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Lung Cancer Risk in Females Due to Exposures to $PM_{2.5}$ in Taiwan

P-H Chiang[1,2,3], Chao W. Chen[*,4], Dennis P.H. Hsieh[5], Ta-Chien Chan[6], Hung-Che Chiang[7] and Chi-Pang Wen[1]

[1]*Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan*

[2]*Department of Health Risk Management, College of Management, China Medical University, Taichung, Taiwan*

[3]*Institute of Biomedical Informatics, National Yang Ming University, Taipei, Taiwan*

[4]*National Center of Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C., USA*

[5]*Department of Environmental Toxicology, University of California, Davis, California, USA*

[6]*Research Center for Humanities and Social Sciences, Academia Sinica, Taipei, Taiwan*

[7]*National Environmental Health Center, National Health Research Institutes, Miaoli, Taiwan*

Abstract: Effects of exposures to the $PM_{2.5}$ in ambient air have increasingly attracted attention of health communities and government regulatory agencies as it has been implicated with a growing list of adverse health effects, including cardiopulmonary issues, premature death and lung cancer. However, the rates of adverse health effects and long term exposure to $PM_{2.5}$ in different populations have not been well quantified due to the lack of data. In this article, 25,427 daily $PM_{2.5}$ concentrations collected from the 73 air monitoring stations throughout Taiwan are extrapolated to 290 townships by Kriging method using GIS data. These townships are then stratified into 5 levels (in $\mu g/m^3$) of $PM_{2.5}$: 20-24, 25-29, 30-34, 35-39, 40 and above. Data on female lung cancer mortality taken from national statistics and the estimated $PM_{2.5}$ concentrations, considered as an exposure biomarker are combined to assess the effect of $PM_{2.5}$ on lung cancer. The average annual $PM_{2.5}$ concentration in Taiwan is 35.6 ± 0.4 $\mu g/m^3$. It is estimated that lung cancer mortality has a mean increase of 16% (6%-25%) for each 10 $\mu g/m^3$ increment of $PM_{2.5}$ concentration and one out of 9 female lung cancer deaths (11%) in Taiwan is attributed to the $PM_{2.5}$ exposures. This assessment is conducted using the commonly accepted principle of making the best use of available data for the stated objective. The limitations of data and the resultant conclusion are carefully articulated and discussed to advance further research.

Keywords: Disease burden, females, Kriging, lung cancer, $PM_{2.5}$, relative risk.

INTRODUCTION

The rate of lung cancer mortality in Taiwan has been the highest among all cancer types in the last two decades, both in men and women. Much of the increase in men has been attributed to cigarette smoking, as every other adult male in Taiwan smoked, with smoking rates sustained around 45%-65% in the last 30 years [1]. In contrast, smoking rate in women was very low, only about one smoker out of 20, and has remained so for decades [2, 3]. However, smoking alone does not explain the alarming increase of lung cancer in Taiwanese women. Attempts had been made previously to identify the burden of lung cancer attributable to environmental risk factors such as smoking, cooking and indoor air pollution in the Taiwanese population [4-8], but the effect of ambient air pollution on lung cancer has not yet been investigated. It has been suggested by Liaw *et al.* [9] that smoking behavior does not seem capable of explaining the epidemiological characteristics of female lung cancer mortality in Asian countries. Liaw *et al.* [9] calculated the ratio of age-standardized mortality rate (ASMR) of lung cancer between males and females are calculated for 23 countries, with sex ratios ranging from 2.10 (Taiwan) to 11.15 (Belgium), and the median 3.92 (Norway). It is unusual that women account for about 33% of total lung cancer deaths in Taiwan, the highest among all the 23 countries studied, considering that the smoking prevalence for females in Taiwan is only about 5%. In contrast, Belgium women, with a sex ratio of 11.15, account for only about 8% of total lung cancer deaths in the population. This unusual observation has motivated us to investigate the effect of ambient air pollution on lung cancer mortality in Taiwanese women, using $PM_{2.5}$ concentrations as an exposure biomarker. In addition to smoking, fine airborne particles have been identified as an important risk factor for lung cancer by IARC [10] in which $PM_{2.5}$ is classified as a human carcinogen (Group 1). The IARC report is based on evidence obtained from several studies around the world, mainly from populations in Western Europe and North America. $PM_{2.5}$ is a fine particulate matter found in the emission of motor vehicles [11], or in the secondary production through

*Address correspondence to this author at the National Center of Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C., USA; Tel: 703-347-0413; Fax: 703-347-8690;
E-mail: chen.chao@epa.gov

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photochemical reactions from hydrocarbons and oxides of nitrogen in the air [12]. $PM_{2.5}$ in ambient air has increasingly attracted attention of health communities and government regulatory agencies because it has been implicated with a growing list of adverse health effects, including cardiopulmonary issues, premature death and lung cancer. The estimates from the existing studies are in the range of 3-5% for the fraction of lung cancer cases attributable to $PM_{2.5}$. Since most scientific evidence is derived from studies in Western Europe and North America, it leaves a potential knowledge gap on fine particle induced health effects in populations of different geographical regions as $PM_{2.5}$ from different regions may have very different characteristics. The compositions of pollution as mixtures and their levels of concentrations may also vary. Furthermore, the public health policy implication of $PM_{2.5}$ reduction may also differ among different regions because the proportion of lung cancer risk attributable to all major risk factors, including $PM_{2.5}$, may differ drastically in developed and developing countries. To what extent the reported exposure-response relationship can be applied to other regions/populations is critical as it is usually the first step in mounting efforts to reduce air pollution-related lung cancer deaths in a country.

Since Taiwan had set up a nationwide network of monitoring stations for $PM_{2.5}$ and other air pollutants, enormous amount of data have been and are being continuously accumulated. Detailed age and gender specific lung cancer deaths are also available for the last 30 years. The objective of this study is to explore the relationship between concentrations of $PM_{2.5}$ and the lung cancer mortality in the female population in Taiwan. The public health implication from the results of our study is discussed in view of the increasing ownership of motor vehicles in Taiwan. Finally, the limitations of our study are scrutinized and future research on $PM_{2.5}$-induced adverse health effects are recommended.

METHODS

Data

The $PM_{2.5}$ concentration data used in this study are obtained from the Environmental Protection Administration in Taiwan. The nationwide network of 73 air quality monitoring stations have been in place for over 15 years, but complete sets of $PM_{2.5}$ concentration data from these stations were only available in August, 2005. The 2006 data are used to construct exposure biomarker for exposure-response modeling in this study. The instrument used for the air quality monitoring was the air monitoring system Verwa 701.

