obtained $PM_{2.5}$ data for study municipalities from the EPA's air quality monitoring stations for 2006–2009. The municipality of residence for all cases and controls was identified from death certificates. The municipality of residence formed the only basis for estimating their fine particulate air pollution exposure.

Mortality

Information concerning both the number of death and Taiwan's midyear population by sex, age, calendar year and municipality from 1999–2008 was obtained from the Department of Health which is in charge of the death registration system in Taiwan. In this study, female breast cancer deaths were those that were defined by the International Classification of Disease, Injury and Causes of Death (ICD-9 code 174). As the age distribution was not comparable among the 61 municipalities, the age standardized rates (ASR) were computed by the direct method, using the world population in 2000 as the standard population (Ahmad *et al.*, 2000).

Fertility

Reproduction, particularly early full-term pregnancy, seems to exert a protective effect against breast cancer (Kelsey, 1979; Wigle, 1977; Rosenwaike, 1980; Remennick,

1989). One indicator of reproduction was available at the municipality level in Taiwan where fertility rates were recorded for different time periods from 1971 till now. In this study the fertility rates from 1971 for females aged 20–24 years were used to study the possible beneficial effect that early pregnancy might have in the prevention of breast cancer mortality (MOI/Taiwan, 1973). Fertility rates for earlier than 1971 would have been preferable; however, data were not available. An assumption was thus made that a municipality with high average fertility rates in 1971 would also have higher than average rates prior to 1971.

Socioeconomic Factors

It was found that mortality attributed to cancer was associated with urbanization gradients (Yang and Hsieh, 1998; Reynolds *et al.*, 2004a; Hall *et al.*, 2005). In this study, an urbanization index (Tzeng and Wu, 1986) was used to adjust for possible confounding resulting from different urbanizational 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 (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, the 61 municipalities were divided into tertiles according to the levels of $PM_{2.5}$ and the fertility rates. The risk ratios were calculated in relation to the group with the lowest exposure level. A weighted multiple regression model was used to calculate the adjusted risk ratio. In addition to the levels of $PM_{2.5}$, both fertility rates and urbanization index were included in the multiple regression analysis to adjust for the possible influence on the increased risk of death from breast cancer and to obtain a better estimate of the impact of $PM_{2.5}$ on the risk of death from breast cancer. Since Taiwan municipalities vary greatly in size, the regression model used took into account the size of the municipalities. For each municipality the weight used was the square root of person-years (Draper and Smith, 1998). A Wald chi-square test for linear trend was also performed by entering $PM_{2.5}$ exposures as a 3-level ordinal variable (with the values 0–2) (Rothman and Greenland, 1998). Values of $p < 0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

Average annual age-standardized breast cancer mortality rates per 100,000 (ASR) for 1999–2008 by tertiles of $PM_{2.5}$ levels and fertility rates are listed in Table 1.

The crude risk ratios for death from breast cancer were significantly higher for the group with the highest levels of $PM_{2.5}$. Further, municipalities with high fertility rates have a statistically significant lower risk of death from breast cancer (Table 2).

Results of the weighted multiple regression analyses are shown in Table 2. Adjustments for possible confounders (the urbanization level and fertility rate) did not markedly alter the risk ratio. The adjusted RR (95% CI) were 1.12 (0.96–1.32) for the group with $PM_{2.5}$ levels between 30.48 $\mu g/m^3$ and 39.41 $\mu g/m^3$ and 1.19 (1.03–1.38) for the group with $PM_{2.5}$ levels between 39.48 $\mu g/m^3$ and 51.10 $\mu g/m^3$, compared to the group with the lowest $PM_{2.5}$ levels. Trend analyses showed statistically significant trend in risk of death attributed to breast cancer with increasing $PM_{2.5}$ levels. When we included $PM_{2.5}$ levels as a continuous variable, similar trend in results were observed as those found when $PM_{2.5}$ levels were examined as a categorical variable (a mortality rate of $0.065/10^5$ increase per 1 $\mu g/m^3$ of $PM_{2.5}$ increase). In contrast, there was a statistically significant decreasing trend in the risk of death from breast cancer with increasing fertility rates.

The results of the present study showed that individuals who resided in municipalities with the highest $PM_{2.5}$ levels, a proxy measure of PAHs, were at a significantly increased risk of death from breast cancer. This finding is essentially consistent with previous epidemiologic studies which examined the hypothesis that breast cancer may be associated with exposure to traffic air pollution (Bonner *et al.*, 2005; Nie *et al.*, 2007; Crouse *et al.*, 2010) and industrial pollution (Pan *et al.*, 2011).

