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# Association between fine particulate matter and oral cancer among Taiwanese men

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## ABSTRACT

The aim of this study was to investigate the association between fine particulate matter 2.5 (PM<sub>2.5</sub>) and oral cancer among Taiwanese men. Four linked data sources including the Taiwan Cancer Registry, Adult Preventive Medical Services Database, National Health Insurance Research Database, and Air Quality Monitoring Database were used. Concentrations of sulfur dioxide, carbon monoxide, ozone, NOx (nitrogen monoxide and nitrogen dioxide), coarse particulate matter (PM<sub>10-2.5</sub>) and PM<sub>2.5</sub> in 2009 were assessed in quartiles. A total of 482 659 men aged 40 years and above were included in the analysis. Logistic regression was used to examine the association between PM<sub>2.5</sub> and oral cancer diagnosed from 2012 to 2013. After adjusting for potential confounders, the ORs of oral cancer were 0.91 (95% CI 0.75 to 1.11) for 26.74 ≤ PM<sub>2.5</sub> < 32.37, 1.01 (95% CI 0.84 to 1.20) for 32.37 ≤ PM<sub>2.5</sub> < 40.37 µg/m<sup>3</sup> and 1.43 (95% CI 1.17 to 1.74) for PM<sub>2.5</sub> ≥ 40.37 µg/m<sup>3</sup> compared with PM<sub>2.5</sub> < 26.74 µg/m<sup>3</sup>. In this study, there was an increased risk of oral cancer among Taiwanese men who were exposed to higher concentrations of PM<sub>2.5</sub>.

## INTRODUCTION

Oral cancer is a serious and growing problem in many parts of the world.<sup>1</sup> In 2012, the global incidence and deaths resulting from oral cancer were estimated at 300 000 and 145 000, respectively.<sup>2</sup> A study reported an increase in the incidence of oral cancer among Taiwanese men.<sup>3</sup> Betel quid chewing, smoking, drinking, and human papillomavirus (HPV) have been associated with an increased risk of oral cancer.<sup>4-7</sup>

Exposure to heavy metals like arsenic, nickel, and chromium especially at higher concentrations, as well as emissions from petroleum and chemical plants have been shown to increase the risk of oral cancer.<sup>8-10</sup> Particulate matter less than or equal to 2.5 microns in diameter (PM<sub>2.5</sub>) is harmful to human health, contributing to respiratory and cardiovascular diseases.<sup>11-13</sup> This risk is partly because PM<sub>2.5</sub> can be inhaled into the lungs and bronchi, owing to its small size.<sup>14</sup> Long-term and short-term exposures to PM<sub>2.5</sub> have also been linked to increased hospital admissions and cardiovascular mortality.<sup>12 15</sup> However, few studies have been conducted to investigate the relationship between PM<sub>2.5</sub> and oral cancer. The aim of this

## Significance of this study

### What is already known about this subject?

- ▶ Exposure to particulate matter 2.5 (PM<sub>2.5</sub>) is associated with an increased risk of cardiovascular diseases and lung cancer.
- ▶ The oral cavity is one of the routes by which PM<sub>2.5</sub> gains access into the lungs and alveoli.
- ▶ The incidence of oral cancer among Taiwanese men is increasing.
- ▶ Some of the known risk factors for oral cancer are betel quid chewing, smoking, and drinking.

### What are the new findings?

- ▶ When compared with PM<sub>2.5</sub> < 26.74 µg/m<sup>3</sup>, PM<sub>2.5</sub> ≥ 40.37 µg/m<sup>3</sup> was significantly associated with an increased risk of oral cancer.
- ▶ Ozone (28.69 ≤ O<sub>3</sub> < 30.97 ppb) was significantly associated with an increased risk of oral cancer.
- ▶ Smoking and frequent betel quid chewing were significantly associated with an increased risk of oral cancer.

### How might these results change the focus of research or clinical practice?

- ▶ These results have increased knowledge regarding fine particulate pollution as a risk factor for oral cancer.
- ▶ This study indicates the need for further research to investigate the association between oral cancer and PM<sub>2.5</sub>, including lower exposure levels.

study was to investigate the association between PM<sub>2.5</sub> and oral cancer among Taiwanese men.

## MATERIALS AND METHODS

### Data sources

Four data sources which included the Taiwan Cancer Registry (TCR), Adult Preventive Medical Services Database (APMSD), National Health Insurance Research Database (NHIRD), and the Air Quality Monitoring Database (AQMD) were used in this study. The data sets were linked using personal identification

numbers of the participants which were protected for privacy reasons.

