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Increased cancers among residents living in the neighborhood of a petrochemical complex: A 12-year retrospective cohort study

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ABSTRACT

This study investigates whether cancers are increased for residents living in the vicinity of a petrochemical complex with coal power plants and refineries. We recruited a residential cohort of 2388 long-term residents aged above 35 years in 2009–2012 who lived within a 40 km radius of the complex. We measured their internal exposure biomarkers of urinary carcinogenic metals and retrospectively compared cancer incidences between those who lived fewer than 10 km from the complex (high exposure, HE) and those who lived more than 10 km from the complex (low exposure, LE). Residents had lived in their respective areas for 12 years, since the complex began operating in mid-1999. This included two periods of operation: 0–9 years and 10–12 years. Crude cumulative incident rates (CIRs) of all cancers were calculated for new cancer cases (ICD-9: 140–165, 170–176, 179–208) recorded in the Taiwan Health Insurance Database over total person-years at risk in each study period. Poisson regression was applied to estimate relative risks for the CIRs of all cancers between HE and LE areas during the 10–12 years since the beginning of the complex's operation, adjusting for age, gender, body mass index, smoking, hepatitis C, and occupational exposure. We found that our study subjects in HE areas had higher urinary carcinogenic metal levels, including As, Cd, Hg, Pb, and V, and higher prevalence rates of hepatitis C than those in LE areas. After the complex had been operating for 10–12 years, SIRs per 1000 person-years for all cancers in HE and LE areas were 4.44 vs. 2.48 for all subjects, 15.2 vs. 4.86 for elder subjects aged above 60 years, and 2.94 vs. 2.71 for female subjects. Correspondingly, the adjusted relative risks of CIRs for all cancers between HE and LE areas were 1.29 (95% CI: 0.99–1.68) for all subjects, 1.52 (1.04–2.22) for elder subjects, 1.41 (1.00–1.97) for female subjects, and 1.91 (1.15–3.19) for female elderly subjects. We conclude that elder and female residents living within 10 km of a petrochemical complex had higher carcinogenic exposure and cancers than those living farther away from the complex after the complex had been operating for 10 years.

1. Introduction

Petrochemical industries have been identified as important sources of emissions of a wide range of chemical substances, including sulfur oxides (SO_2) (Jones and Harrison 2011; Luria et al., 2001); nitrogen oxides; carbon dioxide; carbon monoxide (Castell et al., 2010; Vardar and Yumurtaci 2010); volatile organic compounds (VOCs), such as benzene and vinyl-chloride (Baltrenas et al., 2011; Chan et al., 2006); polycyclic aromatic hydrocarbons (PAHs) (Hu et al., 2011); and metals, such as arsenic, cadmium, mercury, and vanadium (Moreno et al., 2008; Pancras et al., 2011). Some of these substances have been recognized as environmental carcinogens (IARC, 2013).

Occupational exposures resulting from petroleum refining are classified as "probably carcinogenic to humans" by the World Health Organization (IARC, 1989). Occupational epidemiological studies have shown increased risks of liver cancer, skin cancer, bladder cancer, kidney cancer, and lung cancer among employees of petrochemical industries (Fano et al., 2006; Lo Presti et al., 2001; Sorahan et al., 2002; Teta et al., 1991). Two additional retrospective cohort studies of petrochemical industries also reported elevated standardized mortality ratios and incidence ratios for leukemia and lymphohematopoietic cancers among production workers (Koh et al., 2011) and recommended that mesothelioma and brain tumors be followed carefully in petrochemical employees (Huebner et al., 2004). When built in close

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proximity to residential areas, petrochemical industries can also lead to excess exposure through emitted pollutants, increasing the health risks for nearby residents. Previous case-control studies have shown that residents living near petrochemical industries had increased risks of mortality from brain cancer, bladder cancer, lung cancer, leukemia, non-Hodgkin's lymphoma, multiple myeloma, and lymphohematopoietic cancers than their contrast population (Belli et al., 2004; Gazdek et al., 2007; Johnson et al., 2003; Liu et al., 2008; Shore et al., 1993; Tsai et al., 2009). Ecological studies have also shown a higher age-adjusted mortality rate for male liver cancer and higher standardized mortality ratios for female lung cancer among residents living near a petroleum refinery plant in Taiwan compared with nation-wide rates (Yang et al., 1997, 2000).

The above-mentioned studies all had methodological limitations, such as the lack of individual exposure information and key risk factors in ecological studies, the absence of latent periods for cancer cases in case-control studies, and – in all studies – the absence of clear-cut time periods with which to classify petrochemical manufacturing operations. This study sought to overcome all these limitations by using a residential cohort with well-characterized person exposure to carcinogens, as well as information on personal risk factors, to investigate whether cancer incidence was increased for people who had lived in the vicinity of a petrochemical complex for 10–12 years after the complex began operating.