There have been a number of epidemiological studies that assessed the increased risk of death from breast cancer development from living in an urban rather than a rural area. In general, breast cancer mortality had been considerably higher in urban populations than non-urban ones (Blot *et al.*, 1977; Goldsmith, 1980; Greenberg, 1983; Muir *et al.*, 1987; Kelesy and Berkowitz, 1988; Yang and Hsieh, 1998). The only "urban factor" consistently mentioned in the literature is air pollution, suggesting that residing in an urban area is a reliable surrogate for increased air pollution exposure (Greenberg, 1983).

The specific exposure chemicals responsible for the

Table 1. Mortality from breast cancer by $PM_{2.5}$ levels and fertility rates in 61 Taiwan's municipalities, 1999–2008.

	n	ASR[a]
$PM_{2.5}$ ($\mu g/m^3$)		
< 30.39	21	10.83 ± 3.15
30.48–39.41	20	11.90 ± 4.21
39.48–51.10	20	12.69 ± 2.95
Fertility rate (0/00)		
< 190	21	14.21 ± 2.11
191–229	20	12.11 ± 3.45
230–289	20	8.93 ± 2.66

[a] ASR: age-standardized rate ± standard deviation.

Table 2. Risk ratio (RR) of mortality from breast cancer in relation to $PM_{2.5}$ levels based on a weighted multiple regression model.

	n	Crude RR (95% CI)[a]	Adjusted RR (95% CI)[b]
$PM_{2.5}$ ($\mu g/m^3$)			
< 30.39	21	1.00	1.00
30.48–39.41	20	1.10 (0.90–1.34)	1.12 (0.96–1.32)
39.48–51.10	20	1.17 (1.00–1.37)	1.19 (1.03–1.38)
Fertility rate (0/00)			
< 190	21	1.00	1.00
191–229	20	0.85 (0.75–0.97)	0.87 (0.81–0.94)
230–289	20	0.63 (0.55–0.72)	0.63 (0.57–0.69)

[a] 95% confidence interval, [b] Adjusted for urbanization level.

elevation of risk of death from breast cancer have not been identified with certainty, but a possible candidate may be motor exhaust emissions because traffic emissions are the major source of air pollution in urban areas. An effect of vehicle exhaust emissions on the risk of death from breast cancer is plausible. Airborne particles emitted from petroleum or diesel engines contain numerous PAHs and BaP. The mutagenic and carcinogenic effects of PAHs and BaP are well documented in experimental studies (IARC, 1989; Musafia-Jeknic *et al*., 2005; Krewski and Rainham, 2007) and have been shown to cause mammary cancers in female rats (Maltoni *et al.*, 1997). In addition, PAHs may also have estrogenic and antiestrogenic properties that could affect breast cancer risk (Santodonato, 1997; Meek, 1998; Brody and Rudel, 2003). The postulation that a mechanism by which vehicle exhaust emissions might increase the risk of breast cancer occurrence could be that airborne particles containing PAHs, which are lipophilic and may therefore reach elevated concentrations in breast tissue and promote carcinogenesis in the cells of the breast (Morris and Seifter, 1992).

Traffic counts and proximity to roads have commonly served as surrogates for exposure to traffic-related potential carcinogens (Reynolds *et al.*, 2004b). 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). Lewis-Michl *et al.* (1996) conducted a study in Nassau and Suffolk Counties, New York State, suggested a possible increased breast cancer risk among women living close to areas characterized by relatively heavy traffic compared with other areas (OR = 1.29, 95% CI = 0.77–2.15). 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).

Benzene, total suspended particles (TSP) and NO_2 are commonly used markers for traffic-related air pollution (Muzykl *et al.*, 1998; Van Wijnen and Van der Zee, 1998; Raaschou-Nielsen *et al.*, 2001; Bedeschi *et al.*, 2007). 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. Gunier *et al.* (2006) has used geographic information system-based methods to estimate PAH exposure. Crouse *et al.* (2010) developed a land-use regression model to predict concentrations of NO_2 across Montreal and used NO_2 as a marker for traffic-related air pollution. They found evidence of an association between the incidence of postmenopausal breast cancer and exposure to ambient concentrations of NO_2. For each increase of 5 ppb NO_2, the adjusted odds ratio was 1.31 (95% CI = 1.00–1.71). However, it should be noted that NO_2 is only partly related to local sources (mainly traffic) as NO is quickly converted to NO_2 in reaction with ambient ozone. Only in areas with significant use of diesel vehicles reduce the problem of using NO_2 as a proxy for traffic pollution (Palmgren *et al.*, 1996). In the Western New York exposures and breast cancer (WEB) study, Bonner *et al.* (2005) found that TSP exposures, a surrogate for PAHs exposure, were associated with increased postmenopausal breast cancer risk. In a second analysis from that study, Nie *et al.* (2007) used a traffic emission model to estimate BaP exposure, a surrogate for PAHs, found evidence of increased breast cancer risk among women exposed to high traffic emissions exposure. To our knowledge, this study is the first to suggest that exposure to high levels of $PM_{2.5}$, a proxy measure of PAHs, may be associated with an increased risk of death from breast cancer.

