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Brain cancer associated with environmental lead exposure: Evidence from implementation of a National Petrol-Lead Phase-Out Program (PLPOP) in Taiwan between 1979 and 2007

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ABSTRACT

Background and objective: In 1981, a Petrol-Lead Phase-Out Program (PLPOP) was launched in Taiwan for the abatement of environmental lead emissions. The present study was intended to examine whether the high Petrol-Lead Emission Areas (PLEA) would result in an increase in the incidence rate of brain cancer based on a national data bank.
Methods: The national brain cancer incidence data was obtained from the Taiwan National Cancer Registry. Age standardized incidence rates were calculated based on the 2000 WHO world standard population, and gasoline consumption data was obtained from the Bureau of Energy. The differences in the trend tests for age-standardized incidence rates of brain cancer between high, median, low, and small PLEA were analyzed.
Results: A significant increase was found from small to high PLEA in age-standardized incidence rates of brain cancer. By taking six possible confounders into account, the age-standardized incidence rates for brain cancer were highly correlated with the median and high PLEA by reference to the small PLEA.
Conclusion: After being adjusted for a number of relevant confounders, it could be concluded that high PLEA might result in an increase in the incidence rate of brain cancer resulting from high lead exposures.

1. Introduction

Over the past several decades, epidemiologic studies of brain cancer have examined the many risk factors associated with the disease, however there have been few consistent findings (Bondy et al., 2008). Investigations of brain tumor clusters can be time-consuming and are often inconclusive because of disease heterogeneity and unknown or inadequately characterized exposures, latency periods, and/or base populations (Bondy et al., 2008; Ohgaki, 2009; Wrensch et al., 2002). Additionally, the prognosis of brain cancer patients is still poor. Less than 3% of brain cancer patients are still alive at 5 years after diagnosis (Ohgaki, 2009). Hence, investigation of the etiology of brain cancer remains extremely important.

Lead has been added to petrol (gasoline) as an anti-knocking agent since the 1920s in order to improve fuel performance and reduce wear on vehicle engines. Since this time, leaded petrol has been reported to cause more lead exposures than any other source worldwide (Landrigan, 2002). During the 1970s, health impacts associated with lead emissions from vehicles became a widely discussed issue. Many studies have reported that environmental lead emissions have resulted in significant health effects to the central nervous system, haem-synthesis, reproductive system, as well as psychological and neurobehavioral functions, and may even increase the risk of cancer (ATSDR, 2007; Bellinger, 2005; Fewtrell et al., 2004; IARC, 2006; Tong et al., 2000). Many large population-based studies have recently been conducted to explore the relationship between environmental lead emissions and diseases. Strong associations have been found between blood lead levels (BLLs) and increased risk of all-cause, all cancer, stroke and cardiovascular mortality. Even when BLLs were between 5 and 9 μg/dl a significant association with the disease risk could still be found (Lustberg and Silbergeld, 2002; Menke et al., 2006; Schober et al., 2006). However, the epidemiological literature for an association between lead exposure and brain cancer is inconclusive.

In principle, petrol lead emissions are considered to be more representative of environmental lead exposure than BLLs. It has been observed throughout the world that the lead content of various

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environmental components have decreased after the replacement of leaded petrol (Bridbord and Hanson, 2009; Landrigan, 2002; Stromberg et al., 1995). In Taiwan, environmental lead exposure has generally declined since the mid-1990s largely because of the implementation of the Petrol-Lead Phase-Out Program (PLPOP) in 1981 (Hwang et al., 2004). The implemented scenarios provided a unique opportunity to study the long-term effects of the reduction of environmental lead exposure on the development of brain cancer.

In the present study, in order to adjust for possible confounding effects, both potential factors and medical resource data were included in the data analysis. The results obtained from this study allowed the examination of brain cancer to be associated with the environmental lead emissions within any given country.

