

Many clinical studies have revealed that cancer is related

closely to ambient particulate matters (PMs), where the air

pollution is a ubiquitous and complex mixture of pollutants.^[2]

PM of diameter up to $10 \,\mu m$ (PM₁₀) and fine PM, up to $2.5 \,\mu m$

 $(PM_{2.5})$, are known as a significant risk factor for human health status.^[3] Outdoor air pollution and airborne PM were considered

The association between air pollution level and breast cancer risk in Taiwan

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Abstract

Breast cancer has the highest incidence of cancer among women in Taiwan, and air pollutants have been documented to have multiple adverse effects on human health. There is no relevant data, there has been no research in Taiwan to discuss the relevance of air pollutants to breast cancer, and evidence is sparse and inconclusive.

Air quality data used in this study was collected from the 78 air quality monitoring stations situated in 74 municipalities in Taiwan during 2000 to 2011. The daily measurements taken at each monitoring station represented the level of exposure for each participant residing in that zone. The air pollution concentration is partitioned based on the concentration level in Quartile. We calculate the annual average air pollutants concentration (CO, NO, NO₂, PM_{2.5}, THC, and CH₄) and the long-term average exposure levels of these pollutants until diagnosis of breast cancer, ending the study period for each individual.

Patients who were living in areas with the highest air pollutants concentration (Quartile 4) had the most people diagnosed with breast cancer (CO:1.47%, NO:1.41%, NO₂:1.63%, PM_{2.5}:0.91%, THC:1.53%, CH₄:2.33%). The patients who were exposed to Quartile 1 level of CO, NO, and NO₂ concentration were the oldest, and other patients who were exposed to Quartile 4 level of CO, NO, and NO₂ concentration were the oldest urbanization. Participants exposed to Quartile 4 level of CO, NO, and NO₂ concentration soft air pollutants were associated with highest hazards ratios for breast cancer incidences.

Most participants who were exposed to the high concentration of air pollutants (CO, THC and CH₄) had a significantly higher risk of breast cancer. If we can improve air pollution in the environment, we can reduce the incidence of breast cancer and save precious medical resources.

Abbreviations: CIs = confidence intervals, HRs = hazards ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2000 = Longitudinal Health Insurance Database 2000, NHIRD = National Health Insurance Research Databases, PM = particulate matter.

Keywords: air pollution, breast cancer, PM_{2.5}, Taiwan

1. Introduction

Breast cancer has the highest incidence of cancer among women in Taiwan, and the rate is increasing year by year.^[1] On the basis of statistics from the National Health Insurance Research Databases (NHIRD), the incidence and mortality of breast cancer has grown to 69.1 and 12.0 per 100,000 population, respectively.^[1]

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as the group 1 of carcinogen for humans by the International Agency for Research on Cancer.^[4] An American study suggests that exposure to high levels of PM may have injurious effects on the length of survival to breast cancer, particularly among women who were diagnosed with early stage cancers.^[5] Furthermore, a Japanese study found that $PM_{2.5}$ levels estimated from the measured PM_{10} levels has significant association with the mortality of breast, endometrial, and ovarian cancers.^[6] However, there is currently no relevant data and research conducted in Taiwan to discuss the relevance of $PM_{2.5}$ to breast cancer. Thus, we investigated the correlation of breast cancer with common air pollutants by using a nationwide, population-based database in Taiwan.

2. Methods

2.1. Data source

In this retrospective cohort study, we used the data from Longitudinal Health Insurance Database 2000 (LHID2000). LHID2000 is a subset of the NHIRD. The LHID2000 has adopted a sample of one million beneficiaries who were retrieved from NHIRD in 2000. Taiwan launched a National Health Insurance program on March 1, 1995, and 99.9% of Taiwan's population was enrolled in 2014. NHIRD contains demographic information, records of clinical visits, hospitalizations, diagnoses, prescriptions, medical costs for reimbursement and residential area. This study uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to categorize disease diagnoses based on inpatient data. This retrospective cohort study was approved by the Chung Shan Medical University Institutional Review Board, number CS19009.