It is mandatory to register any birth, death, marriage/divorce, and migration in the household registration offices in Taiwan. Demographic and vital statistics data derived from the household registration system are considered to be reliable and complete. Nonetheless, data on the accuracy of breast cancer diagnosis are not available in Taiwan and misclassification is possible. However, this misclassification is likely to be nondifferential (i.e., unlikely to be related $PM_{2.5}$) and therefore would tend to underestimate rather than overestimate the true association.

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 breast cancer patients between high and low $PM_{2.5}$ areas. If there is a trend toward migration to more urban or high $PM_{2.5}$ areas because of proximity to medical care for example, a spurious association between $PM_{2.5}$ and cancer death would

result. Our study population is stable in terms of mobility compared with populations in most industrialized countries, probably of culture factors (Yu *et al.*, 2006). Furthermore, urbanization level was included as a control variable in the analysis. Since it is conceivable that municipalities with similar urbanization levels may have similar migration rates, this probably minimized the migration problem in our study.

Previous studies reported associations between increased risk of breast cancer and early-life exposure (at first birth or menarche) to markers of air pollution (Bonner *et al.*, 2005; Nie *et al.*, 2007), but no associations with exposures 10 to 20 years before diagnosis. The lifetime residential history of each study subject is not available. The $PM_{2.5}$ levels are also not available before 2006. We could not examine associations with early-life exposures. Our study may thus have been limited by potential exposure misclassification. While these sources of misclassification are important, such misclassification of exposure is most likely to be non-differential (i.e., unlikely to be associated with breast cancer), which would reduce the magnitude of association rather than introduce a positive bias in the association.

Our study employed an ecologic design using group level exposure data. It was presumed that individuals residing in the municipalities of higher levels of $PM_{2.5}$ experienced a greater exposure to PAH from motor vehicles. Nonetheless, PAHs 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 (such as environmental tobacco smoke) (Elliott *et al.*, 2000). However, this misclassification is likely to be non-differential. Our results thus probably underestimate the true estimates of the relative risk of death from breast cancer associated with exposure to $PM_{2.5}$.

Body mass index, age at menarche, age at full-term pregnancy, parity, menopausal status and age at menopausal status, duration of lifetime lactation, use of lactation suppression hormones, and use of oral contraceptives are documented risk factors for breast cancer occurrence in Taiwan (Chie *et al.*, 1996a, b, 1997a, b, 1998). These risk factors represent potential confounders which needs to be taken into account when investigating the role of traffic air pollution in breast cancer mortality. There is, unfortunately, no information available on these variables for individual municipalities and thus could not be adjusted for directly in the analysis. In this study, an integrated indicator of urbanization level and a reproductive indicator (fertility rates) were used to adjust for possible confounding factors resulting from different socioeconomic characteristics and childbearing practices in municipalities. Further, even though more complete information would have been desirable, one measure of the study's internal validity is that the observed associations for $PM_{2.5}$ pointed in the direction expected based on previous investigations.

Recent studies suggest that smoking (Cui *et al.*, 2006; Johnson *et al.*, 2011; Luo *et al.*, 2011; Xue *et al.*, 2011) and environmental tobacco smoking (ETS) (Johnson *et al.*, 2011) increase the risk of breast cancer. There is unfortunately no information available on the prevalence rate of smoking and ETS for individual municipality and thus it could not be adjusted for in the analysis. However, the prevalence of smoking among females was very low (only about 4.2%) in Taiwan (Cheng *et al.*, 2001). We think that the degree to which not controlling for this variable may have affected our results should be small if it existed at all. Furthermore, there is no reason to believe that there would be correlation between ETS and the levels of $PM_{2.5}$.

Screening has been shown to be effective in reducing breast cancer mortality (Nelson *et al.*, 2009). Unfortunately, there is no information available on the prevalence of screening utilization for individual municipality studied and therefore it could not be adjusted for directly in the analysis. If breast cancer screening is correlated with the levels of $PM_{2.5}$, a spurious association between $PM_{2.5}$ and breast cancer death could result. However, there is no reason to believe that there would be any correlation between the habits of undergoing breast cancer screening and the levels of $PM_{2.5}$. Nonetheless, this is a limitation that should be considered.

