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Original Contribution

Residential Exposure to Petrochemicals and the Risk of Leukemia: Using Geographic Information System Tools to Estimate Individual-Level Residential Exposure

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The authors conducted a population-based, case-control study in Kaohsiung, southern Taiwan, Republic of China, to investigate the association between residential petrochemical exposure and leukemia risk among subjects 29 years of age and younger. Between November 1997 and June 2003, 171 cases and 410 controls matched for age and sex were recruited. Since assessment of petrochemical impacts depends on accurate exposure estimates, the authors developed a procedure using geographic information system tools to assign subjects' exposure. The resulting individual-level exposure estimates (the exposure opportunity score) are an integrated exposure measure that accounts for subjects' mobility, length of stay at each residence, distance to petrochemical plant(s), monthly prevailing wind direction, and multiple petrochemical pollution sources. Different conditional logistic regression models were fitted for subjects aged 0–19 and 20–29 years to evaluate separately childhood versus adulthood leukemia. No overall association was observed for the younger age group. However, residential petrochemical exposure was a significant risk factor for leukemia for the older age group. For one unit of increase in the log-transformed exposure opportunity score, the adjusted odds ratio was 1.54 (95 percent confidence interval: 1.14, 2.09). This study illustrates the utility of geographic information system tools for providing refined exposure estimates for residential exposure to petrochemical pollution.

environmental exposure; environmental pollution; leukemia

Abbreviation: CI, confidence interval.

Editor's note: *An invited commentary on this article appears on page 208.*

Leukemia is the most frequent childhood cancer. It is also a commonly diagnosed malignancy among adults (1–4).

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Regardless of advances in molecular biology and immunology, elucidation of risk factors for leukemia has been hampered by the rarity of individual disease subtypes. Multiple risk factors are thought to play a role in the hematopoietic carcinogenesis. These factors include environmental origin (benzene, ionizing radiation, nonionizing electromagnetic fields, pesticides, occupations, and parental occupations), diet (vitamins A and D), viral infections (retroviruses), medical and iatrogenic events (diagnostic radiographs, radiation therapy, and chemotherapy agents), and familial and genetic factors (1–3). However, none of these factors, even the established risk factors (e.g., high dose of ionizing radiation, benzene, and smoking), are likely to explain more than a small fraction of all leukemia cases (4).

Some occupational studies have reported an elevated risk or mortality of leukemia among workers in petroleum refineries and petrochemical industries (1, 2). Moreover, paternal occupational exposure to petroleum products has been associated with excess leukemia risk in offspring (2). Particularly, benzene is a well-known hematopoietic carcinogen and is characterized as a group 1 carcinogen by the International Agency for Research on Cancer (5). Only a few studies have examined the associations between residential exposure to petrochemicals and leukemia incidence or mortality (6–9). These studies did not show significant excess in leukemia incidence or mortality for residents living in homes bordering on a petroleum refinery or petrochemical industry.

Since the establishment of Taiwan's first oil refinery in 1968, a number of studies have been conducted in Kaohsiung, southern Taiwan, to evaluate the potential health effects of emissions from the petroleum refinery and petrochemical industry, with a special interest in residents living in the nearby community. Environmental monitoring studies conducted by Lee and Tsai (10) and Lee (11) have reported that, although lower than occupational exposure levels, concentrations of selected polycyclic aromatic hydrocarbons and volatile organic compounds in the vicinity of the petrochemical industry in Kaohsiung can be at least 10 and two times higher, respectively, than those in the industrialized communities of the United States (10, 11). Some epidemiologic studies have focused specifically on the cancerous effects of the industry on the surrounding community (8, 12, 13) and found positive associations between the pollution and cancers of the bone, brain, bladder, liver (male), and lung (female). These studies are ecologic in nature and did not control for confounding factors at the individual level, however.