2. Materials and methods

2.1. Study areas

Situated in Mailiao Township of Yunling County, on the west coast of central Taiwan, the No. 6 Naphtha Cracking Complex is the largest petrochemical complex in Taiwan, with a total area of 2603 ha and more than 64 plants. The major pollution sources at this complex include three oil refineries with an oil production capacity of 25 million tons per year, one coal-fired power plant with an electricity generating capacity of 1.8 million kW per year, three co-generation plants with a total electricity capacity of 2.82 million kW, two naphtha cracking plants producing 160 million tons of ethylene, and several petrochemical processing plants (Fig. 1) (FPCC, 2015). There are other chemical plants might emit pollutants from the complex including the naphtha cracking plant (OL), aromatic plant (ARO), styrene monomer plants (SM), acrylonitrile plant (AN), methyl methacrylate plant (MMA), C4 olefin plant (C4), vinyl chloride monomer plant (VCM), polystyrene plant (PS), acrylonitrile-butadiene-styrene plant (PS/ABS), ethylene glycol plants (EG), and the 1,4-butylene glycol plant (BG) (Fig. 1). This petrochemical complex began operating in mid-1999 and has continued to expand its operations over the years.

Our study area includes ten townships with similar levels of socio–economic development, located 0–40 km away from the No. 6 Naphtha Cracking Complex. These townships, located east and south (90°–180°) of the petrochemical complex, were further classified into high exposure (HE) and low exposure (LE) areas based on administrative divisions. The two adjacent townships of Mailiao and Taishi, located within a 10 km radius of the complex, were classified as HE areas. The more distant townships of Baojhong, Sihhu, Dongshih, Lunbei, Erlun, Citong, Yuanchang, and Huwei are more than 10 km away from the complex and were classified as LE areas (Fig. 1).

2.2. Study subjects

We established a residential cohort of 3230 study subjects; they had lived in the study areas for more than 5 years and were randomly recruited from each of the ten townships during 2009 and 2012. For each subject, we performed a questionnaire survey, biomonitoring, and serological tests for hepatitis B and C. To investigate the carcinogenic effects of petrochemical emissions on adults, we restricted our subjects to those who were older than 35 years at the time of recruitment, which meant that they were older than 20 years when the complex began operating in 1999. A total of 2388 residents from ten townships met the selection criteria, with 782 subjects in HE areas and 1606 subjects in LE areas. The distribution of the residential addresses of these 2388 study subjects is shown in Fig. 1. This study was approved by the Research Ethics Committee of National Taiwan University Hospital, and we obtained informed consent from each participant.

Well-trained interviewers administered face-to-face questionnaire surveys to collect individual data on age, gender, education level, and home address; habits of smoking, alcohol drinking, and betel nut chewing; and work history. Urinary exposure biomarkers of carcinogenic metals including arsenic (As), cadmium (Cd), mercury (Hg), lead (Pb), and vanadium (V), as well as 1-hydroxypyrene (1-OHP), the main metabolite of polyaromatic hydrocarbons (PAHs), were analyzed for the study subjects using inductively coupled plasma mass spectrometry (ICP-MS) and high-performance liquid chromatography (HPLC), respectively, which have been described in detail in previous papers

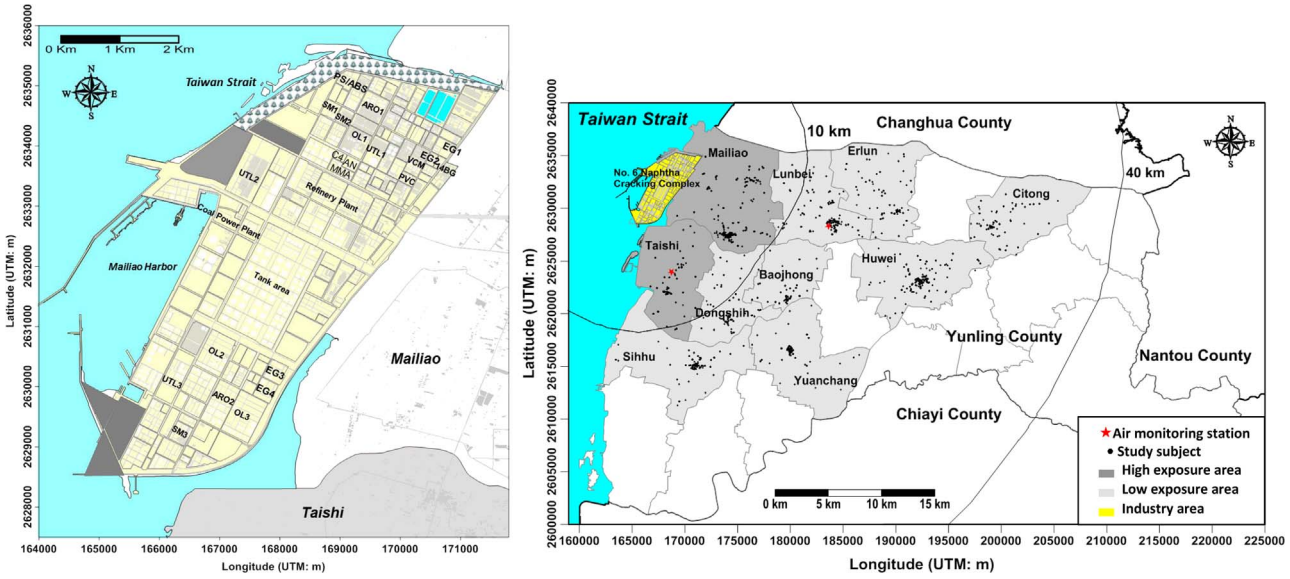

Fig. 1. The map of the No. 6 Naphtha Cracking Complex, study areas, locations of study subjects, and air monitoring stations in Yunling County in Taiwan.