### Air pollutants

Air pollution data were retrieved from the AQMD which had been set up by the Environmental Protection Administration of the Executive Yuan. This database contains daily concentrations of pollutants collected from fully automated air quality monitoring stations. The data are available from 1998 through 2011. Nonetheless, data on PM<sub>2.5</sub> are available only from 2006. The air pollution data used in this study were collected from 66 air quality monitoring stations located in 64 different municipalities. Two municipalities had two monitoring stations each, while the other 62 had only one station each.

The annual average concentrations of sulfur dioxide (SO<sub>2</sub>), carbon monoxide (CO), ozone (O<sub>3</sub>), NOx (nitrogen monoxide (NO), nitrogen dioxide (NO<sub>2</sub>)), PM<sub>10</sub>, PM<sub>2.5</sub>, and PM<sub>10-2.5</sub> in 2009 were determined. The PM<sub>10-2.5</sub> concentration was determined by subtracting the concentration of PM<sub>2.5</sub> from that of PM<sub>10</sub>. The pollution levels in 2009 were selected, because this year marked the midpoint of the available PM<sub>2.5</sub> pollution data. To draw inferences regarding pre-2006 PM<sub>2.5</sub> exposure trends, we examined the correlation between PM<sub>10</sub> and PM<sub>2.5</sub> in the years that data on both pollutants were available.

### Study participants and measures

Since 1996, adults in Taiwan have enjoyed free preventive medical services. Valid electronic records of persons who use the services were established only in 2012. These records are maintained by the Health Promotion Administration of the Ministry of Health and Welfare.

The study participants included men aged 40 years and older who lived in the 64 different municipalities. Birthdate and gender were retrieved from the NHIRD. Age was determined by subtracting the birthdate found in the NHIRD from the enrollment date found in the 2012–2013 APMSD. Air pollution exposure was assigned based on the participants' household registration municipality in the NHIRD. Data on smoking and betel chewing were only available from 2012 and 2013. Hence, the study participants (both cases and controls) were restricted to those who attended the adult preventive medical services in 2012 or 2013 and provided information on smoking and betel chewing. This information was obtained by asking participants whether they have ever chewed betel quid or smoked cigarettes. Those whose response was 'no' were considered as never

chewers/smokers. For those whose response was 'yes', they were further asked how often they chewed betel quid or smoked cigarettes. Those whose response was 'almost every day' were defined as frequent chewers/smokers, while those whose response was 'sometimes or on social occasions' were defined as occasional chewers/smokers.

Oral cancer data diagnosed from 2012 to 2013 were collected from the TCR. The International Classification of Diseases Oncology, third version codes used included C00–C06, C09–C10, and C12–C14. Persons with incomplete personal information were excluded from the study. A total of 482 659 participants were included in the final analysis.

### Statistical analysis

Data were analyzed using SAS V.9.4. Pearson correlation was used to assess the correlation among air pollutants (CO, NOx, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>10-2.5</sub>, PM<sub>2.5</sub>, and SO<sub>2</sub>), while Spearman's correlation was used to assess the PM<sub>2.5</sub> correlation from 2006 to 2011. The collinearity of the air pollutants with PM<sub>2.5</sub> was determined and the variance influence factors >10 were deleted from the regression analysis. Logistic regression analysis was used to assess the relationship between PM<sub>2.5</sub> and oral cancer. Concentrations of air pollutants were stratified into quartiles. PM<sub>2.5</sub><26.74 µg/m<sup>3</sup> (Q1) was set as the reference. The ORs and 95% CI were determined and p<0.05 was considered statistically significant. Adjustments were made for PM<sub>10-2.5</sub>, SO<sub>2</sub>, O<sub>3</sub>, age, betel quid chewing, and smoking.

### RESULTS

The concentrations of the air pollutants are shown in table 1. For PM<sub>2.5</sub>, Q1, median and Q3 were 26.74, 32.37, and 40.37 µg/m<sup>3</sup>, respectively. The correlation among the air pollutants is shown in table 2. After checking for collinearity of the other air pollutants with PM<sub>2.5</sub>, the variance influence factors for CO and NOx were >10 (table not shown) and they were therefore deleted from the regression analysis. The descriptive data of the participants are shown in table 3. There were 1617 oral cancer cases (mean age=60.69±10.89 years) and 481 042 non-oral cancer cases (mean age=61.2±12.77 years). The mean ages of cases and non-cases were not significantly different.