Quality monitoring stations adjacent to, or sharing the same district codes with, the patients' residential area were the sources of the environmental data. Quality monitoring stations, which were built by Taiwan Environment Protection Administration, collect various air concentrations, temperature, and humidity data. Air quality data used in this study was collected from 78 air quality monitoring stations situated in 74 municipalities. The measurement period was from 2000 to 2011. The daily measurements taken at each monitoring station represented the level of exposure for each participant residing in that zone. We calculated the annual average air pollutant concentration (CO, NO, NO₂, PM_{2.5}, THC, and CH₄) to estimate the annual exposed air concentration for each subject. We then computed the long-term average exposure levels of these pollutants until diagnosis of breast cancer, ending the study period for each individual.

2.2. Covariates and outcome

This research data is analyzed in combination with the LHID 2000 and the air quality database. People residing in the area where an air quality monitoring station was located and those in LHID2000 were selected as the study population. The main end point of the study was breast cancer (ICD-9-CM 174.9). All patients were followed from January 1, 2000 until the diagnosis of breast cancer (ICD-9-CM code 174.9), withdrawal from the NHI, or December 31, 2011. This study excludes those who were diagnosed with breast cancer before 2000. Confounding factors such as age, monthly income, and urbanization level were considered. Monthly incomes were divided to 4 groups: <14,400

TWD, 14,400–18,300 TWD, 18,301–21,000 TWD, and 21,000 TWD. Urbanization levels were divided to 4 levels, with level 1 being the highest urbanization area, and level 4 being the lowest. The air pollution concentration is partitioned based on the concentration level in Quartile.

2.3. Statistical analysis

The Chi-Squared test was used to analyze the difference in monthly income, urbanization level, and the incidence of breast cancer. The Student t test was used to analyze the continuous variables like age in different air quality levels. The incidence of breast cancer (per 10,000 person per year) was classified to 4 levels of air pollutant concentrations. Cox proportional hazard regression analysis was used to assess the risk of breast cancer for each pollutant quartile level (Quartiles 2-4), and was compared with Quartile 1 (reference group). The cox proportional hazard regression with hazards ratios (HRs), and 95% confidence intervals (CIs) were used for evaluating the associations between urban air pollutants levels and diagnosis of breast cancer after adjusting age, sex, monthly income, and urbanization level. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC) for Windows 10 and the significance level was set at a 2-tailed P < .05.

3. Results

A total of 98,011 patients with CO concentration data, 98,017 patients with NO and NO₂ concentration data, 96,643 patients with PM_{2.5} concentration data, and 74,016 patients with THC and CH4 concentration data were analyzed. The sociodemographic factors and urbanization level of patients with CO, NO, NO₂, PM_{2.5}, THC and CH₄ are demonstrated in Tables 1–6.

Table 1 shows the baseline characteristics of participants exposed to 4 levels of CO concentration. There were more patients that lived in the highest CO concentration areas (27.4%). Compared with the other CO concentration stratification, those exposed to the Quartile 1 level of CO concentration were the oldest. The distributions of monthly incomes and urbanization levels were similar. Patients living in the highest urbanization areas were exposed to the highest CO concentration (53.9%), and patients who lived in the highest CO concentration had the most people diagnosis breast cancer (1.47%).

Table 2 presents the baseline characteristics of participants exposed to 4 levels of NO concentration. The patients who were exposed the Quartile 1 level of NO concentration were also the oldest. The distributions of monthly incomes and urbanization levels were also similar. Patients who lived in the highest urbanization areas and monthly income is 14,400 to 18,300 were dominant. Patients who lived in the highest NO concentration also had the most people diagnosed with breast cancer (1.41%).

In Table 3, there were more patients living in the Quartile 3 level of NO_2 concentration areas (30.1%) compared to other Quartile levels. The patients who were exposed to the Quartile 1 level of NO_2 concentration were the oldest, while those exposed to the Quartile 3 level of NO_2 concentration were the youngest. Most patients living in the highest NO_2 concentration areas also lived in areas of high urbanization and have monthly incomes between 14,400 and 18,300. Patients who lived in the highest NO concentration also had the most people diagnosis breast cancer (1.63%).