Residence location is a commonly used indicator to assess residential exposure to environmental contaminants from nearby pollution sources (14). Two frequently used approaches to assess environmental exposure using residences are the ''proximity'' indicators and ''zone'' indicators. The former uses the distance between a residence and a pollution source, assuming that the exposure level decreases with the distance; concentric rings of various radii (e.g., 1, 2, or 3 km) around the pollution sources are often drawn in order to classify the study population into different exposure groups (14). The zone-based approach classifies residence location by ''zones'' with explicit boundaries including administrative units such as census tracts; residents in the same zone are assumed to have the same exposure level (14). Previous studies in the study area used a combination of two approaches to assess residential exposure; the investigators first identified the exposed population by proximity to pollution sources (typically 3 km for the study area) and further divided the exposed population into subgroups using zones (typically census tracts) (8, 12, 15). Although these approaches are fairly intuitive and easy to use, they reflect only the spatial distribution of air pollution in a very crude manner. To reduce the extent of exposure misclassification, refinement in exposure assessment is needed when using residence location to estimate environmental exposure (14, 16). In the present study, we use a modified exposure assessment approach, accounting for subject mobility, length of stay at each residence, distance to petrochemical plant(s), monthly prevailing wind direction, and multiple petrochemical pollution sources. The objectives of this study were as follows: 1) to provide a more precise, yet convenient, measure to estimate the individual-level cumulative residential petrochemical exposure from airborne sources, and 2) to examine the association between residential petrochemical exposure and the risk of leukemia among persons 29 years of age and younger.

MATERIALS AND METHODS

Study area

This is an ongoing study conducted in metropolitan Kaohsiung, Taiwan, Republic of China. Among the 38 administrative areas in Kaohsiung, 12 are sparsely populated in which agriculture is the major occupational activity. There is evidence suggesting that pesticide exposure may be related to leukemia (17). To avoid the potential confounding effects from pesticides, we excluded these agricultural areas. Our study area was approximately 657.1 km^2, with a length and width of 49.5 km and 29.5 km, respectively (figure 1).

There are four petrochemical complexes in the study area (figure 1). The Tsoying complex has an area of 4.5 km^2 and includes two naphtha-cracking plants supplying raw petrochemical materials to nearby complexes in Tasheh and Jenwu. The Tasheh complex is 3 km northeast of Tsoying, while the Jenwu complex is 2 km southeast of Tsoying. Both complexes consist of large petrochemical manufacturers and cover areas of 1.1 km^2 and 0.8 km^2, respectively. The Linyuan complex is located in the southern metropolitan area of Kaohsiung and is approximately 3.8 km^2. This complex consists of two naphtha-cracking plants and many midstream/downstream petrochemical plants. Some major products produced by the midstream/downstream plants in the Tasheh, Jenwu, and Linyuan complexes include vinyl chloride monomer, low-density polyethylene, high-density polyethylene, acrylates, acrylonitrile-butadiene-styrene, thermoplastic elastomer, and methyl tertiary butyl ether (18).

Study subjects

This is a large, multiyear, population-based, case-control study conducted in metropolitan Kaohsiung. Subjects recruited between November 1997 and June 2003 were

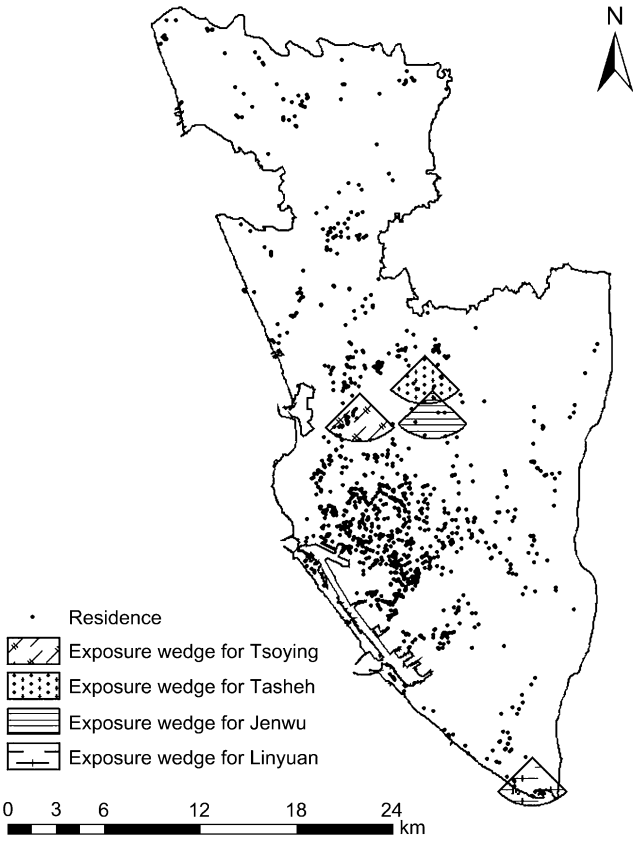

FIGURE 1. Map of the study area, Kaohsiung, southern Taiwan, Republic of China, 1997–2003. Shown is an illustration of exposure wedges when the monthly prevailing wind direction is from the north. Note that, for confidentiality purposes, the residences presented in this figure were not the actual residences used for the analyses.