Temporal and Spatial Distributions of $PM_{2.5}$

The 73 monitoring stations are situated throughout Taiwan as shown in Fig. (**1**). For each station, daily average $PM_{2.5}$ concentrations are calculated from hourly data recorded in the station and annual average daily concentrations are then calculated from daily concentrations. The daily concentrations in 2006 are aggregated to determine the monthly and seasonal variation patterns. These annual average daily concentrations are then used to interpolate for the annual average daily $PM_{2.5}$ concentrations of grids of 0.669 km by 0.669 km, covering the entire Taiwan. Table **1** presents seasonal distribution of aggregated daily $PM_{2.5}$ concentrations of all 73 monitoring stations in 2006. Interpolation was performed with Kriging method [13-15] by Geostatistical Analyst extension of ArcGIS (ArcMap, version9.2; ESRI Inc., Redlands, CA, USA). The Kriging is an interpolation method that combines monitored measurements (concentration of $PM_{2.5}$ in this study) in the neighboring locations to predict a concentration of $PM_{2.5}$ for a targeted area by weighted average. The details of calculations and model choice are presented in Appendix 1.

For exposure estimation, the average daily $PM_{2.5}$ concentration of each township is calculated from the concentrations in the grids included in the townships using Spatial Analyst extension of ArcGIS (ArcMap, version9.2; ESRI Inc., Redlands, CA, USA). The average $PM_{2.5}$ concentration of each township is then used as an exposure biomarker for the residents in the township. For this biomarker to be useful for modeling exposure-response relationship, a crucial assumption must be made that the relative (not absolute) level of exposure concentrations among these townships remains constant over the past decades. This assumption is needed because of the long latency of lung cancer and the fact that the monitored data were taken after the lung cancer deaths. The implication of this assumption is further discussed in the Discussion section.

Demography and Mortality Data

Demographic data from 1998 to 2002 in each township are obtained from census database of the Ministry of the Interior in Taiwan. Female lung cancer mortality (ICD-9 162) is derived from underlying cause of death database of the Department of Health in the same period. The Taiwan population in 2000 is used as a reference population for calculating lung cancer ASMR. The 290 townships subject to the present analysis are those along the west coast of Taiwan, without including the townships in the central mountainous regions and the east coast where the population density, lifestyles and exposure scenarios are distinctly different. The female adult population in the 290 townships during the five year period of 1998-2002 was 7,258,262, representing about 95% of the total female population in Taiwan in the period.

Statistical Analysis

Because of the large variation of $PM_{2.5}$ concentrations in the monitored data and the subsequent statistical manipulations of these data into final exposure estimates, it is clear that these estimated exposures consist of large amount of noise. Therefore, it is necessary to smooth the data to reduce the noise, while retaining the intrinsic information of exposure-response relationship as much as possible. Our strategy is to derive risk estimates on the basis of relative risk, not absolute risk and to classify townships into 5 exposure categories as shown in Table **2** and to use them for calculating population attributable fraction (PAF) of risk. The exposure-response relationship between $PM_{2.5}$ concentration and female adult lung cancer ASMR is determined by linear regression analysis, on the basis of both the original data of the 290 townships and the categorical

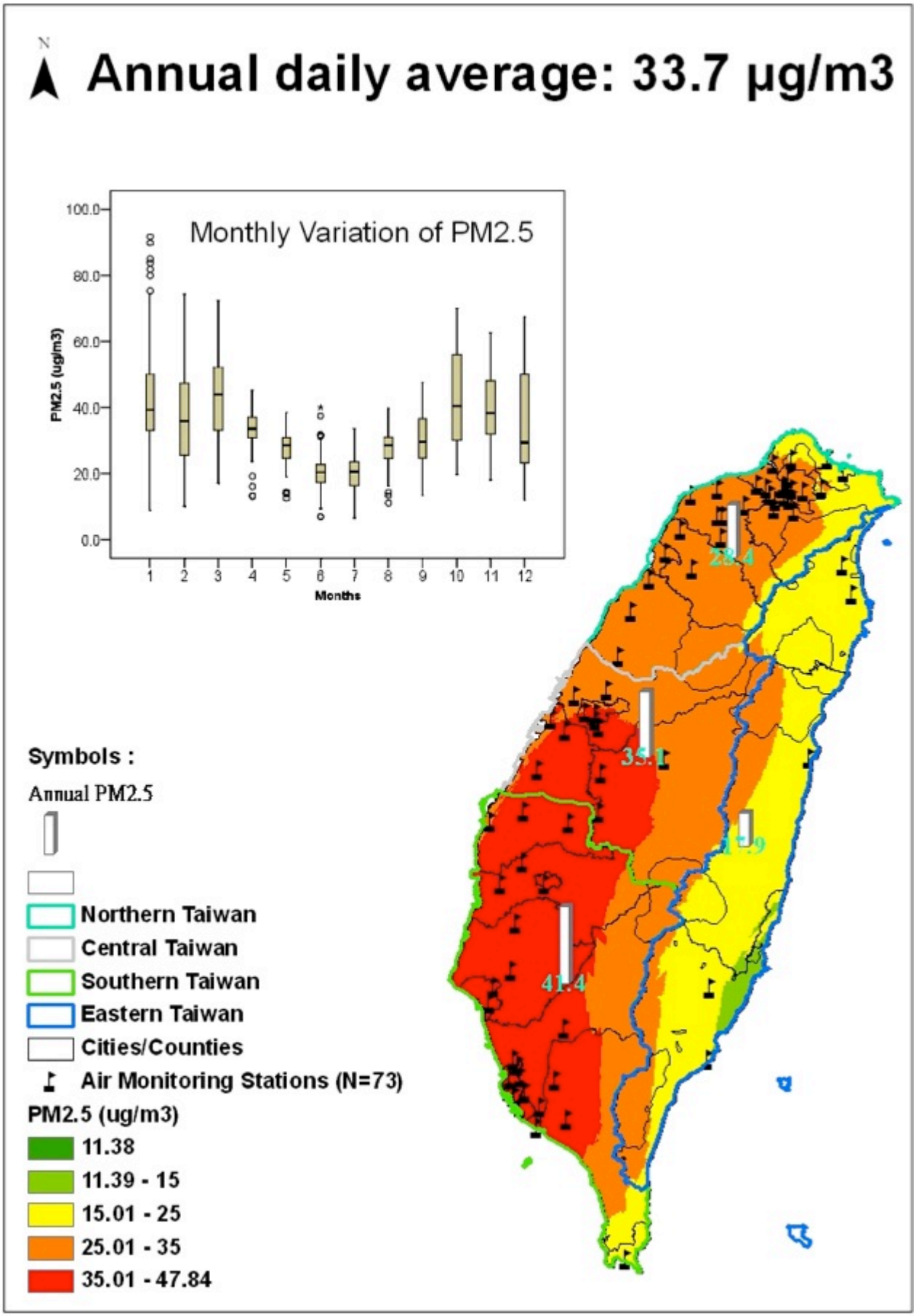

Fig. (1). Spatial distribution of annual average daily $PM_{2.5}$ concentrations in Taiwan in 2006.