Table 1

	CO N=98,011										
	Q1 N=	23,892	Q2 N=2	25,227	Q3 N=	22,007	Q4 N = 26,884				
Variables	n	%	n	%	n	%	n	%	P value		
Age											
Mean, SD*	40.6	15.6	38.7	14.8	38.2	14.7	38.7	14.7	<.001		
Monthly income (NTD) [†]									<.001		
<14,400	3686	15.4	4178	16.6	3734	17.0	4460	16.6			
14,400-18,300	7720	32.3	9485	37.6	8920	40.5	10,084	37.5			
18,300-21,000	7576	31.7	6029	23.9	4281	19.5	6051	22.5			
≥ 21,000	4910	20.6	5536	21.9	5072	23.1	6289	23.4			
Urbanization level [‡]									<.001		
1 (highest)	5278	22.1	6180	24.5	9031	41.0	14,481	53.9			
2	7507	31.4	11,318	44.9	5208	23.7	7542	28.1			
3	3992	16.7	3559	14.1	4875	22.2	3260	12.1			
4 (lowest)	7115	29.8	4170	16.5	2893	13.2	1601	5.96			
Outcome											
Breast cancer	193	0.81	234	0.93	240	1.09	395	1.47	<.001		

Baseline characteristics of participants exposed to various annual average concentrations of CO

Chi-Squared test. * One-way ANOVA.

* Monthly income, new Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD.

* The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.

There were more patients living in the lowest level of $PM_{2.5}$ concentration areas (29.1%) in Table 4. Patients who were exposed to the Quartile 4 level of $PM_{2.5}$ concentration were the oldest, and those exposed to the Quartile 2 level of $PM_{2.5}$ concentration were the youngest. Patients who lived in the highest $PM_{2.5}$ concentration area also had the highest level of breast cancer diagnosis (0.91%). Although the higher the $PM_{2.5}$ concentration in statistics, the higher the diagnosis of breast cancer, but there is no statistically significant difference in the *P* value (*P* value = .36). I think $PM_{2.5}$ may cause a higher risk of breast cancer, but it will not increase as the concentration of $PM_{2.5}$ increases.

Tables 5 and 6 demonstrates the distributions of age, monthly income, and urbanization levels in THC and CH4 data. The

distributions of monthly incomes and urbanization levels were similar between gas concentration stratification in THC and CH4 data. Patients who lived in the highest THC concentration and CH₄ concentration also had the most people diagnosis breast cancer (1.53% and 2.33%, respectively).

Table 7 presents the associations between pollutant levels and the risk of breast cancer. The adjusted hazard ratios of breast cancer after exposure to the Quartile 2, Quartile 3, and Quartile 4 levels were compared with those after exposure to the Quartile 1 level. With an interquartile range increase in each pollutant, adjusted HRs were significant. Compared to the lowest quartile of each air pollutant, subjects who were exposed to the highest quartile (Quartile 4) had a significantly higher risk of breast cancer (CO: adjusted HR=1.85 [95% CI: 1.54–2.21]; NO:

Table 2

Baseline characteristics of participants exposed to various annual average concentrations of NO.

	NO N=98,017										
	Q1 N=	23,723	Q2 N=	24,488	Q3 N=2	22,297	Q4 N=2	27,509			
Variables	n	%	n	%	N	%	n	%	P value		
Age											
Mean, SD*	40.4	15.6	39.3	15.0	37.5	14.6	38.8	14.7	<.001		
Monthly income (NTD) [†]									<.001		
<14,400	3700	15.6	4130	16.9	3664	16.4	4567	16.6			
14,400-18,300	7498	31.6	9383	38.3	9177	41.2	10,152	36.9			
18,300-21,000	7817	33.0	5635	23.0	4614	20.7	5873	21.4			
≥21,000	4708	19.9	5340	21.8	4842	21.7	6917	25.1			
Urbanization level [‡]									<.001		
1 (highest)	5115	21.6	6090	24.9	10,295	46.2	13,470	49.0			
2	8305	35.0	8056	32.9	6914	31.0	8303	30.2			
3	2383	10.1	5930	24.2	3190	14.3	4184	15.2			
4 (lowest)	7920	33.4	4412	18.0	1898	8.51	1551	5.64			
Outcome											
Breast cancer	202	0.85	251	1.02	221	0.99	389	1.41	<.001		

Chi-Squared test.