Table 1
Comparisons of basic characteristics, urinary exposure biomarkers, and health status of subjects in HE and LE areas in the vicinity of the petrochemical complex.

Areas Variables	All (N = 2388)	HE (N = 782)	LE (N = 1606)	p-value[d]
Age, mean ± SD	57.5 ± 13.4	57.8 ± 13.1	57.3 ± 13.5	.5290
BMI, mean ± SD[a]	25.6 ± 3.90	25.9 ± 3.90	25.4 ± 3.60	.0002
Distance-to-complex, mean ± SD[b]	17.5 ± 8.52	9.39 ± 2.20	21.5 ± 6.58	< .0001
Urinary levels, mean ± SD[c]				
As	91.1 ± 443	97.2 ± 168	88.2 ± 527	< .0001
Cd	0.89 ± 0.72	0.90 ± 0.66	0.88 ± 0.74	.0337
Hg	2.25 ± 2.37	2.35 ± 1.95	2.21 ± 2.55	< .0001
Pb	1.22 ± 2.85	1.24 ± 1.44	1.21 ± 3.32	.0378
V	1.01 ± 1.40	1.64 ± 2.03	0.71 ± 0.80	< .0001
1-OHP	0.11 ± 0.27	0.13 ± 0.28	0.10 ± 0.27	.0139
Hepatitis B, N(%)				
Yes	303 (12.7)	98 (12.5)	205 (12.8)	.9078
No	2085 (76.8)	684 (87.5)	1401 (87.2)	
Hepatitis C, N(%)				
Yes	213 (8.90)	142 (18.2)	71 (4.40)	< .0001
No	2175 (91.1)	640 (81.8)	1535 (95.6)	
Gender, N(%)				
Male	917 (38.4)	300 (38.4)	617 (38.4)	.9716
Female	1471 (61.6)	482 (61.6)	989 (61.6)	
Smoking, N(%)				
Yes	519 (21.7)	153 (19.6)	366 (22.8)	.1326
No	1861(77.9)	625 (79.9)	1236 (77.0)	
Missing	8 (0.34)	4 (0.51)	4 (0.20)	
Alcohol intake, N(%)				
Yes	424 (17.8)	131 (16.8)	293 (18.2)	.1616
No	1957(82.0)	647 (82.7)	1310 (81.6)	
Missing	7 (0.29)	4 (0.51)	3 (0.20)	
Nut intake, N(%)				
Yes	323 (13.5)	112 (14.3)	211 (13.1)	.2275
No	2055(86.1)	664 (84.9)	1391 (86.7)	
Missing	10 (0.41)	6 (0.77)	4 (0.20)	
Worked at the complex, N(%)				
Yes	171 (7.16)	102 (13.0)	69 (4.30)	< .0001
No	2207(92.4)	676 (86.4)	1531 (95.3)	
Missing	10 (0.42)	4 (0.52)	6 (0.40)	

[a] Unit: kg/m^2.
[b] Unit: km.
[c] For metals, unit: μg/g-creatinine; for 1-OHP, unit: μmol/mol-creatinine.
[d] Comparison between two areas by Chi-square test for discrete variables, Student's *t*-test for continuous variables, and ANCOVA test adjusting age, gender, smoking, alcohol consumption, betel nut chewing, fish consumption (recent three days), and source of drinking water for log-transformed urinary levels.

(Yuan et al., 2015; Yuan et al., 2016a). Urinary creatinine was analyzed to normalize the urinary exposure biomarkers of our study subjects. The serological hepatitis B and C status of our study subjects was confirmed by HBsAg and Anti-HCV tests at the medical diagnosis laboratory of the Yunlin Branch of National Taiwan University Hospital coupled with the hepatitis B with an HBV infection diagnosis (ICD-9-CM codes 070.2x, 070.3x, and V02.61) and the hepatitis C virus infection with an HCV infection diagnosis (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, and V02.62) from 1998 to 2010.