data in Table **2**. Since estimates from the two data sets are comparable, only the one based on the original 290 township data (mean RR due to per 10 μg/m^3 increment is 1.16 with 95% CI: 1.06-1.25 *vs* 1.15 from the categorical data) is presented in this study. Two types of RR are assessed. Firstly, RR is determined as the slope of the linear dose-response line between $PM_{2.5}$ concentration and the lung cancer ASMR, expressed as the risk increment per 10 μg/m^3. Secondly, exposure groups were stratified by 5 μg/m^3 into 5 subgroups. RR of each subgroup is then calculated by dividing the mortality rate of this subgroup by the mortality rate of the reference group at 20-24 μg/m^3. Trend test by the general linear model showed a statistically significant positive trend between the exposure level and female lung cancer ASMR against the reference level. Disease burden expressed as population attributable fraction (PAF) is calculated by the following equation:

$$PAF=(Prevalence \times (RR-1))/(Prevalence \times (RR-1)+1)$$

where, prevalence = the number of people exposed to an appropriate $PM_{2.5}$ concentration among the total number of exposed people, RR= relative risk of an exposure group. PAF is the fraction of the lung cancer deaths in an exposure subgroup attributable to excessive exposure of $PM_{2.5}$.

RESULTS

Annual Average Daily $PM_{2.5}$ Concentrations

A total of 25,427 daily records from 73 monitoring stations were analyzed. As shown in Fig. (**1**), the annual daily average of $PM_{2.5}$ concentrations throughout Taiwan is 33.7 μg/m^3 (SE, 0.13 μg/m^3) with 25th-75th percentiles at 18.29-44.96 μg/m^3, calculated on the basis of these daily records. The 98th percentile of the daily records are 30.5-70.0 μg/m^3 (25%-75% of 98th percentile). The annual average daily concentration of $PM_{2.5}$ of the 290 townships included in this study is 35.6 μg/m^3 (SE: 0.37 μg/m^3) and that of the 62 townships not included is 24.17 μg/m^3 (SE: 0.76 μg/m^3). Our analyses indicate that nearly 93% of people in Taiwan breathed an ambient air with $PM_{2.5}$ exceeding 25 μg/m^3 and around 40% of people were exposed to $PM_{2.5}$ in ambient air exceeding 30 μg/m^3. The highest $PM_{2.5}$ concentrations are found clustered in Southwestern part of Taiwan. The concentration in the Southwest is triple of those in the East.

Table 1. Seasonal distribution of aggregated daily $PM_{2.5}$ concentrations (μg/m^3) of all 73 monitoring stations in 2006.

Seasons	N	Mean	SE.	25th	50th	75th
Spring	6,410	34.9	0.2	20.8	31.6	46.5
Summer	6,353	22.8	0.2	14.3	20.8	29.0
Autumn	6,354	37.4	0.3	20.8	32.5	49.8
Winter	6,310	39.0	0.3	19.1	33.9	54.9
Total	25,427	33.7	0.1	18.2	28.3	44.8

N = the number of daily concentrations of 73 stations in each season.
Mean = average daily concentrations of 73 stations combined in each season.
SE = standard error.
25th, 50th, 75th h= 25th percentile, 50th percentile and 75th percentile, respectively.

There is a large variation of $PM_{2.5}$ concentrations among geographical regions, among four seasons within each region, as well as a large diurnal variation. As shown in Table **1**, $PM_{2.5}$ concentrations in winter months were nearly twice those in summer months. As a consequence, the exposures to $PM_{2.5}$ in ambient air in the Southwestern Taiwan during the winter months are three times the exposures in the Eastern Taiwan and twice the exposure in the Central Taiwan.

Female Lung Cancer Mortality and Estimated Relative Risk (RR) Due to $PM_{2.5}$

Within the 290 townships selected for this study, there resided an average of 7,258,262 adult females in 1998-2002, representing about 95% of the total female population in Taiwan during the period. The average lung cancer ASMR

Table 2. Distribution of female lung cancer deaths in relation to annual average daily $PM_{2.5}$ concentrations.

$PM_{2.5}$ Concentration (μg/m^3)	Number of Townships	Female Adult[1] Population	Deaths from Lung Cancer (Per Year)	Mortality Rate[2]	RR[3]	PAF[4]
<20	0	NA	NA	NA	NA	NA
20-24	19	208,501	51	14.96	1.00	0.00%
25-29	63	3,080,561	639	15.57	1.04	1.70%
30-34	33	587,823	148	16.19	1.08	0.66%
35-39	97	1,518,033	425	16.61	1.11	2.25%
40-48	78	1,863,344	471	18.53	1.24	5.77%
Total	290	7,258,262	1,734		1.16[5]	10.39%

NA= Data not available.
1. Adult= 20 years old and over.
2. Mortality rate= Adult age-adjusted lung cancer mortality rate (per 100,000) in 1998-2002 (5 years), adjustment was made according to the age distribution of female adult population in Taiwan in 2000. The mean (95% CI) for the five mortality rates are 14.96 (12.46, 17.46), 15.57 (14.44, 16.69), 16.19 (14.32, 18.05), 16.61 (15.33, 17.89) and 18.53 (17.27, 19.78).
3. RR= Relative risk, the ratio of mortality rate at a $PM_{2.5}$ concentration to that (14.96) at 20-24 μg/m^3. The mean (95% CI) for the five relative risks are 1.00 (0.83, 1.17), 1.04 (0.97, 1.12), 1.08 (0.96, 1.21), 1.11 (1.02, 1.20), 1.24 (1.15, 1.32).
4. PAF= Population attributable fraction= (Prevalence×(RR-1))/(Prevalence×(RR-1)＋1). Prevalence= the number of people exposed to an appropriate $PM_{2.5}$ concentration among the total number of exposed people.
5. Total RR= 1.16 (95% CI: 1.06-1.25) was obtained from a linear regression of concentration-specific mortality rates of 290 townships by taking the increment of mortality rate per 10 μg/m^3 increase in $PM_{2.5}$ concentration. Trend test for this regression by general linear model was significant (p-value =0.01).

(per 100,000) in these females during the same period was 16.7 (SE: 0.3). During this five-year period, there were 8,670 female lung cancer deaths, or, equivalently, 1,734 female lung cancer deaths per year. The average female lung cancer ASMR, RR and PAF are calculated for each of the different $PM_{2.5}$ subgroups in Table **2**. RR increased consistently as $PM_{2.5}$ level goes up, with a statistically significant positive trend (p=0.01). The overall PAF of female lung cancer deaths due to $PM_{2.5}$ exposure, in excess of 20 μg/m^3, is 10.39% (Table **2**). Linear regression analysis on $PM_{2.5}$ concentration and lung cancer death data for the 290 townships yielded an overall RR of lung cancer death 1.16 (95% CI: 1.06 ~1.25) with each 10 μg/m^3 increment of $PM_{2.5}$ in air. This risk estimate is comparable to that derived in Turner *et al.* [16] who followed the American Cancer Society (ASC) cohort through 2008 and reported relative risks of lung cancer mortality of 1.15-1.27 for a 10 μg/m^3 increment in $PM_{2.5}$ among 188,000 never-smokers. It should be noted, however, that the approach used for deriving these values are different from the one used in our study; the lower end (1.15) and upper end (1.27) of risk values in Turner *et al.* [16] are derived, respectively, when mean $PM_{2.5}$ concentrations during two different periods, 1979-1983 and 1999-2000, are used as the exposure concentration in the Cox proportional model. Unlike the present study, the Cox analysis does not require to specify a reference population.