2. Methods

2.1. Population in Taiwan

Taiwan, historically known as Formosa, is an island country located in East Asia with a total area of 35,980 km^2. In December 2010 the population of Taiwan was 23,142,460 and the population density within the 25 cities and counties was 688 people per km^2. According to the governmental statistics, 98% of the population is made up of Han Chinese while 2% are Taiwanese aborigines (Ministry of the Interior, 2010). The study focused on the population in Taiwan's 22 counties and cities on the main island and excluded on Taiwan's three offshore island counties.

2.2. Brain cancer data and incidence analysis

Information on the annual age-standardized incidence rates of brain cancer (per 100,000 people) in Taiwan's 22 counties and cities from 1979 to 2007 was retrieved from Taiwan's National Cancer Registry. This information is population-based and has been considered valid and complete. The coding of the brain cancer sites (code C71) was based upon the International Classification of Diseases for Oncology (ICD-O3) issued by the Taiwan Department of Health (Taiwan DOH) (Taiwan DOH, 2009). Direct standardization was applied to produce age-standardized incidence rates for brain cancer (per 100,000 people) by reference to the 2000 WHO world standard population.

2.3. Petrol-lead emission areas (PLEA)

In the present study, the magnitude for all PLEA (in g Pb) were estimated by multiplying the annual motor gasoline consumption (L) to the annual petrol lead content (g Pb/L) based on the data obtained from the Bureau of Energy, Ministry of Economic Affairs. Two kinds of indexes were used to classify PLEA into four categories. Index 1 directly used the petrol-lead emissions of Taiwan's 22 counties to group PLEA into four categories (small = 2.2–4.5, low = 5.3–8.7, median = 12.6–16.7, high = 23.6–32.7 tons). On the other hand, index 2 used the petrol-lead emission multiplying the corresponding population density for each individual county to classify PLEA into four categories (small = 153–880, low = 1576–5564, median = 7427–15885, high = 29670–252934 ton*people per km^2).

2.4. Potential confounding factors

Potential predictors of brain cancer were collected for analysis, such as HIV incidence rates, area served per medical care facility, health personnel per 10,000 populations, concentration of air pollutants, average disposable income per household per year, and average number of cell phone per 100 households within Taiwan's 22 counties and cities. The annual HIV incidence rate (‰) in all areas of Taiwan was acquired from the Taiwan Centers for Disease Control. Information for all areas about the area served per medical care facility (km^2), health personnel per 10,000 population, concentration of air pollutants (PM10 ($\mu g/m^3$), O_3 (ppm), and SO_2 (ppb)), average disposable income per household per year, and average number of cell phone per 100 households were acquired from the Taiwan Directorate General of Budget, Accounting and Statistics. The information on potential predictors for brain cancer relates to the period from 1998 to 2007.

2.5. Statistics

A linear regression model was used to assess the association between years and brain cancer age-standardized incidence rates. This study used one-way analysis of variance (ANOVA) and trend analysis to assess the age-standardized incidence rates differences between PLEA. Multiple linear regression models were used to assess the association between PLEA and age-standardized incidence rates after controlling potential factors. The statistical analyses were performed using SPSS for Windows (version 15.0). All statistical

Table 1
Petrol-lead phase-out program and BLLs in Taiwan.

Phase	Implementation date	Petrol type (lead content)	Blood lead levels *	
Phase 1	Before 1981	Leaded petrol (0.72 g Pb/l)		
	1982	Leaded petrol (0.56 g Pb/l)		
	1983 -1985	Half-leaded petrol (0.34 g Pb/l)	20.14 ± 5.07 μg/dl (N=118)	Chiang et al., 1989
Phase 2	1986	Low-leaded petrol (0.20 g Pb/l)		
	1987	Low-leaded petrol (0.15 g Pb/l)		
	1988 -1992	Low-leaded petrol (0.12 g Pb/l)	6.48 μg/dl (♀; N =168)	Soong et al., 1991
Phase 3	1993~1996	Small-leaded petrol (0.08 g Pb/l)	7.70 ± 5.23 μg/dl (N=8828)	Liou et al., 1996
			8.6 μg/dl (♂; n1=4540)	
			6.7 μg/dl (♀; n2=4288)	
	1997~1999	Small-leaded petrol (0.026 g Pb/l)		
Phase 4	After 2000	Ban of leaded petrol	5.40 μg/dl (N=2565)	Kuo et al., 2006
			5.45 μg/dl (♂; n1=1226)	
			5.35 μg/dl (♀; n2=1339)	
			3.00 μg/dl (N=164)	Chang et al., 2006
			3.23 ± 2.28 μg/dl (♂; n1=81)	
			2.78 ± 2.05 μg/dl (♀; n2=83)	
			2.64 ± 0.84 μg/dl (♀; N=266)	Yang et al., 2007
			1.57 ± 1.01 μg/dl (♀; N=81)	Wu et al., 2009