2.3. Cancer incidence

The health outcome of this study is the incidence of all cancers, recorded as cancer cases of all causes by the International Codes of Disease 9th Edition Clinical Modification (ICD-9-CM codes: 140-165, 170-176, and 179-208) criteria and registered as catastrophic illness in the Taiwan National Health Insurance Research Database. After the Cancer Control Act was promulgated in 2003, the data quality and completeness of the cancer registry database in Taiwan have improved and have remained stable until now. However, the Taiwan Cancer Registry (TCR) within the Health and Welfare Data Science Center (HWDC) database was only provided from 2002 (Chiang et al., 2010, 2016). Therefore, we identified the diagnoses of cancers using records from the Registry of Catastrophic Illness Database that provided from 1996. Patients with a certificate of catastrophic illness can be exempted from related medical costs, especially hospital expenses. Then, patients should provide cytological or pathological reports such as laboratory and imaging data supporting the diagnosis of malignancy that confirmed by at least 2 peer-reviewed to be eligible for a cancer catastrophic illness certificate (Lai et al., 2010). Accordingly, we use the reliable and exhaustive Registry of Catastrophic Illness Database to identify the cancer diagnoses in the present study.

Using a latency period of 10 years for the development of cancer from long-term exposure to petrochemical emissions, we classified cancer cases into two time periods: 1999–2007 and 2008–2010. Cancer cases in 1998 were used as wash-out cases for defining newly diagnosed all-cancer cases in 1999–2007, which was 0–9 years after the complex began operating. Additionally, new cancer cases after 2007 were defined as new all-cancer cases in 2008–2010, which was 10–12 years after the complex began operating. Crude cumulative incidence rates (CIRs) per 1000 person-years were then calculated by dividing new cancer cases over total person-years at risk during each of these two operation periods in both HE and LE areas. We have analyzed the age-adjusted incidence rates (SIRs) with 95% confidence intervals by adjusted to the World Health Organization (WHO) 2000–2025 World Standard Population (Ahmad et al., 2001; Boyle and Parkin, 1991).

2.4. Statistical analysis

Comparisons of basic characteristics, health status, and urinary exposure biomarker levels of study subjects in HE and LE areas were analyzed using the Chi-square test for discrete variables and the

Student's *t*-test for continuous variables. The Poisson regression model was applied to investigate whether HE areas had higher all-cancer CIRs than LE areas after the complex had been in operation for 10–12 years by adjusting age, gender, body mass index (BMI), smoking, hepatitis C, and working in the complex. Since the cancer incidents in our study are rare events, they are Poisson distributed. Therefore, we use the Poisson regression, the most basic statistical model for rare events, to estimate relative risks for the incidence rate of all cancers (Breslow and Day, 1987; Frome, 1983). The incidence rate considers the period in which each individual was at risk of developing all-cancer. This period is designated as person-years and added up for the whole group examined. All statistical analyses were performed using SAS 9.2 for Windows. Differences were considered significant when $p < .05$.

3. Results

The basic characteristics, urinary exposure biomarker levels, and health status of 2388 study subjects in the vicinity of the No. 6 Naphtha Cracking Complex are shown in Table 1. Our study subjects were approximately 57.5 years old at the time of recruitment, and approximately 62% of them were female. The 782 study subjects in HE areas had significantly higher BMI measurements (25.9 ± 3.9) than the 1606 subjects in LE areas (25.4 ± 3.6). Study subjects in HE areas lived approximately 12 km closer to the center of the petrochemical complex (9.39 ± 2.20 km) than those in LE areas (21.52 ± 6.58 km). Study subjects in HE areas had significantly higher urinary levels of As, Cd, Hg, Pb, V, and 1-OHP than study subjects in LE areas. The prevalence rate of hepatitis C in HE areas (18.2%) was significantly higher than that in LE areas (4.4%). In HE areas, there were significantly more study subjects who had ever worked in the No. 6 Naphtha Cracking Complex (13.0%) compared to those in LE areas (4.30%). There were no differences in age, hepatitis B prevalence rate, gender, smoking, alcohol intake, and betel nut chewing between the two areas.

After excluding 5 study subjects had cancer before 1999, the petrochemical complex start operation in mid-1999, the basic characteristics, urinary exposure biomarker levels, and health status of cancer cases and non-cases in 2383 study subjects in the vicinity of the No. 6 Naphtha Cracking Complex are shown in Table 2. The 67 study subjects with cancer had significantly higher BMI measurements (25.9 ± 3.9) than the 2316 subjects without cancer (25.3 ± 3.9). Study subjects with cancer had significantly higher urinary levels of As, Hg, V, and 1-OHP than study subjects without cancer. The prevalence rate of hepatitis C of cancer subjects (16.4%) was significantly higher than non-cancer subjects (8.7%). There were no differences in age, living areas, hepatitis B prevalence rate, urinary levels of Cd and Pb, gender, smoking, alcohol intake, betel nut chewing, and worked in the No. 6 Naphtha Cracking Complex between cancer cases and non-cancer cases. In addition, the cancer cites of case subjects include nasopharyngeal carcinoma, esophageal cancer, small intestine cancer, colorectal cancer, skin cancer, breast cancer, cervical cancer, ovarian cancer, prostate cancer, bladder cancer, renal cancer, brain cancer, thyroid cancer, and liver cancer, where the small intestine cancer, colorectal cancer, and cervical cancer to be the most (data not shown)