included in the study. Cases were diagnosed during the study period. The study protocol was approved by the institutional review boards of both the Harvard School of Public Health and Kaohsiung Medical University. All study subjects (if $\geq$18 years of age) or their parents (if subjects were $<$18 years of age) had consented to participate in the study. Eligibility criteria for cases were all incident, primary leukemia cases (*International Classification of Diseases*, Revision 9, codes 204–208), who were 29 or fewer years of age and were current residents of the study area at the time of enrollment; patients with secondary or recurrent tumors were excluded. Cases' recruitment was performed through either the rapid case ascertainment system or the computerized files from the Department of Health of Kaohsiung. The former was set up by the Kaohsiung Medical University Hospital to obtain information regarding newly diagnosed cases from the large referral hospitals in the study area (Kaohsiung Medical University Hospital, Kaohsiung Chang-Gung Memorial Hospital, and Kaohsiung Veterans General Hospital). The remaining cases were identified through computerized files abstracted from records of the mandatory national health insurance system operated by the Department of Health of Kaohsiung, Taiwan. With these two case ascertainment approaches combined, most of the cases occurring in metropolitan Kaohsiung could be identified. All case diagnoses were confirmed by an experienced pathologist in the Kaohsiung Medical University Hospital. One leukemia case was excluded because of missing residential information. A total of 171 histologically confirmed incident leukemia cases were enrolled in the study.

Controls were healthy, cancer-free, current residents of the study area selected randomly from the population registry data for the study area on the basis of a personal identification number. In Taiwan, each person is assigned a personal identification number by the Household Registration Office at the time of birth. The number is assigned independently of current residence and, thus, would not bias control selection due to residence. Cases and controls were matched on age ($\pm$1 year) and gender by use of a 1:3 matching ratio. Persons with known tumors of any kind were excluded from the study. Three controls were excluded because of missing residential information. A total of 410 controls were included in the study. Each case was not necessarily matched with three controls at the time of the analysis because the study is still ongoing.

Questionnaire data collection

An in-person interview was conducted on each study subject by a trained interviewer. Follow-up interviews by telephone may have been required occasionally. Either the biologic mother of the subject or the subject himself/herself answered the questionnaire. The questionnaire covered information regarding descriptive characteristics, medical history, residential history up to 2 years prior to birth, locations of schools and kindergartens, occupational history (if the subject was $\geq$16 years of age), dietary habits, and exposure to various hazardous agents. For younger study subjects (i.e., subjects aged 0–19 years), a similar questionnaire was administered to the parents to obtain information on parental factors.

Exposure assessment

Address geocoding. Exposure to petrochemicals was assessed on the basis of the residential history section of the questionnaire. Information on long-term residences (i.e., subject spent $\geq$1 year) for each subject was collected. These residences and locations of petrochemical plants were geocoded by a commercial company (MapAsia, Hong Kong, People's Republic of China). Geocoding results were classified into three categories: nongeocodable addresses, partial addresses, and matched addresses. For an address to be classified as a matched address, the study subject must have provided his or her address up to the precision level of the street number so that the address could be geocoded into an exact location. On the other hand, an address was classified as nongeocodable when the study subject provided only the name of an administrative unit or the name of a long street (i.e., a street that is divided into multiple sections by the Taiwan government). An address was classified as a partial address when the study subject provided only a landmark or

the name of a short street. For a partial address with only the street name but not the street number, the address was geocoded to the geographic centroid of the street.