CONCLUSION

We have found in this Asian population a strong dose-response relationship between lung cancer mortality rate in females and concentrations of $PM_{2.5}$ above the reference group at about 20 μg/m^3. Based on the relative risks established in this study, the proportion of lung cancer deaths attributable to $PM_{2.5}$ is approximately 11%, or one out of 9 lung cancer deaths, in the Taiwan female population. This magnitude of lung cancer hazards due to $PM_{2.5}$ in ambient air is similar to that generated by active smoking [17].

Our study finds that for every 10-unit increase of $PM_{2.5}$ beyond 20 (1 unit being 1 μg/m^3), a 16% increase in lung cancer mortality rate is predicted. With the median exposure concentration for females being about 32.5 μg/m^3 in Taiwan, half of the female population would experience a 20% (12.5 x 0.016=0.2) increase in deaths due to lung cancer. In other words, for half of female population, the relative risk of dying from $PM_{2.5}$-induced lung cancer is 1.20 that is almost half of the relative risk of 2.73 predicted for smokers in Taiwan [18], or equivalently, these female lung cancers are about 12% of lung cancer deaths among smokers (calculated by (1.20-1)/(2.71-1)=0.12). Considering the fact that only about 5% of females in Taiwan smoke, this observation seems to suggest that females are very sensitive to $PM_{2.5}$ exposures, an issue that requires further investigation.

DISCUSSION

At present, the carcinogenicity of $PM_{2.5}$ in ambient air is not well understood despite being classified as a human carcinogen by IARC in 2013. Since $PM_{2.5}$ may consist of different organics and metal components, in addition to the carbon black core which is chemically inert but may be biologically active, the adverse health effect can come from the indirect effect of the components consisting of heavy metals such as As, Cr and Ni [19], or the "direct" effect of the particles ($PM_{2.5}$) *per se* [20, 21]. In this study, the observation that incremental $PM_{2.5}$ concentration is associated with increasing lung cancer rate seems to favor the "direct" $PM_{2.5}$ effects. However, since the $PM_{2.5}$ may also contain organics, in addition to carbon blacks, its adverse health effects may be due to the effect of organics, or carbon black, or both. Understanding the composition of $PM_{2.5}$ may help to create an effective strategy for controlling emission sources. An insight into this issue can be found in Chen and Oberdorster [22] in which the organic component of diesel exhaust emission particles is shown to play a relatively more important role, than carbon black, at low exposure concentrations, but at very high concentration, the role is reversed; at high $PM_{2.5}$ concentrations, carbon blacks alone can play almost the complete role of lung cancer induction. This concept is useful when emission standard for motor engines are under consideration. For instance, it may be economically more efficient to reduce one of the two components (organics, or carbon black) to achieve the same level of improvement on public health impact. Because air pollutants are complex mixtures, understanding their geographic uniqueness may be valuable in developing sound environmental management strategies and may help to better understand reasons why females (or other sub-populations such as never smokers) are more susceptible to $PM_{2.5}$ in air.

The average concentration of $PM_{2.5}$ in winter months (39.0 μg/m^3) is 1.7 times of those in summer months (22.8 μg/m^3), while that in southern Taiwan (41.4 μg/m^3) is nearly 1.5 times of that in northern Taiwan (28.4 μg/m^3). The factors causing these large seasonal and geographical variations might be due to winter monsoons with dominant Northwest winds carrying dusts from Mainland China and temperature inversions [23] due to terrain features of high elevation and steep slope in southern Taiwan. In addition, high traffic density (e.g., 7,554 motorcycles per km^2 and 2,814 cars per km^2 in Kaohsiung City) and clusters of petrochemical plants in the South may also contribute to the high concentrations of $PM_{2.5}$. It should be noted that this seasonal and geographical variation of $PM_{2.5}$ concentrations should not impact the resultant risk estimates in this study because the use of annual mean concentrations as exposures in the exposure-response modeling is reasonable. This is so because lung cancer has long latency and thus, it is unnecessary to consider lingering effect within a year, a concept discussed in Chen [24]. Conceivably, however, it would be important to incorporate seasonal variation in exposure-response modeling if acute diseases, rather than lung cancer, are assessed.

The 16% increase of lung cancer mortality per 10 μg/m^3 of $PM_{2.5}$ found in this study is higher than the 8% reported for the largest US population studied by Pope [25], but is comparable to that found in never-smokers in the US [16]. On this basis, our study and [16] seem to suggest that females in Taiwan and never-smokers in US were affected more adversely by $PM_{2.5}$ exposure, a noteworthy subject for further research. However, these risk estimates are very uncertain. When 1999-2000 exposure data are averaged with the previously used exposure data (1979-1983), the increase of lung cancer mortality per 10 μg/m^3 of $PM_{2.5}$ is changed from 8% to 14% [25]. Furthermore, the high level of exposure (40-48 μg/m^3) in our study is higher than the range

of exposures in Pope [25], a factor that may induce higher risk estimate, considering that the increased lung cancer deaths observed for the exposure group at 30-34 μg/m^3 is also 8%. In contrast, previous reports by other investigators have indicated that the RR for lung cancer mortality in US White smokers ranges from 8.1-22.4 that is much greater than those found in Asians, ranging from 2.7 to 3.8 [18]. As less than 5% of the female population in Taiwan smoke [2, 3], the $PM_{2.5}$ breathed by Asian females seems to be responsible for a larger proportion of lung cancer deaths than those that could possibly be predicted by the first and second hand smoking. One reason could be due to the difference in the exposure concentrations (mean: 35.6 in Taiwan *vs* less than 20 μg/m^3 in the US) and/or the difference in the component composition of $PM_{2.5}$.

Most risk assessments on carcinogens are based on linear non-threshold assumption. Both ACS [25] and Harvard six-cities studies [26] on $PM_{2.5}$ followed this non-threshold assumption. The 20 μg/m^3 floor set up in our study may seem like a threshold, but this was done out of the reality that the lowest mean concentration throughout Taiwan was around 20 μg/m^3 and not much less in each of the 290 townships. The floor of 20 μg/m^3 reflects the high $PM_{2.5}$ exposure in Taiwan and the necessity to have a reference exposure group for calculating relative risks. The use of exposure at 20-24 μg/m^3 as a reference group in this study should not be interpreted as a threshold exposure level below which no carcinogenic effect exists.