$PM_{2.5}$ is considered to be the most relevant measure for biological effects of air pollution because these fine particles are respired into the lower respiratory tract (Pope and Dockery, 2006). Our findings should not be interpreted as meaning that $PM_{2.5}$ is a causal factor; it is more likely a marker of the complex mixture that is derived from motor vehicle exhaust (Crouse *et al.*, 2010). We speculated that PAHs physically associated with $PM_{2.5}$ may be the agent responsible for the association between $PM_{2.5}$ and risk of death from breast cancer risk. However, it is important to note that there are numerous other potential carcinogens in traffic emissions as well as PAHs (Nie *et al.*, 2007). We cannot rule out the possibility that other compounds present in $PM_{2.5}$ are affecting breast cancer risk or are acting synergistically with PAHs (Bonner *et al.*, 2005).

CONCLUSIONS

In summary, this study is the first to suggest that exposure to high levels of $PM_{2.5}$, a proxy measure of PAHs, may be associated with an increased risk of death from breast cancer. The findings of this study warrant further investigation into the role of air pollutants in the etiology of breast cancer development.

ACKNOWLEDGMENTS

This study was partly supported by a grant from the National Science Council, Executive Yuan, Taiwan (NSC-100-2314-B-037-023-MY2).

REFERENCES

Ahmad, O.E., Boschi-pinto C, Lopez, A.D., Murray, C.J.L., Lozano, R. and Inoue, M. (2000). Age Standardization of Rates: A New WHO Standard, GPE Discussion Paper

Series No. 31, Geneva: WHO.

Bedeschi, E., Campari, C., Candela, S., Collini, G., Caranci, N., Frasca, G., Galassi, C., Francesca, G. and Vigotti, M.A. (2007). Urban Air Pollution and Respiratory Emergency Visits at Pediatric Unit, Reggio Emilia, Italy. *J. Toxicol. Environ. Health Part A* 70: 261–265.

Blot, W.J., Fraumeni, J.F. and Stone, B.J. (1977). Geographic Patterns of Breast Cancer in the United States. *J. Nat. Cancer Inst.* 59: 1407–1411.

Boffetta, P. (2006). Human Cancer from Environmental Pollutants: The Epidemiologic Evidence. *Mutat. Res.* 608: 157–162.

Boffetta, P. and Nyberg, F. (2003). Contribution of Environmental Factors to Cancer Risk. *Br. Med. Bull.* 68: 71–94.

Bonner, M.R., Han, D., Nie, J., Rogerson, P., Vena, J.E., Muti, P., Trevisan, M., Edge, S.B. and Freudenheim, J.L. (2005). Breast Cancer Risk and Exposure in Early Life to Polycyclic Aromatic Hydrocarbons Using Total Suspended Particulates as a Proxy Measure. *Cancer Epidemiol. Biomarkers Prev.* 14: 53–60.

Brody, J.G. and Rudel, R.A. (2003). Environmental Pollutants and Breast Cancer. *Environ. Health Perspect.* 111: 2007–2019.

Chang, K.F., Fang, G.C., Chen, J.C. and Wu, Y.S. (2006). Atmospheric Polycyclic Aromatic Hydrocarbons (PAHs) in Asia: A Review from 1999 to 2004. *Environ. Pollut.* 142: 388–396.

Chang, K.F., Fang, G.C., Lu, C. and Bai, H. (2003). Estimation of PAH Dry Deposition by the Measurement of Both Gas and Particle Phase Concentrations. *Aerosol Air Qual. Res.* 3: 41–53.

Chen, C.J. and Wang, C.J. (1990). Ecological Correlations between Arsenic Level in Well Water and Age-adjusted Mortality from Malignant Neoplasms. *Cancer Res.* 50: 5470–5474.

Cheng, T.Y., Wen, C.P., Tsai, M.C. and Tsai, S.P. (2003). The Current Status of Smoking Behavior in Taiwan: Data Analysis from National Health Interview Survey in 2001. *Taiwan J. Public Health* 22: 453–464.

Cheng, Y.H. and Li, Y.S. (2010). Influences of Traffic Emissions and Meterological Conditions on Ambient PM_{10} and $PM_{2.5}$ Levels at a Highway Toll Station. *Aerosol Air Qual. Res.* 10: 456–462.

Chie, W.C., Chen, C.F., Lee, W.C. and Chen, C.J. (1996a). Body Size and Risk of Pre- and Post-manopausal Breast Cancer in Taiwan. *Anticancer Res.* 16: 3129–3132.