Exposure opportunity score. Based on previous studies conducted in Kaohsiung (8, 12, 13, 15, 19), this study defined potentially exposed areas as areas located within a 3-km radius from the geographic centroid of any of the four petrochemical complexes. All distance measures and exposed-area definitions were performed by ArcInfo map-digitizing software (Environmental Systems Research Institute (ESRI), Redlands, California). To account for the effects from monthly prevailing wind, we defined exposure wedges for each month by the monthly prevailing wind direction. Monthly exposure wedges were defined as the 90-degree areas (i.e., ±45-degree angle from the downwind direction) within potentially exposed areas. We defined four exposure wedges for each month (i.e., one wedge for each petrochemical complex; figure 1). Only addresses located within the exposure wedges were considered exposed during the particular month, and the exposure opportunity scores for these residences were assigned by the inverse of distance (in km) to the relevant petrochemical complex(es). For a particular month, if a residence had been located in the exposure wedges for more than one petrochemical complex, the score of this residence would be the total of the inverse of distances to all relevant petrochemical complexes. In contrast, residences located in the nonexposed area (i.e., outside the 3-km boundary of all four petrochemical complexes) would be assigned a score of zero. The monthly exposure opportunity score ranged from 4.22 for a residence at 236.71 m from a complex to 0.33 for a residence at 3 km. There were no residences closer than 236.71 m to the centroid of a petrochemical complex. Monthly scores were added across time to obtain a cumulative exposure score for each individual.

Statistical analysis

Data were analyzed using SAS, version 8.2, software (SAS Institute, Inc., Cary, North Carolina). Although 96 residences (from 40 subjects) were nongeocodable, these addresses were located outside the potentially exposed areas and thus would not affect the assignment of the exposure opportunity score for these subjects. Consequently, these subjects were retained in our analysis.

Analyses of petrochemical exposure association with leukemia risk were performed by conditional logistic regression models. The exposure opportunity score was log transformed for normality. Analyses were performed separately for subjects who were aged 0–19 versus 20–29 years so that childhood leukemia and adult leukemia could be evaluated separately. The variables included in the final model were exposure opportunity score (log transformed), maternal educational status (for subjects aged 0–19 years), educational status of the subject (for subjects aged 20–29 years), and smoking status.

RESULTS

Table 1 presents the participation data for cases and controls. From the originally identified 188 leukemia cases and 769 controls, 171 cases and 410 controls participated in the study, giving participation rates of 91 percent and 53 percent, respectively. To evaluate whether proximity between current residence and petrochemical plants would affect control participation, we calculated percentages of ''exposed'' current address (i.e., within a 3-km distance to any of the petrochemical plants) for both responding controls and nonresponding controls. The 142 nonresponding controls classified as ''could not be contacted'' in table 1 were excluded from the calculation, because the majority of these persons were studying or working outside Kaohsiung and did not live in the addresses recorded in the population registry data. Eighteen percent of responding controls and 16 percent of the remaining nonresponding controls lived in currently exposed areas; the difference in the percentages was not statistically significant between responding controls and nonresponding controls (χ^2, 1 df; $p = 0.54$).

TABLE 1. Participation of leukemia cases and controls, Kaohsiung, southern Taiwan, Republic of China, 1997–2003

Category*	Cases		Controls	
	No.	%	No.	%
Originally selected	188	100	769	100
Could not be contacted†	4	2.1	142	18.5
Refused to participate	7	3.7	200	26.0
Noneligible because parents were divorced or widowed	3	1.6	11	1.4
Noneligible because of other reasons	2	1.1	3	0.4
Noneligible because of missing address information	1	0.5	3	0.4
Final sample size	171	91.0	410	53.3

* Categories for nonparticipation are mutually exclusive; percentages may not add up to 100 because of rounding.

† Includes subjects whose addresses from the population registry were invalid, subjects studying/working in another city, or subjects who could not be reached after several attempts.

A summary of geocoding results is shown in table 2. The average numbers of residences held by cases and controls were 2.05 and 1.78, respectively. Cases and controls provided comparable quality on their address information (χ^2, 2 df; $p = 0.62$). For cases, the percentages of nongeocodable address, partial address, and matched address were 10 percent, 22 percent, and 68 percent, respectively. These percentages for controls were 8 percent, 21 percent, and 71 percent.

Table 3 shows the distribution of selected demographic and risk factors by disease status. For the younger age group (i.e., subjects aged 0–19 years), acute lymphocytic leukemia was the most predominant disease type and accounted for 72 percent of recruited cases. In contrast, for subjects aged 20–29 years, the distribution of disease type was more heterogeneous; acute lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia each accounted for approximately one third of recruited cases. In this older age group, more controls (56 percent) than cases (30 percent) completed beyond high school (table 3).