One-way ANOVA.

Table 3

Baseline characteristics of participants exposed to various annual average concentrations of NO2.

	NO ₂ N = 98,017										
	Q1 N=21,406		Q2 N = 28,475		Q3 N = 29,531		Q4 N = 18,605				
Variables	n	%	n	%	N	%	n	%	P value		
Age											
Mean, SD*	40.6	15.6	39.2	15.1	37.9	14.4	38.8	14.8	<.001		
Monthly income (NTD) [†]									<.001		
<14,400	3302	15.4	4888	17.2	4786	16.2	3085	16.6			
14,400-18,300	6840	32.0	10,728	37.7	11,719	39.7	6923	37.2			
18,300-21,000	6923	32.3	6839	24.0	6275	21.3	3902	21.0			
≥ 21,000	4341	20.3	6020	21.1	6751	22.9	4695	25.2			
Urbanization level [‡]									<.001		
1 (highest)	5048	23.6	6844	24.0	13,671	46.3	9407	50.6			
2	6519	30.5	11,141	39.1	8624	29.2	5294	28.5			
3	3084	14.4	4478	15.7	5266	17.8	2859	15.4			
4 (lowest)	6755	31.6	6011	21.1	1970	6.67	1045	5.62			
Outcome											
Breast cancer	196	0.92	269	0.94	294	1.00	304	1.63	<.001		

Chi-Squared test.

* One-way ANOVA.

Table 4

Baseline characteristics of participants exposed to various annual average concentrations of PM_{2.5}.

	PM _{2.5} N=161,970										
	Q1 N=28,162		Q2 N=21,596		Q3 N=23,372		Q4 N = 23,513				
Variables	n	%	n	%	Ν	%	n	%	P value		
Age											
Mean, SD*	38.8	14.8	38.1	14.4	38.7	14.8	39.4	14.8	<.001		
Monthly income (NTD) [†]									<.001		
<14,400	4468	15.9	3332	15.4	3665	15.7	4091	17.4			
14,400-18,300	9853	35.0	8408	38.9	8911	38.1	8753	37.2			
18,300-21,000	6386	22.7	4604	21.3	5932	25.4	6572	28.0			
≥21,000	7455	26.5	5252	24.3	4864	20.8	4097	17.4			
Urbanization level [‡]									<.001		
1 (highest)	13,795	49.0	9097	42.1	6543	28.0	5165	22.0			
2	7702	27.4	6182	28.6	8099	34.7	9145	38.9			
3	3078	10.9	3519	16.3	3358	14.4	5500	23.4			
4 (lowest)	3587	12.7	2798	13.0	5372	23.0	3703	15.8			
Outcome											
Breast cancer	224	0.80	181	0.84	179	0.77	213	0.91	.36		

Chi-Squared test.

* One-way ANOVA.

Table 5

Baseline characteristics of participants exposed to various annual average concentrations of THC.

	THC N=74,061										
	Q1 N = 19780		Q2 N = 18791		Q3 N = 18335		Q4 N = 17155				
Variables	n	%	n	%	N	%	n	%	P value		
Age											
Mean, SD*	38.4	14.2	39.0	14.7	38.3	15.0	38.3	14.7	<.001		
Monthly income (NTD) [†]									<.001		
< 14,400	3263	16.5	3199	17.0	2971	16.2	2718	15.8			
14,400-18,300	7772	39.3	6720	35.8	6955	37.9	6855	40.0			
18,300-21,000	4774	24.1	4671	24.9	4093	22.3	3783	22.1			
≥ 21,000	3971	20.1	4201	22.4	4316	23.5	3799	22.2			
Urbanization level*									<.001		
1 (highest)	5850	29.6	4748	25.3	8529	46.5	7880	45.9			
2	4917	24.9	7231	38.5	4860	26.5	5765	33.6			
3	4148	21.0	3108	16.5	3390	18.5	2494	14.5			
4 (lowest)	4865	24.6	3704	19.7	1555	8.48	1016	5.92			
Outcome											
Breast cancer	89	0.45	87	0.46	248	1.35	263	1.53	<.001		

Chi-Squared test.