Chie, W.C., Chen, C.F., Lee, W.C. and Chen, C.J. (1996b). Socioeconomic Status, Lactation and Breast Cancer Risk of Parous Women in Taiwan. *Oncol. Rep.* 3: 497–501.

Chie, W.C., Chung, Y.L., Huang, C.S., Chang, K.J., Yen, M.L. and Lin, R.S. (1998). Oral Contraceptives and Breast Cancer Risk in Taiwan, a Country of Low Incidence of Breast Cancer and Low Use of Oral Contraceptives. *Int. J. Cancer* 77: 219–223.

Chie, W.C., Fu, C.M., Lee, W.C., Li, C.Y., Huang, K.J. and Lin, R.S. (1997b). Ages at Different Reproductive Events, Number of Menstrual Cycles in between and Breast Cancer Risk. *Oncol. Rep.* 4: 1039–1043.

Chie, W.C., Lee, W.C., Li, C.Y., Huang, K.J., Chang, K.J., Yen, M.L. and Lin, R.S. (1997a). Lactation, Lactation Suppression Hormones and Breast Cancer: A Hospital-based Case-control Study for Parous Women in Taiwan. *Oncol. Rep.* 4: 319–326.

Chiu, H.F., Cheng, M.H., Tsai, S.S., Wu, T.N., Kuo, H.W. and Yang, C.Y. (2006). Outdoor Air Pollution and Female Lung Cancer in Taiwan. *Inhal. Toxicol.* 18: 1025–1031.

Chuang, S.C., Chen, S.J., Huang, K.L., Chang-Chien, K.P., Wang, L.C. and Huang, Y.C. (2010b). Emissions of Polychlorinated Dibenzo-*p*-dioxins and Polychlorinated Dibenzofuran from Motorcycles. *Aerosol Air Qual. Res.* 10: 533–539.

Chuang, S.C., Chen, S.J., Huang, K.L., Wu, M.Y., Chang-Chien, G.P. and Wang, L.C. (2010a). Gas/Particle Partitioning of Dioxins in Exhaust Gases from Automobiles. *Aerosol Air Qual. Res.* 10: 489–496.

Coyle, Y.M. (2004). The Effect of Environment on Breast Cancer Risk. *Breast Cancer Res. Treat.* 84: 273–288.

Craig, L., Brook, J.R., Chiotti, Q., Croes, B., Gower, S., Hedley, A., Krewski, D., Krupnick, A., Krzyzanowski, M., Moran, M.D., Pennell, W., Samet, J.M., Schneider, J., Shortreed, J. and William, M. (2008). Air Pollution and Public Health: A Guidance Document for Air Quality Management. *J. Toxicol. Environ. Health Part A* 71: 588–698.

Crouse, D.L., Goldberg, M.S., Ross, N., Chen, H. and Labreche, F. (2010). Postmenopausal Breast Cancer is Associated with Exposure to Traffic-related Air Pollution in Montreal, Canada: A Case–control Study. *Environ. Health Perspect.* 118: 1578–1583.

Cui, Y., Miller, A.B. and Rohan, T.E. (2006). Cigarette Smoking and Breast Cancer Risk: Update of a Prospective Cohort Study. *Breast Cancer Res. Treat.* 100: 293–299.

Curtis, L., Rea, W., Smith-Willis, P., Fenyves, E. and Pan, Y. (2006). Adverse Health Effects of Outdoor Air Pollutants. *Environ. Int.* 32: 815–830.

Department of Health, Taiwan. Cancer Registry Annual Report, 2008 (2010). Taipei: Bureau of Health Promotion, Department of Health.

Department of Health, Taiwan. Statistics of Causes of Death (2010). Taipei: Department of Health.

Dominici, F., McDermott, A., aniels, M., Zeger, S. and Samet, J.M. (2005). Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study: Mortality among Residents of 90 Cities. *J. Toxicol. Environ. Health Part A* 68: 1071–1092.

Draper, N.R. and Smith, H. (1998). *Applied Regression Analysis*, Wiley-Interscience Publication, New York.

Dubowsky, S., Wallace, L. and Buckley, T. (1999). The Concentration of Traffic to Indoor Concentrations of Polycyclic Aromatic Hydrocarbons. *J. Exposure Anal. Environ. Epidemiol.* 9: 312–321.

Elliott, P., Wakefield, J.C., Best, N.G. and Briggs, D.J. (2000). *Spatial Epidemiology*, Oxford University Press, New York.