Table 3 shows the crude CIRs and SIRs of all cancers per 1000 person-years for the two operation periods in both HE and LE areas, classified by all subjects, adults aged above 60 years (elder subjects), and female subjects. Most CIRs and SIRs increased from the first operation period to the second period for all study subjects, elder subjects only, and female subjects only in both HE and LE areas regardless of whether the personal risk factors of smoking, alcohol drinking, and nut chewing, as well as hepatitis C, were considered in the calculation. For example, SIRs of all cancers per 1000 person-years in HE areas increased from 1.53 (95% CI: 0.59, 2.47) in the first operational period to 4.44 (95% CI: 0.72, 8.16) in the second period. A similar trend was observed for the LE area, with CIRs per 1000 person-years increasing from 1.45 (95% CI: 0.78, 2.12) to 2.48 (95% CI: 1.22, 3.74) over the two operational periods. We also observed a contrast in the SIRs of all cancers between HE and LE areas as relative risks (RRs). For example, RRs of SIRs for all cancers per 1000 person-years between HE and LE areas after the complex had been operating for 10–12 years were 1.79 (95% CI: 0.56, 5.75) for all subjects, 3.14 (95% CI: 0.79, 12.5) for elder subjects only, and 1.08 (95% CI: 0.38, 3.11) for female subjects only. A similar contrast in SIRs between HE and LE areas still existed for study subjects without the personal risk factors of smoking, alcohol drinking, and nut chewing, as well as hepatitis C. We did not perform sub-analysis for male and younger subjects because the limited sample size precluded the estimation of stable CIRs for them in the present study.

Table 4 shows the effects of several factors – exposure area, age, gender, BMI, smoking, hepatitis C, and ever having worked at the No. 6 Naphtha Cracking Complex – on cumulative all-cancer CIRs for study subjects after the complex had operated for 10–12 years; these results were obtained using Poisson regression models. We found that the RR of all-cancer CIR in HE areas was marginally significant (p = 0.06) by comparing HE with LE areas (RR: 1.29; 95% CI: 0.99–1.68). We also found significant effects of age (1.05; 1.04–1.06) and hepatitis C (2.15; 1.57–2.94) on the CIRs of all cancers for all study subjects. By restricting our analysis to elder subjects only, we found the RR of all-cancer CIR was significant between HE and LE areas (RR: 1.52; 95% CI:

Table 2
Comparisons of basic characteristics, urinary exposure biomarkers, and health status of cancer cases and non-cases in study subjects in the vicinity of the petrochemical complex.

Areas Variables	All	Cancer cases	Non-cases	p-value[c]
	(N = 2383)	(N = 67)	(N = 2316)	
Age, mean ± SD	57.3 ± 13.4	57.8 ± 13.1	57.0 ± 13.5	.2150
BMI, mean ± SD[a]	25.5 ± 3.9	25.9 ± 3.9	25.3 ± 3.9	.0002
Areas				
HE	780 (32.7)	25 (37.3)	755 (32.6)	.4175
LE	1603 (67.3)	42 (62.7)	1561 (67.4)	
Urinary levels, mean ± SD[b]				
As	91.2 ± 444	97.3 ± 169	88.2 ± 528	< .0001
Cd	0.89 ± 0.72	0.90 ± 0.66	0.88 ± 0.74	0.1044
Hg	2.26 ± 2.37	2.35 ± 1.95	2.21 ± 2.55	< .0001
Pb	1.22 ± 2.85	1.24 ± 1.45	1.21 ± 3.32	0.0619
V	1.01 ± 1.40	1.65 ± 2.03	0.71 ± 0.80	< .0001
1-OHP	0.11 ± 0.27	0.13 ± 0.28	0.10 ± 0.27	.0058
Hepatitis B, N(%)				
Yes	302 (12.7)	10 (14.9)	292 (12.6)	.5740
No	2081 (87.3)	57 (85.1)	2024 (87.4)	
Hepatitis C, N(%)				
Yes	213 (8.9)	11 (16.4)	202 (8.7)	.0295
No	2170 (91.1)	56 (83.6)	2114 (91.3)	
Gender, N(%)				
Male	914 (38.4)	27 (40.3)	887 (38.3)	.7400
Female	1469 (61.6)	40 (59.7)	1429 (61.7)	
Smoking, N(%)				
Yes	517 (21.7)	11(16.4)	506(21.8)	.3371
No	1858 (78.0)	54(80.6)	1804(77.9)	
Missing	8 (0.3)	2(3.0)	6(0.3)	
Alcohol intake, N(%)				
Yes	422 (17.7)	6(9.0)	416(18.0)	.0557
No	1954 (82.0)	61(91.0)	1893(81.7)	
Missing	7 (0.3)	0(0.0)	7(0.3)	
Nut intake, N(%)				
Yes	321 (13.5)	6(9.0)	315(13.6)	.2670
No	2052 (86.1)	61(91.0)	1991(86.0)	
Missing	10 (0.4)	0(0.0)	10(0.4)	
Worked at the complex, N(%)				
Yes	171 (7.2)	2(3.0)	169(7.3)	.2316
No	2202 (92.4)	65(97.0)	2137(92.3)	
Missing	10 (0.4)	0(0.0)	10(0.4)	

[a] Unit: kg/m^2.
[b] For metals, unit: μg/g-creatinine; for 1-OHP, unit: μmol/mol-creatinine.
[c] Comparison between two areas by Chi-square test for discrete variables, Student's *t*-test for continuous variables, and ANCOVA test adjusting age, gender, smoking, alcohol consumption, betel nut chewing, fish consumption (recent three days), and source of drinking water for log-transformed urinary levels.