Table 4 presents the association of oral cancer with PM<sub>2.5</sub> after multivariable adjustments. The ORs of oral cancer were 0.91 (95% CI 0.75 to 1.10) for 26.74≤PM<sub>2.5</sub><32.37, 1.00 (95% CI 0.84 to 1.20) for 32.37≤PM<sub>2.5</sub><40.37 µg/m<sup>3</sup> and 1.42 (95% CI 1.17 to 1.73) for PM<sub>2.5</sub>≥40.37 µg/m<sup>3</sup> after adjusting for PM<sub>10-2.5</sub>, SO<sub>2</sub>, O<sub>3</sub>,

**Table 1** Concentrations of air pollutants in Taiwan (2009)

Air pollutants	Unit	Mean	Q1	Median	Q3	Min.	Max.	Range
Carbon monoxide	ppm	0.47	0.36	0.43	0.53	0.17	1.29	1.12
Nitrogen oxides	ppb	22.06	15.17	20.42	26.55	3.64	80.71	77.07
Sulfur dioxide	ppb	4.11	2.96	3.61	4.43	1.82	11.43	9.60
Ozone	ppb	30.88	28.69	30.97	33.79	21.67	43.88	22.21
PM <sub>2.5</sub>	µg/m <sup>3</sup>	33.10	26.74	32.37	40.37	13.79	50.30	36.51
PM <sub>10</sub>	µg/m <sup>3</sup>	58.93	47.15	56.04	74.51	26.74	93.69	66.95
PM <sub>10-2.5†</sub>	µg/m <sup>3</sup>	25.87	18.97	23.82	32.68	11.57	49.70	38.13

PM, particulate matter.

†PM<sub>10</sub> minus PM<sub>2.5</sub>.

**Table 2** Correlation among air pollutants (CO, NOx, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, SO<sub>2</sub>, and PM<sub>10-2.5</sub>) using Spearman's analysis

Pollutants	CO	NOx	O <sub>3</sub>	PM <sub>10</sub>	PM <sub>2.5</sub>	SO <sub>2</sub>	PM <sub>10-2.5</sub>
CO	1.000	0.945*	-0.570*	0.040*	0.068*	0.196*	-0.004*
NOx	-	1.000	-0.547*	0.057*	0.105*	0.232*	-0.017*
O <sub>3</sub>	-	-	1.000	0.249*	0.141*	-0.083*	0.307*
PM <sub>10</sub>	-	-	-	1.000	0.892*	0.495*	0.843*
PM <sub>2.5</sub>	-	-	-	-	1.000	0.418*	0.508*
SO <sub>2</sub>	-	-	-	-	-	1.000	0.446*
PM <sub>10-2.5</sub> †	-	-	-	-	-	-	1.000

CO, carbon monoxide; NOx, nitrogen oxides; O<sub>3</sub>, ozone; PM, particulate matter; SO<sub>2</sub>, sulfur dioxide.

\*P < 0.05.

†PM<sub>10</sub> minus PM<sub>2.5</sub>.

age, and betel quid chewing (table 4, Model 1). After a further adjustment including smoking (table 4, Model 2), the effect of PM<sub>2.5</sub> on oral cancer risk did not change. In both models, PM<sub>10-2.5</sub> and SO<sub>2</sub> had no significant association with oral cancer regardless of their concentrations. However, O<sub>3</sub>, frequent betel quid chewing, occasional, as well as frequent smoking were significantly associated with oral cancer (table 4, Models 1 and 2). Spearman's analysis showed that PM<sub>2.5</sub> concentrations were highly correlated from 2006 to 2011 (table 5).