*The BLLs of subject were selected from no occupational lead exposure population or control group in those studies.

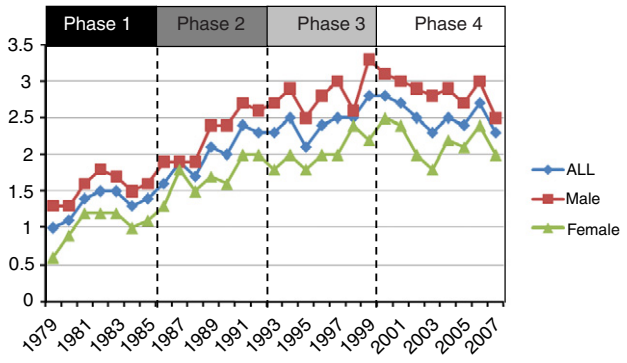

Fig. 1. Long-term trend of brain cancer age-standardized incidence rates (per 100,000 people) in Taiwan from 1979 to 2007.

tests were two-sided with $p<0.05$ as the level of statistical significance.

3. Results

The results show that the PLPOP implemented in Taiwan consists of four phases: (1) leaded petrol phase (before 1985, the petrol lead content was between 0.72 and 0.34 g Pb/l), (2) low leaded petrol phase (1986–1992, the petrol lead content was between 0.20 and 0.12 g Pb/l), (3) transitional phase (1993–1999, the petrol lead content was between 0.08 and 0.026 g Pb/l), and (4) lead-free petrol phase (after 2000, the petrol lead content was <0.013 g Pb/l). Recent studies have shown that the mean BLLs were substantially lower than those obtained from previous studies. Environmental lead exposures were found with a positive correlation on BLLs. The mean BLLs were sharply decreased from approximately 20 μg/dl in the leaded petrol phase to 3.00 μg/dl or lower in the unleaded petrol phase (Chang et al., 2006; Chiang and Chang, 1989; Kuo et al., 2006; Liou et al., 1996; Soong et al., 1991; Wu et al., 2009; Yang et al., 2007) (Table 1).

In Fig. 1 the time trend in incidence of brain cancer was presented. This study used a linear regression model to judge a watershed in the long-term trend of brain cancer incidence (Table 2). The result includes the years from 1999 to 2007 and from 1981 to 1999 that were respectively associated with age-standardized incidence rates of brain cancer ($p=0.053$ and $p<0.001$). Therefore, year 1999 could be a watershed in long-term trend observation of brain cancer incidence.

We analyzed the differences in the trend tests of age-standardized incidence rates between high, median, low, and small PLEA from 1999 to 2007 (Table 3). The results in index 1 show that age-standardized incidence rates of brain cancer have a significant increased trend from small to high PLEA ($p=0.034$). In index 2, the results show that there was a marginal effect on the trend of age-standardized incidence rates for brain cancer (p-value = 0.065).

Table 4 shows results based on multiple linear regression models with determinants of age-standardized incidence rates in brain cancer. Explanatory variables included in the model were PLEA, HIV incidence rates (‰), area served per medical care facility (km^2), health personnel per 10,000 population, concentration of air pollutants (PM10 ($\mu g/m^3$), O_3 (ppm), and SO_2 (ppb)), average disposable income per household per year, and average number of cell phone per 100 households. Using index 1 for this analysis, the age-standardized incidence rates for brain cancer were shown to be highly correlated with the median and high PLEA as in comparison with small PLEA (p-values were 0.048, and 0.012, respectively). In index 2, the age-standardized incidence rates for brain cancer were also shown to be highly significantly correlated with the low, median and high PLEA by reference to small PLEA ($p<0.001$).