Another potentially beneficial research is to evaluate those risk factors that were known to be related to lung cancer by identifying those that have been rapidly increasing in prevalence or in intensity in the last few decades. Because of industrial developments along with increasing ownership of motor vehicles over years, the quality of air breathed in Taiwan has been deteriorating, as in most Asian cities [27]. During last 30 years, a phenomenal increase of ownership has been observed for cars, buses and motorcycles in the street [27]. The number of motor vehicles has increased by six folds in this period and the rate of motorcycle ownership, by five folds, from 121 to 593 per 1,000 adults (Fig. **2**). As

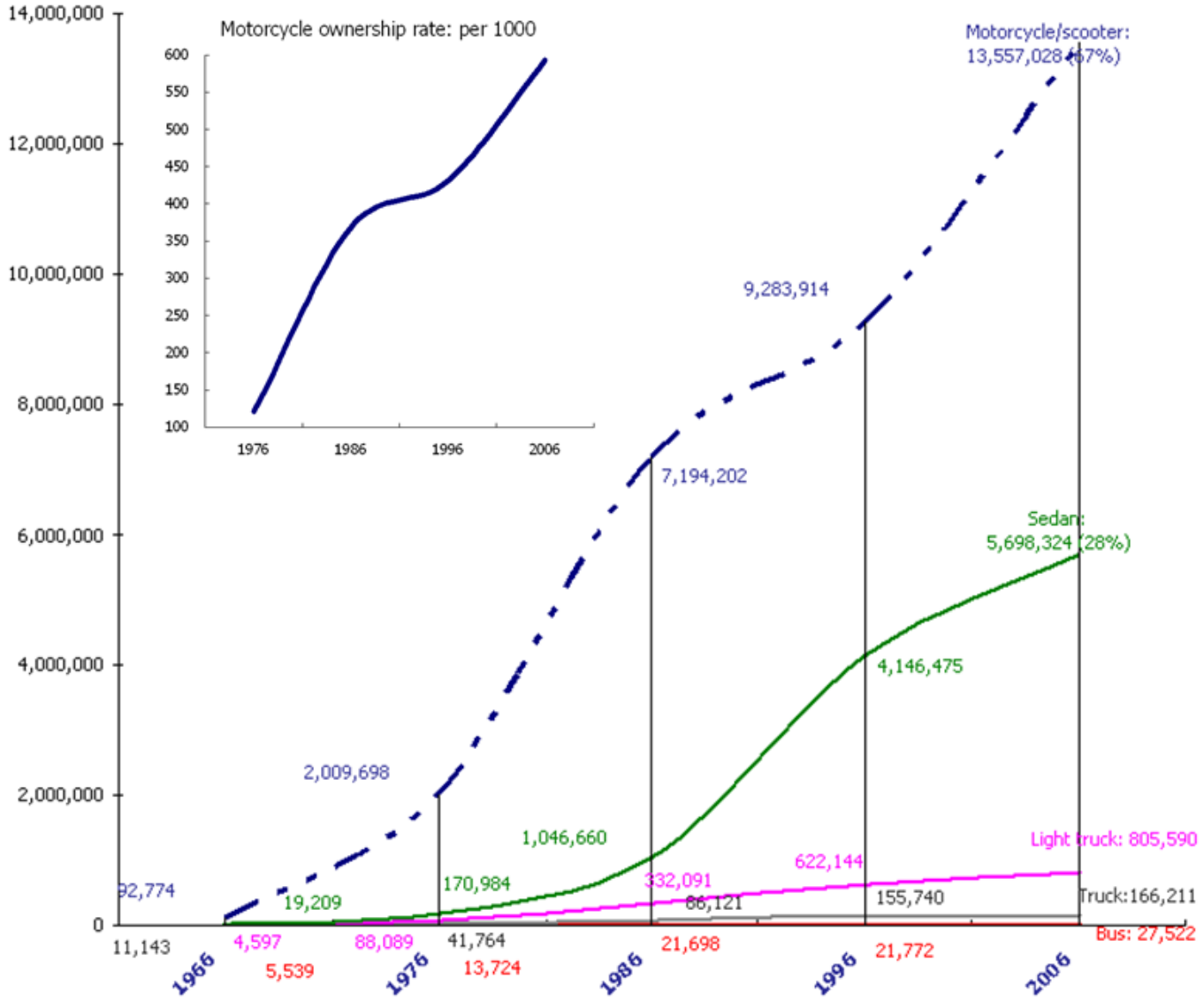

Fig. (2). Increasing numbers of different types of motor vehicles in Taiwan during 1966-2006 (with motorcycle ownership rate shown in the inset).

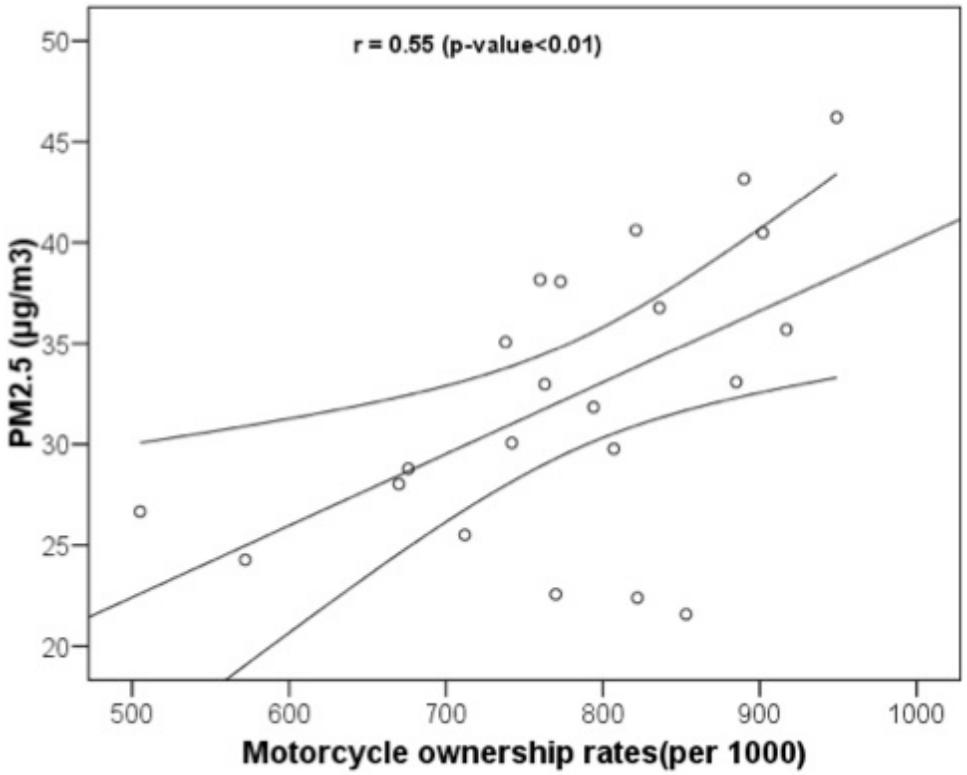

Fig. (3). Correlation between motorcycle ownership and $PM_{2.5}$ concentration across 22 cities/counties in Taiwan. Each data point (○) represents one city/county, motorcycle ownership represents the number of motorcycles per 1,000 adults aged 20 or above, $PM_{2.5}$ concentration represents the calculated annual daily average in each city/county.