**Table 3** Descriptive data of the participants

Variable	Non-oral cancer cases (n=481 042)	Oral cancer cases (n=1617)	P values
PM <sub>2.5</sub>			
PM <sub>2.5</sub> <26.74	110 752 (23.02)	356 (22.02)	<0.0001*
26.74≤PM <sub>2.5</sub> <32.37	152 790 (31.76)	432 (26.72)	
32.37≤PM <sub>2.5</sub> <40.37	109 291 (22.72)	330 (20.41)	
PM <sub>2.5</sub> ≥40.37	108 209 (22.49)	499 (30.86)	
PM <sub>10-2.5</sub> †			
PM <sub>10-2.5</sub> <18.88	115 603 (24.03)	351 (21.71)	<0.0001*
18.88≤PM <sub>10-2.5</sub> <23.66	141 381 (29.39)	408 (25.23)	
23.66≤PM <sub>10-2.5</sub> <32.42	141 433 (29.4)	524 (32.41)	
PM <sub>10-2.5</sub> ≥32.42	82 625 (17.18)	334 (20.66)	
SO <sub>2</sub>			
SO <sub>2</sub> <2.96	74 999 (15.59)	269 (16.64)	<0.0001*
2.96≤SO <sub>2</sub> <3.61	138 189 (28.73)	380 (23.5)	
3.61≤SO <sub>2</sub> <4.43	134 173 (27.89)	497 (30.74)	
SO <sub>2</sub> ≥4.43	133 681 (27.79)	471 (29.13)	
O <sub>3</sub>			
O <sub>3</sub> <28.69	198 106 (41.18)	583 (36.05)	<0.0001*
28.69≤O <sub>3</sub> <30.97	146 672 (30.49)	567 (35.06)	
30.97≤O <sub>3</sub> <33.79	74 951 (15.58)	235 (14.53)	
O <sub>3</sub> ≥33.79	61 313 (12.75)	232 (14.35)	
Age (mean±SD)	61.2±12.77	60.69±10.89	0.0614
Betel chewing (%)			
Never	444 633 (92.43)	1456 (90.04)	<0.0001*
Occasional	22 631 (4.70)	79 (4.89)	
Frequent	13 778 (2.86)	82 (5.07)	
Smoking (%)			
Never	366 597 (76.21)	1131 (69.94)	<0.0001*
Occasional	84 315 (17.53)	341 (21.09)	
Frequent	30 130 (6.26)	145 (8.97)	

PM, particulate matter; SO<sub>2</sub>, sulfur dioxide.

\*P<0.05.

†PM<sub>10</sub> minus PM<sub>2.5</sub>.

## DISCUSSION

This study, with a large sample size, is the first to associate oral cancer with PM<sub>2.5</sub> using the aforementioned databases. After adjusting for the potential confounders, higher concentrations of PM<sub>2.5</sub> (≥40.37 µg/m<sup>3</sup>) were significantly associated with oral cancer in Taiwanese men. These findings add to the growing evidence on the adverse effects of PM<sub>2.5</sub> on human health.<sup>11-13</sup> The adverse health effects of PM<sub>2.5</sub> could be linked to its relatively smaller diameter, yet a larger surface area which may potentially facilitate the adsorption and condensation of higher concentration of toxic substances and other pollutants.<sup>16 17</sup> Some of the components of PM<sub>2.5</sub> including metals like lead, cadmium, arsenic, chromium, and nickel, as well as organic compounds like polycyclic aromatic hydrocarbons (PAHs), among others<sup>17-19</sup> are carcinogenic. For instance, exposure to heavy metal pollutants like arsenic, nickel, and chromium has been associated with oral cancer risk.<sup>8 9</sup> Moreover, exposure to asbestos and PAHs adsorbed on PM<sub>2.5</sub> is reported to have increased the risk of oral cancer.<sup>20</sup> The carcinogenicity of PM<sub>2.5</sub> has been linked to oxidative DNA damage, metabolism of organic compounds as well as inflammatory injury.<sup>16 18 21 22</sup> Undetoxified carcinogenic substances and unrepaired damaged DNA, as well as replication of damaged DNA can aggravate carcinogenicity.<sup>23 24</sup>

In the current study, O<sub>3</sub> was significantly associated with an increased risk of oral cancer. The deleterious effects of ozone on the respiratory tract are well known.<sup>25</sup> Nonetheless, ozone was inversely associated with oral cancer risk though not statistically significant.<sup>26</sup> Besides O<sub>3</sub>, smoking and betel quid chewing were associated with an increased risk of oral cancer in this study. Similar results have been previously reported.<sup>4 5</sup>

This study is not without limitations. First, the concentration of PM<sub>2.5</sub> that is delivered to mouth is not known. Second, there were no PM<sub>2.5</sub> exposure data before 2006. Nevertheless, those for PM<sub>10</sub> were available from 1998 to 2011. The concentrations of PM<sub>2.5</sub> from 2006 to 2011 were highly correlated. In addition, the concentrations of PM<sub>10</sub> from 1998 to 2011 were highly correlated. Furthermore, there were high correlations between PM<sub>2.5</sub> and PM<sub>10</sub> from 2006 to 2011. These indicate that the participants might have been previously exposed to PM<sub>2.5</sub> for quite some time. Therefore, we believe that high correlations could have also existed if there were historical data on PM<sub>2.5</sub> exposure before 2006. The concentrations of PM<sub>2.5</sub> and PM<sub>10</sub> (µg/m<sup>3</sup>)