Gammon, M.D., Santella, R.M., Neugut, A.L., Eng, S.M., Teitelbaum, S.L., Paykin, A., Levin, B., Terry, M.B.,

Young, T.L., Wang, L.W., Wang, Q., Britton, J.A., Wolff, M.S., Stellman, S.D., Hatch, M., Kabat, G.C., Senie, R., Garbowsli, G., Maffeo, C., Montalvan, P., Berkowitz, G., Kemeny, M., Citron, M., Schnabel, F., Schuss, A., Hajdu, S. and Vinceguerra, V. (2002). Environmental Toxins and Breast Cancer on Long Island. I. Polycyclic Aromatic Hydrocarbon DNA Adducts. *Cancer Epidemiol. Biomarkers Prev.* 11: 677–685.

Goldsmith, J.R. (1980). The "Urban Factor" in Cancer: Smoking, Industrial Exposures, and Air Pollution as Possible Explanations. *J. Environ. Pathol. Toxicol.* 3: 205–217.

Greenberg, M.R. (1983). *Urbanization and Cancer Mortality: The United States Experience, 1950-1975*, Oxford University Press, New York.

Gunier, R.B., Reynolds, P., Hurley, S.E., Yerabati, S., Hertz, A., Strickland, P. and Horn-Ross, P.L. (2006). Estimating Exposure to Polycyclic Aromatic Hydrocarbons: A Comparison of Survey, Biological Monitoring, and Geographic Information System-based Methods. *Cancer Epidemiol. Biomarkers Prev.* 15: 1376–1381.

Hall, S.A., Kaufman, J.S., Milikan, R.C., Ricketts, T.C., Herman, D. and Savitz, D.A. (2005). Urbanization and Breast Cancer Incidence in North Carolina, 1995-1999. *Ann. Epidemiol.* 15: 796–803.

Huang, C.J., Chen, K.S., Lai, Y.C., Wang, L.C. and Chang-Chien, G.P. (2011a). Characteristics of Atmospheric Dry Deposition of Polychlorinated Dibenzo-*p*-dioxins/ Dibenzofuran in a Rural Area of Taiwan. *Aerosol Air Qual. Res.* 11: 448–459.

Huang, C.J., Chen, K.S., Lai, Y.C., Wang, L.C. and Chang-Chien, G.P. (2011b). Wet Deposition of Polychlorinated Dibenzo-*p*-dioxins/Dibenzofuran in a Rural Area of Taiwan. *Aerosol Air Qual. Res.* 11: 732–748.

International Agency for Research on Cancer (IARC) (1989). *Diesel and Gasoline Engine Exhaust and some Nitroarenes*, IARC, Lyon.

Johnson, K.C., Miller, A.B., Collishaw, N.E., Palmer, J.R., Hammond, S.K., Salmon, A.G., Cantor, K.P., Miller, M.D., Boyd, N.F., Millar, J. and Turcotte, F. (2011). Active Smoking and Secondhand Smoke Increase Breast Cancer Risk: The Report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). *Tob. Control* 20: e2.

Kao W.Y., Ma, H.W. and Chang-Chien, G.P. (2011). Evaluation of Incremental Population and Individual Carcinogenic Risks of PCDD/Fs from Steel and Iron Industry in Taiwan by a Site- specific Health Risk Assessment Method. *Aerosol Air Qual. Res.* 11: 716–731.

Kelsey, J.L. (1979). A Review of the Epidemiology of Human Breast Cancer. *Epidemiol. Rev.* 1: 74–109.

Kelsey, J.L., Berkowitz, G.S. (1988). Breast Cancer Epidemiology. *Cancer Res.* 48: 5615–5623.

Krewski, D. and Rainham, D. (2007). Ambient Air Pollution and Population Health: Overview. *J. Toxicol. Environ. Health Part A* 70: 275–283.

Labreche, F., Goldberg, M.S., Valois, M.F. and Nadon, L. (2010). Postmenopausal Breast Cancer and Occupational Exposures. *Occup. Environ. Med.* 67: 263–269.

Laden, F. and Hunter, D.J. (1998). Environmental Risk Factors and Female Breast Cancer. *Auun. Rev. Publ. Health* 19: 101–123.

Leung, P.L. and Harrison, R.M. (1999). Roadside and In-vehicle Concentrations of Monoaromatic Hydrocarbons. *Atmos. Environ.* 33: 191–204.

Lewis-Michl, E.L., Melius, J.M., Kallenbach, L.R., Ju, C.L., Talbot, T.O., Orr, M.F. and Lauridsen, P.E. (1995). Breast Cancer Risk and Residence near Industry or Traffic in Nassau and Suffolk Counties, Long Island, New York. *Arch. Environ. Health* 51: 255–265.