4. Discussion

In this study, the age-standardized incidence rates of brain cancer were shown to be highly significantly correlated with the high and median PLEA compared to small PLEA. The authors believe that this is the first evidence ever being shown in the lead literature based on the long-term observation of petrol lead emissions and brain cancer incidence.

Globally, the annual age-standardized incidence rates of brain cancer are 3.7 per 100,000 for men and 2.6 per 100,000 for women. Rates appear to be higher in more developed countries (men: 5.8 and women: 4.1) than in less developed countries (men: 3.0 and women: 2.1) (Bondy et al., 2008). The results indicated that the varieties of age-standardized incidence rates of brain cancer were from 3.3 to 2.5 per 100,000 for men and 2.5 to 1.8 per 100,000 for women during 1999–2007. The lower incidences in the study may be partly due to ethnic differences in susceptibility to development of brain cancer. Some reports indicated that Caucasians are more frequently affected than people of African or Asian descent (Ohgaki, 2009).

The present study found an association between environmental lead exposure and risk of brain cancer: the populations living in higher PLEA experienced an increase in cancer incidence. Historical organic lead exposure was largely confined to tetra-ethyl lead used as an additive in gasoline; tetra-ethyl lead was broken down into inorganic lead when gasoline was burned. Cancer researchers have classified lead as possible human carcinogen (group 2B) and its inorganic compounds as probable human carcinogens (group 2A) (IARC, 2006). Although the etiology of brain cancer remains largely unknown, there are several known mechanisms that show lead exposure impacting the risk of brain cancer (Bondy et al., 2008). Lead has been shown to pass the blood–brain barrier which may result in elevated lead levels in brain tissue (ATSDR, 2007). Lead is thought to play a facilitative role in carcinogenesis, involving inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor suppressor proteins (IARC, 2006; Silbergeld, 2003; Silbergeld et al., 2000). Besides, brain tissues are reported to be relatively susceptible to oxidative stress and lipid peroxidation, suggesting that the brain may be sensitive to the lead toxicity effects (Bolin et al., 2006; Halliwell, 2006). Wijngaarden and Dosemeci (2006) studied brain cancer in the National Longitudinal Mortality Study, a prospective census-based cohort study of the United States population in 1979–1989 ($n=317,968$). Using a job-exposure matrix and industry and occupation statistics from the

Table 2
Linear regression results for per year of age-standardized incidence rates of brain cancer (per 100,000 people) in Taiwan population.

Study period	B	SE	p-value
Year (1999–2007)	−0.048	0.021	0.053
Year (1979–1999)	0.080	0.006	<0.001

Table 3
The trend of brain cancer age-standardized incidence rates (per 100,000 people) for the four categorized PLEA from 1999 to 2007.

Type of index	Small PLEA		Low PLEA		Median PLEA		High PLEA		p-value [a]	p-value for trend
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Index1	2.36	0.72	2.51	0.79	2.50	0.55	2.73	0.45	0.143	0.034
Index2	2.31	0.73	2.53	0.82	2.44	0.58	2.64	0.53	0.135	0.065

[a] AVOVA.

Table 4
Multiple linear regression results for age-standardized incidence rates of brain cancer (per 100,000 people) for the four categorized PLEA from 1999 to 2007 using small PLEA as the reference.

Variables	B	SE	p-value
Index 1 (small PLEA = ref.)[a]			
Low PLEA	0.144	0.148	0.333
Median PLEA	0.316	0.159	0.048
High PLEA	0.474	0.186	0.012
Index 2 (small PLEA = ref.)[a]			
Low PLEA	0.966	0.239	<0.001
Median PLEA	1.064	0.260	<0.001
High PLEA	1.471	0.286	<0.001

[a] Adjusted potential predictors of HIV incidence rates (‰), area served per medical care facility (km^2), health personnel per 10,000 population, concentration of air pollutants (PM10 ($\mu g/m^3$), O_3 (ppm), and SO_2 (ppb)), average disposable income per household per year, and average number of cell phone per 100 households.

census, the authors found increased risk of brain cancer in jobs likely to have involved lead exposure (RR = 1.5, 0.9–2.3) (Wijngaarden and Dosemeci, 2006). Rajaraman et al. (2006) also found weak evidence of an association between cumulative lead exposure and risk of meningioma, especially in males. Risk of meningioma consistently increased with all lead exposure metrics for individuals carrying the ALAD2 allele (Rajaraman et al., 2006).