**Table 4** Association of oral cancer with PM<sub>2.5</sub> in Taiwanese men

Variables	Model 1			Model 2		
	OR	95% CI	P values	OR	95% CI	P values
<b>PM<sub>2.5</sub></b>						
PM <sub>2.5</sub> <26.74	1	–	–	1	–	–
26.74≤PM <sub>2.5</sub> <32.37	0.91	0.75 to 1.10	0.332	0.91	0.75 to 1.11	0.342
32.37≤PM <sub>2.5</sub> <40.37	1.00	0.84 to 1.20	0.964	1.01	0.84 to 1.20	0.955
PM <sub>2.5</sub> ≥40.37	1.42	1.17 to 1.73	0.001*	1.43	1.17 to 1.74	<0.0001*
<b>PM<sub>10-2.5</sub>†</b>						
PM <sub>10-2.5</sub> <18.88	1	–	–	1	–	–
18.88≤PM <sub>10-2.5</sub> <23.66	0.95	0.80 to 1.11	0.511	0.95	0.81 to 1.12	0.517
23.66≤PM <sub>10-2.5</sub> <32.42	1.06	0.91 to 1.25	0.451	1.07	0.91 to 1.25	0.447
PM <sub>10-2.5</sub> ≥32.42	1.10	0.89 to 1.37	0.367	1.10	0.89 to 1.36	0.373
<b>SO<sub>2</sub></b>						
SO <sub>2</sub> <2.96	1	–	–	1	–	–
2.96≤SO <sub>2</sub> <3.61	0.82	0.67 to 1.01	0.064	0.83	0.67 to 1.02	0.070
3.61≤SO <sub>2</sub> <4.43	0.92	0.75 to 1.14	0.454	0.93	0.75 to 1.14	0.464
SO <sub>2</sub> ≥4.43	0.86	0.70 to 1.07	0.171	0.86	0.70 to 1.07	0.174
<b>O<sub>3</sub></b>						
O <sub>3</sub> <28.69	1	–	–	1	–	–
28.69≤O <sub>3</sub> <30.97	1.26	1.12 to 1.42	<0.0001*	1.26	1.11 to 1.42	<0.0001*
30.97≤O <sub>3</sub> <33.79	0.94	0.79 to 1.11	0.472	0.94	0.80 to 1.11	0.480
O <sub>3</sub> ≥33.79	1.00	0.84 to 1.19	0.975	1.00	0.84 to 1.19	0.984
Age	1.00	0.99 to 1.00	0.286	1.00	0.10 to 1.00	0.769
<b>Betel chewing</b>						
Never	1	–	–	1	–	–
Occasional	1.01	0.81 to 1.28	0.905	0.88	0.70 to 1.12	0.306
Frequent	1.74	1.39 to 2.18	<0.0001*	1.42	1.11 to 1.83	0.006*
Test for trend	<0.0001*			0.0297*		
<b>Smoking</b>						
Never	–	–	–	1	–	–
Occasional	–	–	–	1.29	1.14 to 1.47	<0.0001*
Frequent	–	–	–	1.40	1.15 to 1.70	0.001*

Model 1: adjusted for PM<sub>10-2.5</sub>, SO<sub>2</sub>, O<sub>3</sub>, age, and betel quid chewing.

Model 2: adjusted for PM<sub>10-2.5</sub>, SO<sub>2</sub>, O<sub>3</sub>, age, betel quid chewing, and smoking.

\*P<0.05.

†PM<sub>10</sub> minus PM<sub>2.5</sub>.

O<sub>3</sub>, ozone; PM, particulate matter; SO<sub>2</sub>, sulfur dioxide.

**Table 5** Correlation of particulate matter 2.5 (PM<sub>2.5</sub>) concentrations from 2006 to 2011 using Spearman's analysis

Year	2006	2007	2008	2009	2010	2011
2006	1.00	0.97*	0.96*	0.96*	0.95*	0.94*
2007	–	1.00	0.98*	0.97*	0.97*	0.95*
2008	–	–	1.00	0.98*	0.96*	0.94*
2009	–	–	–	1.00	0.98*	0.96*
2010	–	–	–	–	1.00	0.96*
2011	–	–	–	–	–	1.00

\*P<0.05.

between 2006 and 2011 are shown in the online Supplementary tables 1 and 2, respectively.

## CONCLUSION

In conclusion, higher concentrations of PM<sub>2.5</sub> may be associated with increased risk of oral cancer in Taiwanese men. The mechanism through which this occurs is not clearly understood, hence further investigations are required.

**Contributors** Y-HC, S-WK, P-CK, S-JL and Y-PL designed the study and analyzed the data. Y-HC and DMT reviewed the manuscript. All the authors interpreted the data, drafted the manuscript and approved the final version of the manuscript.

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**Patient consent** Not required.

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