Liu, C.C., Tsai, S.S., Chiu, H.F., Wu, T.N. and Yang, C.Y. (2008). Ambient Exposure to Criteria Air Pollutants and Female Lung Cancer in Taiwan. *Inhal. Toxicol.* 20: 311–317.

Luo, J., Horn, K., Ockene, J.K., Simon, M.S., Stefanick, M.L., Tong, E. and Margolis, K.L. (2011). Interaction between Smoking and Obesity and the Risk of Developing Breast Cancer among Postmenopausal Women. *Am. J. Epidemiol.* 174: 919–928.

Maltoni, C., Ciliberti, A., Pinto, C., Soffritti, M., Belpoggi, F. and Menarini, L. (1997). Results of Long-term Experimental Carcinogenicity Studies of the Effects of Gasoline, Correlated Fuels, and Major Gasoline Aromatics on Rats. *Ann. N.Y. Acad. Sci.* 837: 15–52.

Meek, M.D. (1998). AH Receptor and Estrogen Receptor-dependent Modulation of Gene Expression by Extracts of Diesel Exhaust Particles. *Environ. Res.* 79: 114–121.

Ministry of Interior (MOI), Taiwan. (1973). *1972 Taiwan Demographic Fact Book*, MOI, Taipei.

Morris, J.J. and Seifter, E. (1992). The Role of Aromatic Hydrocarbons in the Genesis of Breast Cancer. *Med. Hypotheses* 38: 177–184.

Muir, C., Waterhouse, J. and Mack, T. (1987). Cancer Incidence in Five Continents, IARC, Lyon.

Musafia-Jeknic, T., Mahadevan, B., Pereira, C. and Baird, W.M. (2005). Long-term Effects of a Standardized Complex Mixture of Urban Dust Particulate on the Metabolic Activation of Carcinogenic Polycyclic Aromatic Hydrocarbons in Human Cells in Culture. *Toxicol. Sci.* 88: 358–366.

Muzykl, W., Veimer, S. and Schmidt, N. (1998). Particle-bound Benzene from Diesel Engine Exhaust. *Scand. J. Work Environ. Health* 24: 481–485.

National Health Research Institute (NHRI), Taiwan (2004). Atlas of Health in Taiwan, NHRI, Taipei.

Nelson, H.D., Tyne, K., Naik, A., Bougatsos, C., Chan, B.K. and Humphrey, L. (2009). Screening for Breast Cancer: Systematic Evidence Review Update for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 151: 727–737.

Nie, J., Beyea, J., Bonner, M.R., Han, D., Vena, J.E., Rogerson, P., Vito, D., Muti, P., Trevisan, M., Edge, S.B. and Freudenheim, J.L. (2007). Exposure to Traffic Emissions throughout Life and Risk of Breast Cancer: the Western New York Exposures and Breast Cancer (WEB) Study. *Cancer Causes Control* 18: 947–955.

Palmgren, F., Berkowicz, R., Hertel, O. and Vignati, E. (1996). Effects of Reduction of NO_x on the NO_2 Levels in

Urban Streets. *Sci. Total Environ.* 190: 409–415.

Pan, S.Y., Morrison, H., Gibbons, L., Zhou, J., Wen, S.W., DesMeules, M. and Mao, Y. (2011). Breast Cancer Risk Associated with Residential Proximity to Industrial Plants in Canada. *J. Occup. Environ. Med.* 53: 522–529.

Petralia, S.A., Vena, J.E., Freudenheim, J.L., Dosemeci, M., Michalek, A., Goldberg, M.S., Brasure, J. and Graham, S. (1999). Risk of Premenopausal Breast Cancer in Association with Occupational Exposure to Polycyclic Aromatic Hydrocarbons and Benzenes. *Scand. J. Work Environ. Health* 25: 215–221.

Pope, C.A. and Dockery, D.W. (2006). Health Effects of Fine Particulate Air Pollution: Lines that Connect. *J. Air Waste Manage. Assoc.* 36: 709–742.

Raaschou-Nielsen, O. and Reynolds, P. (2006). Air Pollution and Childhood Cancer: A Review of Epidemiological Literature. *Int. J. Cancer* 118: 2920–2929.

Raaschou-Nielsen, O., Hertel, O., Thomsen, B.L. and Olsen, J.H. (2001). Air Pollution from Traffic at the Residence of Children with Cancer. *Am. J. Epidemiol.* 153: 433–443.

Raaschou-Nielsen, O., Hertel, O., Vignati, E., Berkowicz, R., Jensen, S.S., Larsen, V.B., Lohse, C. and Olsen, J.H. (2000). An Air Pollution Model for Use in Epidemiological Studies: Evaluation with Measured Levels of Nitrogen Dioxide and Benzene. *J. Exposure Anal. Environ. Epidemiol.* 10: 4–14.