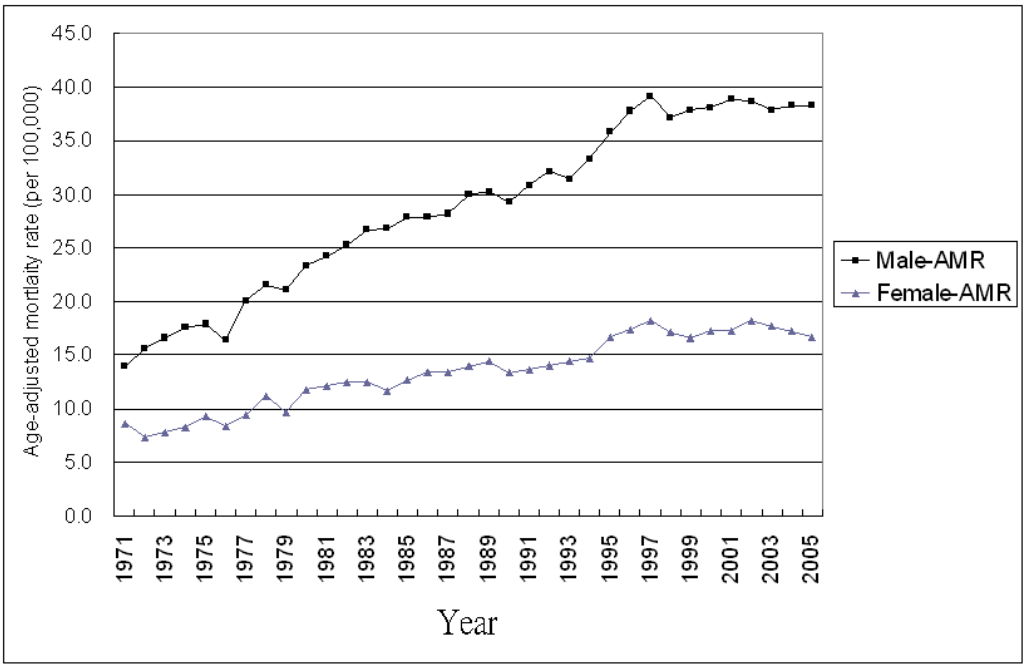

Fig. (4). Lung cancer age-adjusted mortality rate during 1971-2005 (35 years).

shown in Fig. (**3**), there is a high correlation between $PM_{2.5}$ concentrations and motorcycle ownership across 22 cities/counties in Taiwan. The rate of increase of motorcycles, expressed in slope terms, was faster than that of lung cancer mortality, both in men and in women (Fig. **4**). In fact, the increase in ownership rate of motorcycles alone was 4-5 times greater than the increase in lung cancer. In the last decade, more than every other adult in Taiwan owned or regularly used motorcycle, with some geographic areas having as much as one motorcycle per adult.

Our study, like most other studies, assumed that the values at monitoring stations were highly correlated with values at breathing zone [28] and all subjects in the same

area are assumed to have same exposures, estimated by mean concentrations. There are two important limitations of our study: (1) only an ecological mean exposure concentration is used for all individuals in a township, ignoring the fact that individuals in the same township may be subjected to different exposure concentrations and the time spent indoor and outdoor and (2) for the estimated exposure biomarker to be useful for modeling the exposure-response relationship, an assumption must be made that the relative magnitude of exposure concentrations among these townships remains constant over decades in the past. This assumption is needed because of the long latency of lung cancer and the fact that the lung cancer mortality data precede the monitored $PM_{2.5}$ data when they became available.

The assumption of constant relative level of exposure increase among these townships seems reasonable because we believe that most of the increase in $PM_{2.5}$ is due to the rapid increase of motor vehicles and the relative rate of increase of motor vehicle ownership among these townships should remain roughly similar over years.