Brain cancer is a rare outcome, and thus, the sample size of individuals in this study is important. The present study obviously took the advantage for having a large number of populations with size greater than 23 millions. Since all cancer patients were required by law to register by their physicians in Taiwan, and therefore our population-based data are complete and accurate. Additionally, the petrol lead emissions reported in the governmental documents of Taiwan were not only representative of the environmental lead amounts, but also reflected the actual changes in environmental lead exposure in the Taiwanese population. In studying the effect of the PLPOP, this measurement is in general more suitable than that based on the blood lead level.

In the results, year 1999 could be a watershed in long-term trend observation of brain cancer incidence. This time period corresponds with the latency periods of brain cancers from 1981 in Taiwan. The Brain Tumor Epidemiology Consortium (BTEC) has proposed the following as possible risk factors for primary brain cancer: radiation to the head, an inherited (genetic) risk, HIV infection, cigarette smoking, and environmental pollutions (for example, chemicals used in oil refineries, embalming chemicals, rubber industry chemicals) (Bondy et al., 2008). Access to health care is one influential factor, as reported rates for primary malignant brain tumors tend to be higher in countries with more accessible and highly developed medical care (Wrensch et al., 2002). These aforementioned potential risk factors for brain cancer have all been considered in the present study in order to control the possible bias in our findings.

Several limitations of this study should be considered. First, our study was based on the population data rather than individual data. It is known that the population-based data may not be appropriate for testing etiologic hypothesis. However, this study did present a moderate but sound correlation between environmental lead exposure and brain tumor, which warrants further study based on individual data to explore the potential causal relationship between them. Second, long-term observations progress in diagnostic technologies and ascertainment, particularly for nonmalignant benign brain tumors (BTs), may account for much of the modest increase in incidence. Meanwhile, changes in tumor classification and coding are likely responsible for some of the increases in incidence for BTs histology. Nevertheless, diagnostic technologies and classification for BTs have become stable and fixed since 1999. Therefore, simply using data starting from years 1999 to 2007 for conducting regression analyses (see Tables 3–4 and Fig. 1), could be appropriate. Third, the present population-based study was unable to adjust for smoking due to unavailability of lifestyle data. It is true that some previous studies have indicated that tobacco may increase the risk of brain cancer (Bondy et al., 2008). In addition, it is known that some carcinogenic components of tobacco smoke can penetrate the blood–brain barrier. Therefore, it has been hypothesized that they may be involved in the development of some brain tumors. However, both a meta-analysis and a review (Boffetta et al., 2000; Norman et al., 1996) found no clear association between a mother's smoking tobacco during pregnancy and risk for a brain tumor in the child. The above inconsistent findings among different studies suggest that the effect associated with lacking of lifestyle data to adjust for smoking might not be significant in the present study. Finally, mobile move may result in petrol-lead emission moving from one designated PLEA category to another. Additionally, migrant effect could result in people with a given lead exposure level migrant to the area of different PLEA category. If the net effect of the above two factors on assigning people to a correct PLEA category can be determined, it would be helpful to reduce the bias in investigating the relationship between lead exposure and brain cancer. Obviously, both effects were not considered in this study which warrants the need for further investigation in the future.

Progress in understanding primary brain cancer might result from studies of well-defined histological and molecular tumor types incorporating assessments of potentially relevant information on subject susceptibility and environmental and noninherited endogenous factors. The present study is the first one which provides the evidence that the age-standardized incidence rates of brain cancer could be highly correlated with petrol lead emissions. The above finding can serve as a basis in the future for conducting more well-defined studies to investigate the relationship between the primary brain cancer and environmental lead exposures.

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