Ravindra, K., Mittal, A.K. and Van Grieken, R. (2001). Health Risk Assessment of Urban Suspended Particulate Matter with Special Reference to Polycyclic Aromatic Hydrocarbons: A Review. *Rev. Environ. Health* 16: 169–189.

Remennick, L.I. (1989). Reproductive Patterns and Cancer Incidence in Women: A Population-based Correlation Study in the USSR. *Int. J. Epidemiol.* 18: 498–510.

Reynolds P., Von Behern J., Gunier, R.B., Goldberg, D.E., and Hertz, A. (2004b). Residential Exposure to Traffic in California and Childhood Cancer. *Epidemiology* 15: 6–12.

Reynolds, P., Behren, J.V., Gunier, R.B., Goldberg, D.E., Hertz, A. and Smith, D.F. (2003). Childhood Cancer Incidence Rates and Hazardous Air Pollutants in California: An Exploratory Analysis. *Environ. Health Perspect.* 111: 663–668.

Reynolds, P., Hurley, S., Goldberg, D.E., Anton-Culver, H., Bernstein, L., Deapen, D. Horn-Ross, P.L., Peel, D., Pinder, R., Ross, R.K., West, D., Wright, W.E. and Ziogas, A. (2004a). Regional Variations in Breast Cancer among California Teachers. *Epidemiology* 15: 746–754.

Rosenwaike, I. (1980). Breast Cancer Mortality in Relation to a Measure of Early Childbearing. *Int. J. Epidemiol.* 9: 317–323.

Rothman, K.J. and Greenland, S. (1998). Modern Epidemiology, Lippincott-Raven, Philadelphia.

Samet, J., Krewski, D. (2007). Health Effects Associated with Exposure to Ambient Air Pollution. *J. Toxicol. Environ. Health Part A* 70: 227–242.

Santodonato, J. (1997). Review of the Estrogenic and Antiestrogenic Activity of Polycyclic Aromatic Hydrocarbons: Relationship to Carcinogenicity. *Chemosphere* 34: 835–848.

Schottenfeld, D. and Frauimeni, J.F. (1996). *Cancer Epidemiology and Prevention*, Oxford University Press, New York.

Shen, Z., Han, Y., Cao, J., Tian, J., Zhu, C., Liu, S., Liu, P. and Wang, Y. (2010). Characteristics of Traffic-related Emissions: A Case Study in Roadside Ambient Air over Xi'an China. *Aerosol Air Qual. Res.* 10: 292–300.

Tsai, H.H., Yuan, C.S., Hung, C.H. and Lin. C. (2011). Physicochemical Properties of $PM_{2.5}$ and $PM_{2.5\text{-}10}$ at Inland and Offshore Sites over Southeastern Coastal Region of Taiwan Strait. *Aerosol Air Qual. Res.* 11: 664–678.

Tzeng, G.H. and Wu, T.Y. (1986). Characteristics of Urbanization Levels in Taiwan Districts. *Geog. Res.* 12: 287–323.

Van Wijnen, J.H. and Van der Zee, S.C. (1998). Traffic-Related Air Pollutants: Exposure of Road Users and Populations Living near Busy Roads. *Rev. Environ. Health* 13: 1–25.

Wigle, D.T. (1977). Breast Cancer and Fertility Trends in Canada. *Am. J. Epidemiol.* 105: 428–438.

Wu, Y.L., Li, H.W., Chien, C.H., Lai, Y.C. and Wang, L.C. (2010). Monitoring and Identification of Polychlorinated Dibenzo-*p*-dioxins and Dibenzofurans in the Ambient Central Taiwan. *Aerosol Air Qual. Res.* 10: 463–471.

Xue, F., Willett, W.C., Rosner, B.A., Hankinson, S.E. and Micheis, K.B. (2011). Cigarette Smoking and the Incidence of Breast Cancer. *Arch. Intern. Med.* 171: 125–133.

Yang, C.Y. and Hsieh, Y.L. (1998). The Relationship between Population Density and Cancer Mortality in Taiwan. *Jpn. J. Cancer Res.* 89: 355–360.

Yu, C.L., Wang, S.F., Pan, P.C., Wu, M.T., Ho, C.K., Smith T.J., Li, Y., Pothier, L. and Christiani, D.C. (2006). Residential Exposure to Petrochemicals and the Risk of Leukemia: Using Geographical Information System Tools to Estimate Individual-level Residential Exposure. *Am. J. Epidemiol.* 164: 200–207.

Received for review, September 29, 2011
Accepted, January 19, 2012