LIST OF ABBREVIATIONS

ASC = American Cancer Society

ASMR = Age-standardized mortality rate

IARC = International Agency for Research on Cancer

PAF = Population attributable fraction

RR = Relative risk

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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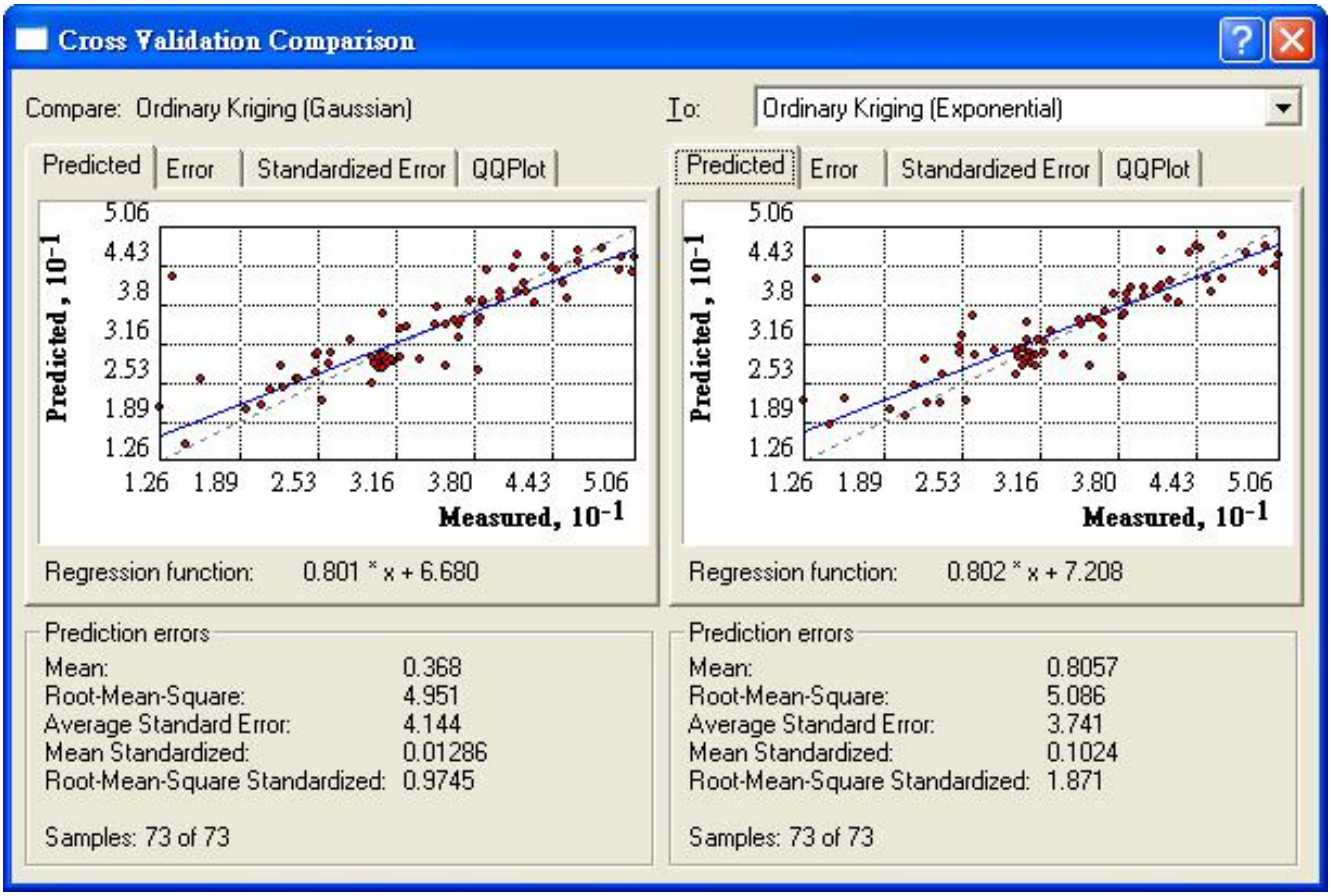
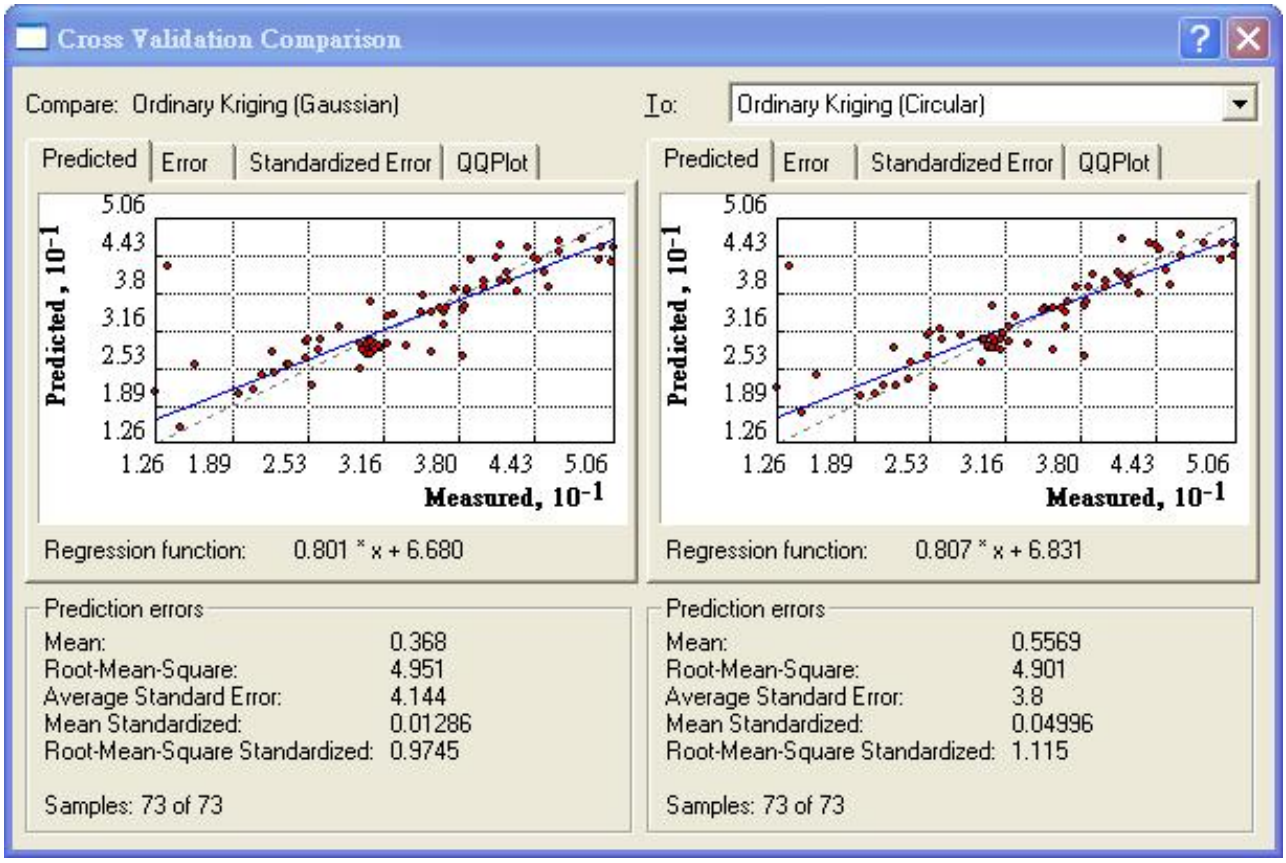
APPENDIX 1: CROSS VALIDATION AMONG DIFFERENT SEMIVARIOGRAMS