Table 3
All-cancer incidence rates of study subjects in HE and LE areas adjacent to the petrochemical complex since the beginning of operation.[a]

	Operated 0–9 years			Operated 10–12 years		
	CIR[b]	SIR[c]	95% CI for SIR	CIR	SIR	95% CI for SIR
Subjects						
All						
HE	1.86	1.53	(0.59, 2.47)	5.24	4.44	(0.72, 8.16)
LE	1.74	1.45	(0.78, 2.12)	3.60	2.48	(1.22, 3.74)
RR[d]	1.07	1.06	(0.50, 2.23)	1.46	1.79	(0.56, 5.75)
Elder[e]						
HE	2.90	2.70	(0.86, 4.54)	9.87	15.2	(3.14, 27.3)
LE	3.26	3.17	(1.69, 4.64)	5.26	4.86	(1.64, 8.08)
RR	0.89	0.85	(0.38, 1.92)	1.88	3.14	(0.79, 12.5)
Women						
HE	1.39	1.06	(0.11, 2.01)	4.94	2.94	(0.63, 5.24)
LE	1.92	1.64	(0.76, 2.53)	3.44	2.71	(0.95, 4.47)
RR	0.72	0.65	(0.24, 1.72)	1.44	1.08	(0.38, 3.11)
Subjects without hepatitis C, smoking, alcohol drinking, and nut chewing.						
All						
HE	1.54	1.28	(0.18, 2.37)	4.69	5.52	(0.00, 11.4)
LE	2.08	1.77	(0.86, 2.68)	3.80	2.59	(1.00, 4.17)
RR	0.74	0.72	(0.28, 1.84)	1.23	2.13	(0.45, 10.2)
Elder						
HE	2.96	2.38	(0.04, 4.71)	9.14	16.7	(0.00, 35.0)
LE	3.67	3.26	(1.52, 4.99)	5.66	4.97	(1.15, 8.78)
RR	0.81	0.73	(0.26, 2.06)	1.61	3.36	(0.49, 23.1)
Women						
HE	0.34	0.37	(0.00, 1.09)	1.07	0.84	(0.50, 1.83)
LE	1.94	1.73	(0.71, 2.75)	1.17	0.90	(0.29, 1.51)
RR	0.18	0.21	(0.05, 0.88)	0.91	0.93	(0.26, 3.40)

[a] ICD-9-CM codes of all cancer: 140–165, 170–176, and 179–208.
[b] Crude cumulative incidence rates, unit: per 1000 person years.
[c] Age-standardized incidence rates, unit: per 1000 person years.
[d] The relative risk of crude incidence rates or age-standardized incidence rates in HE over LE.
[e] Subjects aged above 60.

1.04–2.22), and hepatitis C (2.42; 1.61–3.63) remained a significant risk factor for the CIRs of all cancers. By focusing on female subjects only, we also found a significant exposure area effect on elevating the RRs of the all-cancer CIR for female subjects only (1.41; 1.00–1.97) and elder female subjects only (1.91; 1.15–3.19), as well as significant effects of age (1.05; 1.04–1.06) for women subjects. In both analyses for female subjects, hepatitis C remained as a significant risk factor for all-cancer CIRs for female subjects only (2.37; 1.61–3.48) and elder female subjects only (2.89; 1.73–4.82). It should be noted that the variables of smoking and ever having worked at the No. 6 Naphtha Cracking Complex were not included in these subgroup analyses, as the numbers of female cases with these risk factors were too small.

4. Discussion

This study observed that the incidence of all cancers increased for adult residents in general, and for the elderly and females specifically, who had lived within a 10 km radius of a petrochemical complex in Taiwan that had operated for 10 years. Our study is consistent with a study conducted in Italy, which also reported that residents living near an oil refinery plant had significantly higher standardized incidence rates for all cancers when compared to the reference population (Salerno et al., 2012). Our study, however, found a carcinogenic effect on residents who lived within a broader radius of petrochemical industries compared to previous studies, which have reported a higher risk of cancers in study areas that were mostly within 3 km of petrochemical plants (Belli et al., 2004; Sans et al., 1995; Simonsen et al., 2010). This may be attributable to the larger petrochemical operation in our study compared to previous studies. The advantage of our retrospective cohort study design, which offers better characterization of individual environmental exposures both spatially and temporally, may be another reason that we have found carcinogenic effects of petrochemical industries in a wider area; such effects cannot be readily detected by either the case-control or ecological design approaches used in previous studies. A well-defined starting point for the operation of the petrochemical complex provides us with an unusual opportunity to observe small, yet significant, carcinogenic effects of petrochemical industries that were more difficult to identify in previous studies. The availability of home addresses in our study allows us to determine the distance-to-source effect from petrochemical industries for our resident cohorts more precisely than could be done in previous studies, which lacked this information.