TABLE 2. Summary of address geocoding by disease status and address, Kaohsiung, southern Taiwan, Republic of China, 1997–2003

Address*	Cases							Controls						
	Nongeocodable		Partial		Matched		Total no.	Nongeocodable		Partial		Matched		Total no.
	No.	%†	No.	%†	No.	%†		No.	%‡	No.	%‡	No.	%‡	
Address 1	19	11.1	40	23.4	112	65.5	171	27	6.6	90	22.0	293	71.5	410
Address 2	6	5.1	22	18.6	90	76.3	118	15	7.8	39	20.2	139	72.1	193
Address 3	6	17.7	10	29.4	18	52.9	34	10	13.7	17	23.3	46	63.0	73
Address 4	3	16.7	4	22.2	11	61.1	18	7	20.6	6	17.1	21	61.8	34
Address 5	1	12.5	0	0	7	87.5	8	1	6.7	1	6.7	13	86.7	15
Address 6	0	0	0	0	1	100	1	1	33.3	0	0	2	66.7	3
Address 7	0	0	0	0	0	0	0	0	0	0	0	1	100	1
Total	35	10.0	76	21.7	239	68.3	350	61	8.4	153	21	515	70.6	729

* Addresses were labeled in chronologic order (oldest address first). Each study subject was recorded for up to seven addresses.
† Percentage of geocoding results by address among cases; percentages may not add up to 100 because of rounding.
‡ Percentage of geocoding results by address among controls; percentages may not add up to 100 because of rounding.

The proportions of exposed subjects by disease status are listed in table 4. For the younger age group, the proportions of exposed subjects did not vary by disease status. The proportions of exposed subjects were still comparable between cases and controls when restricting the analysis to the acute lymphocytic leukemia subgroup aged 0–19 years. On the contrary, the proportion of exposed subjects was significantly higher for cases (35 percent) than controls (11 percent) for subjects aged 20–29 years; ever residing in an exposed area was associated with an adjusted odds ratio of 4.56 (95 percent confidence interval (CI): 1.66, 12.54) for this older age group. Among younger subjects who had nonzero scores, cases and controls had median log-transformed exposure opportunity scores of 1.98 and 2.04, respectively. For the older exposed subjects, median scores for cases and controls were 3.15 and 3.54, respectively (table 4). Table 4 also presents regression results for modeling the log-transformed exposure opportunity score as a continuous variable. For the younger age group, there was no statistically significant association between petrochemical exposure and leukemia risk, whether the analysis was performed on all cases and controls or on the acute lymphocytic leukemia subgroup only. For the older age group, however, residential petrochemical exposure was a significant risk factor for leukemia. In this age group, each unit increase in the log-transformed score was associated with an adjusted odds ratio of 1.54 (95 percent CI: 1.14, 2.09). A unit increase in the log-transformed exposure opportunity score corresponds to a score of 2.71 or residing 2.7 months at 1 km downwind from a petrochemical pollution source.

DISCUSSION

In our study, residential exposure to petrochemicals is defined as a general term that may represent a complex mixture of different gaseous components and particulate matter (20). Numerous components present in the petrochemical pollution mix are hazardous and include known and suspected human carcinogens, such as benzo[*a*]pyrene, benzene, and fine combustion particles (20). Previous studies provide an unclear spatial association between residential petrochemical exposure and leukemia (7–9, 21, 22). We observed a positive association between residential petrochemical exposure and risk of leukemia for subjects aged 20–29 years. For one unit increase in the log-transformed exposure opportunity score, the adjusted odds ratio was 1.54 (95 percent CI: 1.14, 2.09).

We applied geographic information system tools for exposure assessment. Our approach allows us to account for subject mobility, length of stay at each residence, distance to petrochemical plant(s), monthly prevailing wind direction, and multiple petrochemical pollution sources. In contrast to previous studies (8, 9, 21), which typically used either the longest held residence or the current residence for the basis of exposure assessment, our exposure assessment approach used the complete residential history of each subject, weighted by the length of stay at each residence. Our approach allows us to account for both spatial and temporal variations in individual-level exposure. One of the major strengths of our study is that, compared with populations in most industrialized countries, our study population is much more stable in terms of mobility, probably because of cultural factors and the age distribution of our study population. The average numbers of residences held by cases and controls were 2.05 and 1.78, respectively. The low turnover of residence among our study population enabled us to use the entire residential history for exposure assessment and enabled us to calculate the lifetime cumulative exposure on a relative scale.