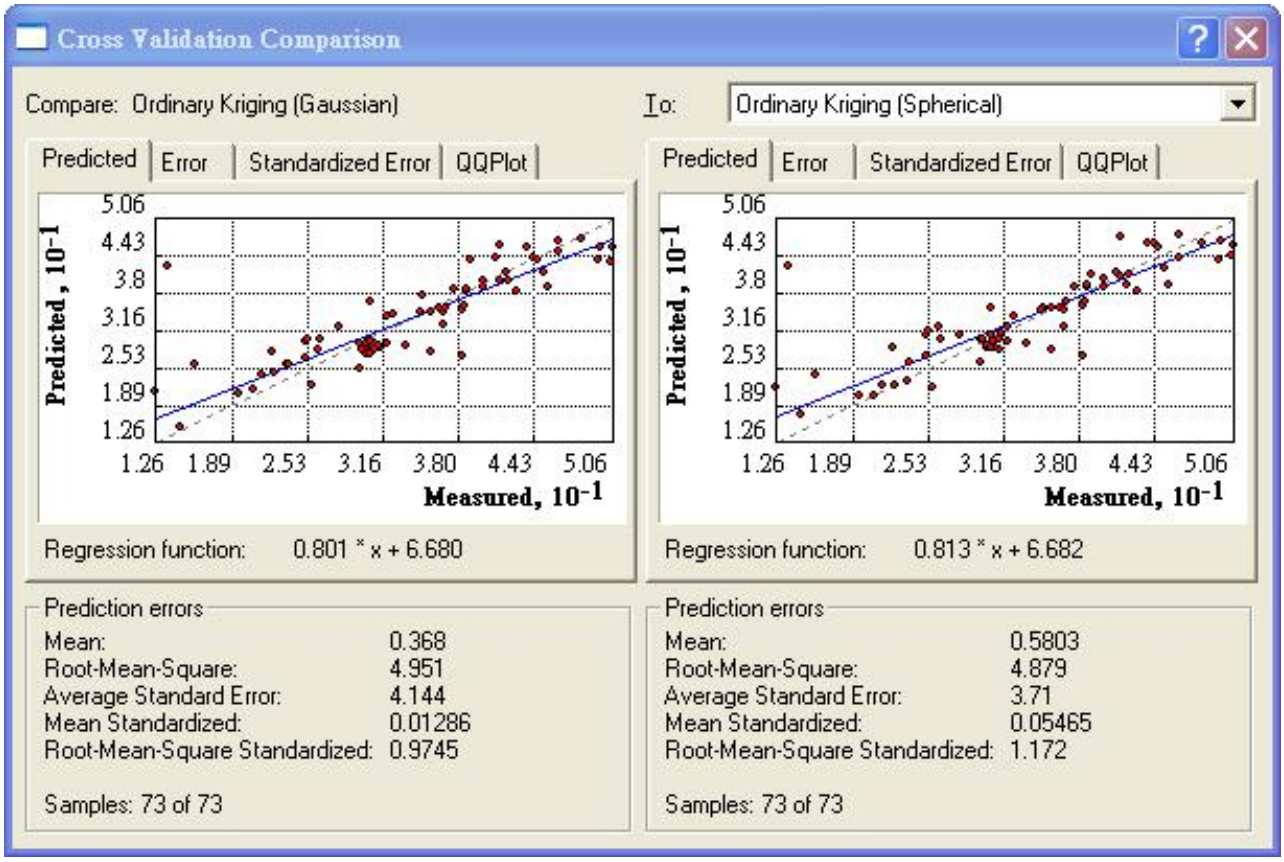
When Kriging, parameters of partial sill, range, nugget effect and semivariogram were selected to minimize the uncertainty of prediction and to fit the normal distribution assumption. The data were used as such in model fitting. Different semivariograms, including spherical, exponential and Gaussian model, were compared to examine the best fit of the data (See Appendix 1-a, b and c). Root mean square error (RMSE) was used to select the best estimate of the distribution of $PM_{2.5}$ concentrations. Spherical semivariogram (Nugget: 3.79, Range: 353820.10, Partial sill: 147.27) was determined as the model of choice. We found that log transformation of data did not improve the shape of assumed normal distribution (Appendix 2).



Appendix 1a. Gaussian semivariogram *versus* exponential semivariogram.

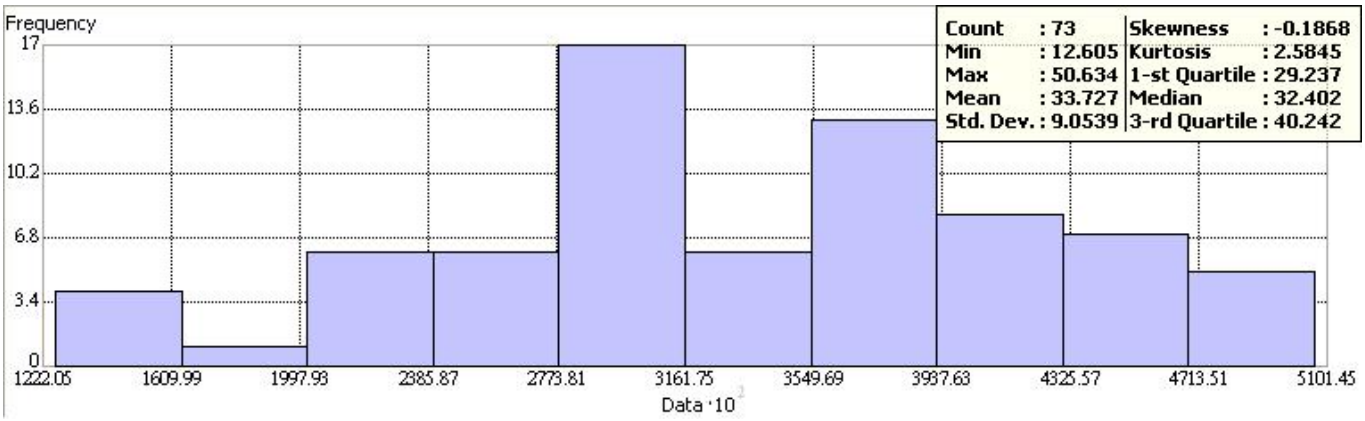


Appendix 1b. Gaussian semivariogram *versus* circular semivariogram.

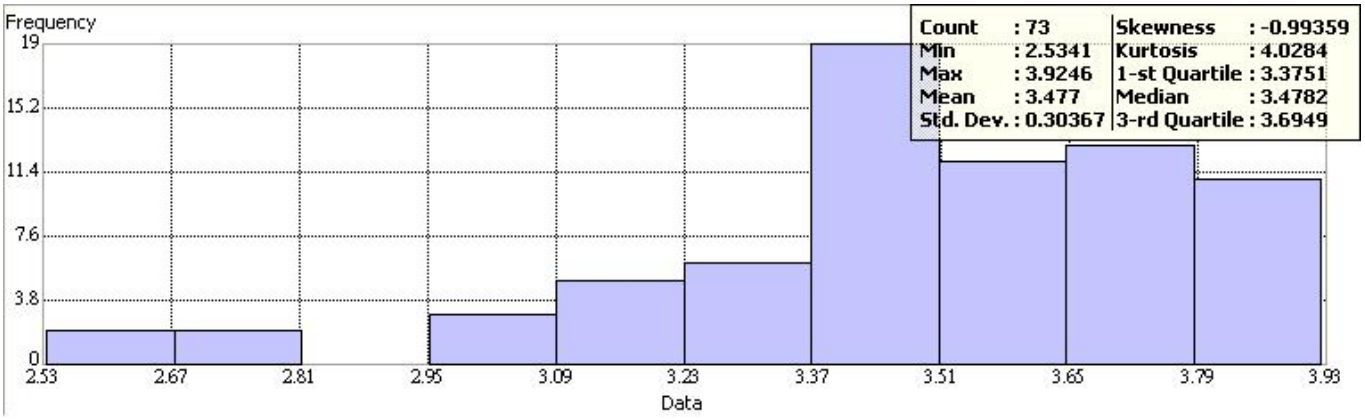


Appendix 1c. Gaussian semivariogram *versus* spherical semivariogram.

APPENDIX 2: DISTRIBUTION OF $PM_{2.5}$ CONCENTRATION



Appendix 2a. Original annual $PM_{2.5}$ concentration in 2006.



Appendix 2b. Log-transformed annual $PM_{2.5}$ concentration in 2006.

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