One-way ANOVA.

Table 6

	CH4 N=74061										
	Q1 N=	19406	Q2 N =	16914	Q3 N=	24110	Q4 N =	13631			
Variables	n	%	n	%	N	%	n	%	P valu		
Age											
Mean, SD*	38.2	14.1	38.3	14.2	37.6	14.4	40.8	16.1	<.001		
Monthly income (NTD) [†]									<.001		
<14,400	3185	16.4	2615	15.5	3973	16.5	2373	17.5			
14,400-18,300	7813	40.3	6263	37.0	9660	40.1	4566	33.5			
18,300-21,000	4511	23.3	3705	21.9	5414	22.5	3691	27.1			
≥ 21,000	3897	20.1	4331	25.6	5063	21.0	2996	22.0			
Urbanization level [‡]									<.001		
1 (highest)	5961	30.7	6416	37.9	9590	39.8	5040	37.0			
2	5086	26.2	5446	32.2	8429	35.0	3812	28.0			
3	4675	24.1	3013	17.8	3525	14.6	1927	14.1			
4 (lowest)	3684	19.0	2039	12.1	2566	10.6	2851	20.9			
Outcome											
Breast cancer	90	0.46	77	0.46	202	0.84	318	2.33	<.001		

Chi-Squared test.

* One-way ANOVA.

adjusted HRs=1.63 [95% CI: 1.37–1.95]; and NO₂: adjusted HR=1.79 [95% CI: 1.45–2.15]; PM_{2.5}: adjusted HRs=1.29 [95%CI:1.07–1.56]; THC: adjusted HRs=3.53 [95%CI:2.76–4.50]; CH4: adjusted HRs=4.95 [95%CI:3.92–6.26]).

4. Discussion

In this study, we examined the association between air pollutant levels and risk of adult-onset breast cancer, and showed a significant higher risk in higher pollution level areas. We found

Table 7

Comparisons of differences in breast cancer incidences and associated HRs in participants exposed to various daily average concentrations of air pollutants.

	Event	PY	IR	cHR	95%CI	aHR	95%CI
CO							
Q1	193	278,407	6.93	Ref.		Ref.	
Q2	234	294,954	7.93	1.14	(0.95, 1.38)	1.19	(0.98, 1.44)
Q3	240	254,873	9.42	1.36	(1.13, 1.64)**	1.44	(1.19, 1.75)***
Q4	395	310,571	12.7	1.84	(1.13, 1.64) ^{**} (1.55, 2.18) ^{***}	1.85	(1.19, 1.75) ^{***} (1.54, 2.21) ^{***}
NO							
Q1	202	276,283	7.31	Ref.		Ref.	
Q2	251	285,068	8.80	1.21	(1.08, 1.45)*	1.24	(1.03, 1.50)*
Q3	221	259,543	8.51	1.17		1.20	(0.99, 1.46)
Q4	389	317,928	12.2	1.68	(0.96, 1.41) (1.41, 1.99) ^{***}	1.63	(1.37, 1.95)***
NO ₂							
Q1	196	249,256	7.86	Ref.		Ref.	
Q2	269	331,040	8.13	1.03	(0.86, 1.24)	1.07	(0.89, 1.29)
Q3	294	344,485	8.53	1.09	(0.91, 1.30)	1.11	(0.92, 1.33)
Q4	304	214041	14.2	1.81	(1.51, 2.17)***	1.79	(1.48, 2.15)***
$PM_{2.5}$							
Q1	224	330,849	6.77	Ref.		Ref.	
Q2	181	254,009	7.13	1.05	(0.87, 1.28)	1.11	(0.92, 1.36)
Q3	179	274,489	6.52	0.96	(0.79, 1.17)	1.08	(0.89, 1.32)
Q4	213	275,358	7.74	1.14	(0.95, 1.38)	1.29	(1.07, 1.56)**
THC							
Q1	89	233,698	3.81	Ref.		Ref.	
Q2	87	221,785	3.92	1.03	(0.77, 1.39)	0.90	(0.74, 1.34)
Q3	248	211,402	11.7	3.10	(2.44, 3.95)***	3.08	(2.41, 3.94)***
Q4	263	197,729	13.3	3.51	(0.77, 1.39) (2.44, 3.95) ^{***} (2.76, 4.47) ^{***}	3.53	(2.76, 4.50)***
CH4							
Q1	90	229,472	3.92	Ref.		Ref.	
Q2	77	199,976	3.85	0.98	(0.72, 1.33)	0.92	(0.68, 1.25)
Q3	202	282,632	7.15	1.83	(1.43, 2.34) ^{****} (4.27, 6.82) ^{****}	1.76	(1.37, 2.26)***
Q4	318	152,533	20.9	5.39	(4.27, 6.82)***	4.95	(3.92, 6.26)***