We reported a distance-to-complex gradient in the levels of airborne vanadium and urinary vanadium, an IARC Group 2B carcinogen, and arsenic, an IARC Group 1 carcinogen, in previous papers (IARC, 2013; Yuan et al., 2016a). Furthermore, our study subjects in HE areas have significantly higher levels of the internal biomarkers of carcinogenic chemicals associated with different types of cancers (IARC, 2013), including As, Cd, Hg, Pb, and V, than those in LE areas. We believe these heavy metals are mainly emitted from the coal power plants and oil refinery plants of the No. 6 petrochemical complex (Fig. 1). The normal human urinary levels based on the data of ATSDR were As $<$ 100 μg/L, Cd $<$ 1 μg/L, Hg $<$ 4 μg/L, Pb $<$ 1 μg/L, and V around 0.5 μg/L, respectively (ATSDR, 2017). In the present study, the mean of urinary As and Cd levels in all study subjects were close to the upper limits of normal ranges, and it was even higher than the normal human levels for urinary Pb and V in study subjects (Table 1). High-concentration hotspots of carcinogenic 4- and 5-ring PAHs were reported in the vicinity of the petrochemical complex (Yuan et al., 2015). A similar distance-to-complex gradient exists for the organic carcinogens of PAHs and VCM in the study area. Ambient PAH concentrations at each study subject's

Table 4
Poisson regression of cumulative all-cancer incidence rates for study subjects stratified by age and gender after the petrochemical complex had operated for 10–12 years.

Groups Variables	All subjects	Elder subjects[b]	Women subjects	Elder women subjects
	RR (95% CI)[a]	RR (95% CI)	RR (95% CI)	RR (95% CI)
HE vs. LE	1.29 (0.99–1.68)	1.52 (1.04–2.22)*	1.41 (1.00–1.97)*	1.91 (1.15–3.19)*
Age (year)	1.05 (1.04–1.06)**	1.01 (0.98–1.04)	1.04 (1.02–1.05)**	0.98 (0.94–1.02)
Gender (male)	1.05 (0.78–1.40)	1.45 (0.98–2.15)	–	–
BMI (kg/m^2)	0.99 (0.96–1.02)	0.94 (0.90–1.00)	1.01 (0.97–1.05)	0.97 (0.91–1.03)
Smoking (yes)	0.91 (0.64–1.31)	0.81 (0.50–1.32)	–	–
Hepatitis C (yes)	2.15 (1.57–2.94)**	2.42 (1.61–3.63)**	2.37 (1.61–3.48)**	2.89 (1.73–4.82)**
Worked at No. 6 complex	0.79 (0.41–1.51)	1.26 (0.57–2.78)	–	–

[a] Relative risk of cumulative incidence rate with 95% confidence interval.
[b] Subjects with age above 60.
* $p < .05$.
** $p < .0001$.

Table 5
Comparisons of daily SO_2 concentrations against WHO guidelines per year in HE and LE areas from 1999 to 2010.[a]

Year	HE				LE			
	No. of days	Mean	Min	Max	No. of days	Mean	Min	Max
1999	12	26.8	20.7	42.1	18	24.0	20.3	32.9
2000	1	20.6	20.6	20.6	0	–	–	–
2001	24	29.1	20.4	74.3	1	20.3	20.3	20.3
2002	20	28.4	20.6	43.8	0	–	–	–
2003	28	29.3	20.0	67.2	2	24.9	23.4	26.5
2004	21	32.4	20.9	62.3	1	24.7	24.7	24.7
2005	65	36.5	20.5	113.3	9	24.5	20.3	32.4
2006	24	30.1	20.9	62.2	3	21.3	20.6	22.7
2007	40	26.5	20.1	43.6	12	23.5	20.5	28.8
2008	53	32.5	20.0	68.3	3	22.3	22.1	22.6
2009	28	28.4	20.0	93.9	0	–	–	–
2010	14	24.9	21.0	33.6	0	–	–	–

[a] The air quality guideline of the WHO is 20 μg/m^3 24-h mean for SO_2.

home address decreased with distance from the complex and were correlated with the study subject's urinary 1-OHP levels, a PAHs biomarker, as reported in one previous paper (Yuan et al., 2015). The urinary 1-OHP levels of study subjects in the present study were similar to those in a previous study conducted in Taiwan (Chuang and Chang, 2007). According to the above-mentioned, the study subjects in the present study were with higher normal levels of these urinary biomarkers, especially for those in HE areas. In a previous study, urinary biomarker levels of TDGA, a vinyl chloride monomer (VCM), in school-aged children decreased with distance from their respective schools to the petrochemical complex (Huang et al., 2015). Our previous air sampling in the study area found that 1.3-butadiene and vinyl chloride were only detected in HE areas (YLEPB, 2012). Both air pollutants are IARC class 1 carcinogens and are mainly emitted from the olefin-related plants and VCM/PVC plants, respectively, of the petrochemical complex in our study area (Fig. 1).