Few studies have investigated the association between residential petrochemical exposure and leukemia risk (8, 9, 21). These studies focused primarily on mortality data and reported an unclear association between residential exposure to petrochemicals and leukemia mortality. Some of these previous studies used an ecologic study design, raising concerns about the ecologic fallacy (8, 21). On the contrary, our study used individual-level point data for exposure assessment. Count data use the aggregated summaries,

TABLE 3. Demographic and risk characteristics of cases and controls, Kaohsiung, southern Taiwan, Republic of China, 1997–2003

Characteristic	Cases*	Controls*
Age† 0–19 years (131 cases and 314 controls)		
Age (years)		
Median	8.04	6.90
Gender (%)		
Female	40.5	38.5
Male	59.5	61.5
International Classification of Diseases (%)		
Acute lymphocytic leukemia	71.8	
Acute myeloid leukemia	19.1	
Chronic myeloid leukemia	6.1	
Others	3.1	
History of smoking (%)		
Yes	0.8	2.3
No	99.2	97.8
Maternal educational status (%)		
Primary school or less	10.7	15.6
Junior high school	20.6	14.0
High school	51.2	50.3
College or above	17.6	20.1
Age† 20–29 years (40 cases and 96 controls)		
Age (years)		
Median	25.39	24.98
Gender (%)		
Female	47.5	46.9
Male	52.5	53.1
International Classification of Diseases (%)		
Acute lymphocytic leukemia	32.5	
Acute myeloid leukemia	30.0	
Chronic myeloid leukemia	35.0	
Others	2.5	
History of smoking (%)		
Yes	25.6	26.0
No	74.4	74.0
Educational status (%)		
Junior high school	7.5	7.3
High school	62.5	36.5
College or above	30.0	56.3

* Percentages may not add up to 100 because of rounding or missing values.

† Age at diagnosis for cases; age at referent date for controls.

whereas point data consist of exact locations and are less likely to contain inaccuracies (23). In addition, previous studies used proximity to pollution source as the only basis of exposure assessment without accounting for other important factors, such as wind direction, which can also affect exposure level.

There are several limitations to a case-control study like ours, and the results should be interpreted with caution. Selection bias is considered a threat to the validity of a study (24). In this study, we used random sampling of controls based on population registry. This sampling scheme is usually considered the most desirable option for control selection (24). Moreover, when the percentages of exposed current residence were calculated for responding versus nonresponding controls, there was no indication of differential participation due to current residence (and consequently exposure status) among controls.

Recall bias is another concern for case-control studies. Such bias results from differential recall of exposure among cases and controls, as cases may recall exposure more thoroughly than controls do (24). In the present study, however, the proportions of ''matched address'' did not vary by disease status (table 2). Since we used geocoded addresses as the basis of exposure assessment, recall bias is unlikely to be a major threat to our study.

In the present study, the exposure-disease relation is found only among subjects aged 20–29 years, raising concerns about effects from occupational exposure. However, when we created a dichotomous indicator of ''ever worked in the petrochemical industry/occupation'' using the standardized four-digit industry/occupation codes of Taiwan (25), none of the cases or controls was ever employed in the petrochemical occupation/industry. In addition, we tested the effect of paternal and/or maternal employment in petrochemical-related occupations/industries in the younger age group, and the inclusion of these variables did not materially affect our conclusion. Thus, we are confident that occupational exposure to petrochemicals is unlikely to explain the observed positive association between residential petrochemical exposure and leukemia among the older age group.

Residence location has been a commonly used indicator for environmental exposure in environmental epidemiologic studies (14). However, a major drawback of this exposure assessment approach is the inadequate characterization of air pollution exposure, raising concern for measurement error and increased uncertainties in risk estimates (26). In the present study, we geocoded each long-term residence of each subject and used the geocoded data as the basis to assign an exposure score for each residence. It is important to note that, in general, geocoding has been considered a challenging process with match rates ranging from 20 to 98 percent, depending on the level of urbanization (27, 28). Several factors can cause low match rates: small deviations in street names, changes of street numbering over time, or incomplete street reference map. In addition, because of positional inaccuracies in the street reference map, even a matched address does not necessarily indicate an accurate assignment on the map projection (28). In our study, we acknowledge that positional inaccuracies may have resulted in exposure misclassification. However, these inaccuracies are most likely to be nondifferential by disease status and are unlikely to explain the positive association between petrochemical exposures and leukemia in the older age group.