aHR = adjusted hazard ratio of a multivariate analysis, after adjustment for age, sex, monthly income, and urbanization level, cHR = crude hazard ratio, CI = confidence interval, IR = incidence rate, (per 10,000 person-years), PY = person-years, Ref. = reference group.

that while individual characteristics of the urbanization level consistently associated with increased breast cancer risk, the relationship of NO and $PM_{2.5}$ between Q2, Q3 did not show clear correlation.

Previous study suggested that the high incidence rate of female breast cancer in the US was associated with high air pollutants emission regions (NO and CO), which was consistent with our results.^[7] However, 2 previous studies found no obvious association between long-term exposure to air pollution and breast cancer incidence,^[8,9] while 1 found traffic-related childhood exposure was not associated with an increase to breast cancer risk.^[10] Reding et al showed no significant associations between air pollution and breast cancer risk. On the other hand, they found NO2 was associated with an increased risk of ER+/PR+ breast cancer via their cohort study result.^[11] Garcia et al studied the correlation between an increase of breast cancer risk and several air pollutant compounds, including acrylamide, carbon tetrachloride, chloroprene, 4,4'-methylene bis (2-chloroaniline), propylene oxide, and vinyl chloride, but hazard ratios were not statistically significant.^[12] In addition, 1 reviewing study summarized the results for 8 case-control studies and 9 cohort studies and suggested little evidence to support a relationship between PM and breast cancer risk.^[14] There were also studies that supported our hypothesis. Goldberg et al reported that exposure to ambient NO2 and UFPs may increase the risk of incident postmenopausal breast cancer, especially women with positive estrogen and progesterone receptor status.^[13] The different outcomes and conclusions can be explained with climate, cultural differences, or population density, but more studies and analysis are needed in order to draw conclusive correlation between air pollution and breast cancer risk in Taiwan.

There are some limitations in this study. First, there are several confounders, such as demographic variables, lifestyle, diet habits, underlying disease, and genetic background that maybe to effect the incidence of breast cancer. Second, we did not analyze which type of breast cancer is highly associated with air pollutants because it is closely related to the prognosis of breast cancer. In this study, we tried to analyze the relationship between pollutants and the risk of breast individually. But in the real world, these pollutants do not exist individually, they always exist with other molecular compounds. In the future, we may consider collecting more information such as living habits, eating habits, past medical history, or genetic factors for further statistical analysis and using SPSS software to do multivariate analysis may make this research more rigorous and precise.

5. Conclusion

Although the risk factors that increase cancer are numerous and complex, they are often accompanied by more than 1 risk factor. According to research statistics, some air pollutants are closely related to the risk of breast cancer, we are not clear about the time of exposure to air pollution or the mechanism of carcinogenesis. With the progress of urbanization in Taiwan, the effect of environmental air pollution becomes more and more serious, and the incidence rate of cancer in Taiwan is also rising. Ambient air pollution may be an important factor in the increase of breast cancer incidence. Research into environmental chemical exposure helps prevent and promote public health benefits.

Author contributions

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