SO_2 is a major air pollutant emitted from petrochemical refineries, coal-fired power plants and co-generation plants in our study area, as reported in one previous study (Shie et al., 2013). To pay attention on the effect of wind direction, the pollution roses summarized hourly SO_2 concentrations at the Taishi air quality monitoring station according to wind direction during the preoperational period (1995–1999) and two postoperational periods (2000–2004 and 2005–2009) of the complex. It found the 99th percentile of hourly SO_2 concentrations downwind from the complex increased from 28.9 ppb in the preoperational period to 86.2–324.2 ppb in the two postoperational periods. Hourly SO_2 levels exceeded the U.S. Environmental Protection Agency (EPA) health-based standard of 75 ppb only in the postoperational periods, with 65 exceedances from downwind directions during 2001–2009 (Shie et al., 2013). Exposure to SO_2 in the vicinity of the petrochemical industry was reported to be associated with the development of bladder and breast cancer (Liu et al., 2009; Wei et al., 2012) and with a higher standardized mortality rate of all cancers (Triolo et al., 2008). To represent our study subjects' long-term exposure to petrochemical pollution since the complex began operating in 1999, we used SO_2 concentrations measured at two Taiwan Environmental Protection Administration (TEPA) air quality monitoring stations in our study area, the Taishi station in an HE area, which is located 8.1 km south of the complex, and the Lunbei station in a LE area, which is located 16.2 km southeast of the complex, and compared their numbers of days above the World Health Organization's guideline for the 24-h mean concentration of 20 μg/m^3 between the two exposure areas (Table 5). A summary of the number of days above the WHO guideline every year during 1999–2010 in both HE and LE areas is shown in Table 5. We observed a significant contrast in SO_2 pollution between HE and LE areas in terms of days exceeding the WHO guideline and the SO_2 concentrations of those exceeding days. For example, there were 95 days exceeding the SO_2 guideline level (8.7%) in the HE area but only 3 days (0.3%) in the LE area, respectively, over the three years of 2008–2010. The HE area had 330 (7.5%) cumulative days exceeding the SO_2 guideline over the 12 years since the petrochemical complex began operating, with a maximum SO_2 concentration of 113.3 μg/m^3, but there were only 49 such days (1.1%) in the LE area, with a maximum SO_2 concentration of 32.9 μg/m^3.

One previous study reported that aging was coupled with increasing ROS levels and oxidative stress products related to the incidence of cancer (Kudryavtseva et al., 2016), and our study of residents in the current study area showed that oxidative/nitrosative stress, related to some changes in metabolites, was elevated for those with higher heavy metal exposure (Yuan et al., 2016b). This indicates that the higher cancer incidence among the elderly in the HE area compared to the LE area may be attributable to a synergistic effect of aging and environmental pollution in our study area. It should be noted that all cancers were increased for subjects with the hepatitis C virus, which is classified as a Group 1 human carcinogen by the IARC and can increase the risk of hepatocellular carcinoma through chronic inflammation (Chen et al., 2014; Lee et al., 2014). Considering the target organs of some chemical carcinogens found in the study area, such as VCM, there is a double burden of cancer risk for residents who may be affected by both viral infection and high chemical pollution. For other potential risk factors, there was no difference between cancer cases and noon-cases, and there were few cancer subjects with smoking (n = 11), alcohol drinking (n = 6), betel nut chewing (n = 6), and worked at the complex (n = 2) as shown in Table 2. Therefore, it is difficult to observe the effects of these risk factors on all-cancer incidence in present study. Due to the simple characteristics of study subjects in the present study, it strengthens the credibility on the petrochemical environmental effect on cancer incidence of residents nearby.

The present study has some limitations. First, we can only report our findings for all cancers rather than site-specific cancers because of the small population size of our residential cohort. Such a limited cohort size is also a reason why we cannot perform stable analysis and report either positive or negative findings for males and younger subjects. Second, it is hard to accurately assess the cancer risk without risk estimates before operation, and we cannot compare changes in cancer incidence before and after the operation of the complex because national health insurance data only allow us to trace the study subjects' cancer status back to one year before the operation of the petrochemical complex began. Therefore, we set up a 10 years latency period for the development of cancer in the present study, and focused on the difference in cancer incidence rate of the present cohort after the operation of petrochemical complex for 10–12 years. However, the long-term follow-up study should be conducted in advanced to observe the trend of cancer incidence and mortality more precisely. Third, we cannot establish direct linkages between specific carcinogenic pollutants and cancers, as long-term environmental monitoring data of specific carcinogens emitted from petrochemical industries are not available in our study.

Regardless of these limitations on data availability, our overall results support the conclusion that cancers were increased for residents living within 10 km of a petrochemical complex 9 years after the complex began operating and that this occurred via elevated pollution from a mixture of carcinogenic air pollutants emitted from power plants, oil refineries and petrochemical manufacturing plants.

Competing financial interests

The authors declare they have no actual or potential competing financial interests.

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