TABLE 4. Distribution and odds ratios* for leukemia, Kaohsiung, southern Taiwan, Republic of China, 1997–2003

	Exposed subjects		Log-transformed score among the exposed		Odds ratio*,†	95% confidence interval*
	No.	%	Median	Minimum, maximum		
Age 0–19 years (131 cases and 314 controls)‡						
Cases (all disease types)	20	15.3	1.98	0.40, 4.75	1.04	0.79, 1.38
Controls§	48	15.3	2.04	0.33, 4.49		
Acute lymphocytic leukemia cases	16	17.0	1.98	0.40, 4.75	1.21	0.89, 1.65
Controls§	33	14.1	1.85	0.46, 4.49		
Age 20–29 years (40 cases and 96 controls)						
Cases	14	35.0	3.15	1.72, 4.80	1.54	1.14, 2.09
Controls§	11	11.5	3.54	1.17, 4.79		

* Odds ratios and confidence intervals calculated for one unit of increase in the log-transformed exposure opportunity score.

† Calculated from conditional logistic regression and adjusted for smoking status and maternal educational status (if the subject was aged 0–19 years) or the subject's educational status (if the subject was aged 20–29 years).

‡ Included are 94 acute lymphocytic leukemia cases and 234 controls.

§ Referent category.

This study uses an exposure assessment approach that quantitatively assesses the carcinogenetic effects of pollutants from the petrochemical industry on a relative scale. However, there are certain limitations in our approach. When assigning exposure opportunity scores for each residence, we did not account for the fact that a variety of pollutants were produced in each of the four petrochemical complexes. Different pollutants were likely to have various carcinogenic effects, but our exposure assessment approach was unable to capture these variations. Moreover, since production levels and control technologies are likely to vary across time, exposure intensity may have changed, and we were not able to adjust for this. Although wind direction is a major driving force for pollutant transport and dispersion and was accounted for in our approach, we did not take into account other contributing factors in pollutant dispersion, such as wind speeds, topographic environments (e.g., open fields vs. hills), and physical/chemical processes that can change pollutant concentrations and/or nature (29). In addition, although our approach accounted for the long-term movement of each subject by using the complete residential history for exposure assessment, we did not take direct account of the time-activity and behavioral patterns of each subject (30). Nonetheless, all the listed limitations in our exposure assessment approach are likely to result in nondifferential misclassification of exposure, which generally attenuates the odds ratio estimates to bias toward the null. Therefore, it is unlikely that the observed positive association between petrochemical exposure and leukemia was a result of exposure misclassification.

Furthermore, it is worth noting that other pollution sources, in addition to the petrochemical industry, can expose humans to the same (or similar) carcinogens present in petrochemical pollutants. These other sources include auto and truck traffic outdoors (benzene), indoor air pollution from second-hand smoke (e.g., benzene), and emission from furnishings (total volatile organic compounds) (31–33). Our approach implies that outdoor pollution sources are the main sources of human exposure to these carcinogens. Previous studies have shown, however, that personal exposure levels can differ vastly from outdoor air concentrations, and the significance of indoor and mobile exposure sources should not be ignored (31–33). Our approach did not account for indoor and mobile pollution sources, and the bias introduced is hard to evaluate in both direction and magnitude.

Most likely, different cell types of leukemia have different etiology (1–3). Because of limited sample size, we were unable to perform separate analyses for each cell type except for the younger acute lymphocytic leukemia subgroup. Additionally, separate analyses by gender could not be conducted. Future studies with larger sample sizes are warranted in order to delineate these issues.

To summarize, we found residential petrochemical exposure to be positively associated with leukemia risk among subjects aged 20–29 years. Future studies taking into account other indoor or mobile pollution sources are warranted to fully understand the carcinogenic effects of petrochemical exposure. In addition, a more refined approach in spatial interpolation combining monitoring data would help to quantify the effects of residential petrochemical exposure on leukemia risk. Finally, for the study of the effects of residential petrochemical exposure by leukemia cell type and gender, studies with larger sample sizes are warranted.

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