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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 ($PM_{2.5}$) 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 ($PM_{10-2.5}$) and $PM_{2.5}$ 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 $PM_{2.5}$ 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 $26.74 \leq PM_{2.5} < 32.37$, 1.01 (95% CI 0.84 to 1.20) for $32.37 \leq PM_{2.5} < 40.37\ \mu g/m^3$ and 1.43 (95% CI 1.17 to 1.74) for $PM_{2.5} \geq 40.37\ \mu g/m^3$ compared with $PM_{2.5} < 26.74\ \mu g/m^3$. In this study, there was an increased risk of oral cancer among Taiwanese men who were exposed to higher concentrations of $PM_{2.5}$.

Significance of this study

What is already known about this subject?

- Exposure to particulate matter 2.5 ($PM_{2.5}$) is associated with an increased risk of cardiovascular diseases and lung cancer.
- The oral cavity is one of the routes by which $PM_{2.5}$ 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 $PM_{2.5} < 26.74\ \mu g/m^3$, $PM_{2.5} \geq 40.37\ \mu g/m^3$ was significantly associated with an increased risk of oral cancer.
- Ozone ($28.69 \leq O_3 < 30.97$ 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 $PM_{2.5}$, including lower exposure levels.

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

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.[8–10] Particulate matter less than or equal to 2.5 microns in diameter ($PM_{2.5}$) is harmful to human health, contributing to respiratory and cardiovascular diseases.[11–13] This risk is partly because $PM_{2.5}$ can be inhaled into the lungs and bronchi, owing to its small size.[14] Long-term and short-term exposures to $PM_{2.5}$ have also been linked to increased hospital admissions and cardiovascular mortality.[12 15] However, few studies have been conducted to investigate the relationship between $PM_{2.5}$ and oral cancer. The aim of this study was to investigate the association between $PM_{2.5}$ 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

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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 $PM_{2.5}$ 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_2), carbon monoxide (CO), ozone (O_3), NOx (nitrogen monoxide (NO), nitrogen dioxide (NO_2)), PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in 2009 were determined. The $PM_{10-2.5}$ concentration was determined by subtracting the concentration of $PM_{2.5}$ from that of PM_{10}. The pollution levels in 2009 were selected, because this year marked the midpoint of the available $PM_{2.5}$ pollution data. To draw inferences regarding pre-2006 $PM_{2.5}$ exposure trends, we examined the correlation between PM_{10} and $PM_{2.5}$ 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_3, PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, and SO_2), while Spearman's correlation was used to assess the $PM_{2.5}$ correlation from 2006 to 2011. The collinearity of the air pollutants with $PM_{2.5}$ was determined and the variance influence factors >10 were deleted from the regression analysis. Logistic regression analysis was used to assess the relationship between $PM_{2.5}$ and oral cancer. Concentrations of air pollutants were stratified into quartiles. $PM_{2.5}<26.74\,\mu g/m^3$ (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 $PM_{10-2.5}$, SO_2, O_3, age, betel quid chewing, and smoking.

RESULTS

The concentrations of the air pollutants are shown in table 1. For $PM_{2.5}$, Q1, median and Q3 were 26.74, 32.37, and 40.37 $\mu g/m^3$, respectively. The correlation among the air pollutants is shown in table 2. After checking for collinearity of the other air pollutants with $PM_{2.5}$, 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 $PM_{2.5}$ after multivariable adjustments. The ORs of oral cancer were 0.91 (95% CI 0.75 to 1.10) for $26.74\le PM_{2.5}<32.37$, 1.00 (95% CI 0.84 to 1.20) for $32.37\le PM_{2.5}<40.37\,\mu g/m^3$ and 1.42 (95% CI 1.17 to 1.73) for $PM_{2.5}\ge 40.37\,\mu g/m^3$ after adjusting for $PM_{10-2.5}$, SO_2, O_3,

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
$PM_{2.5}$	$\mu g/m^3$	33.10	26.74	32.37	40.37	13.79	50.30	36.51
PM_{10}	$\mu g/m^3$	58.93	47.15	56.04	74.51	26.74	93.69	66.95
$PM_{10-2.5}$†	$\mu g/m^3$	25.87	18.97	23.82	32.68	11.57	49.70	38.13

PM, particulate matter.
†PM_{10} minus $PM_{2.5}$.

Table 2 Correlation among air pollutants (CO, NOx, O3, PM10, PM2.5, SO2, and PM10–2.5) using Spearman's analysis

Pollutants	CO	NOx	O_3	PM_{10}	$PM_{2.5}$	SO_2	$PM_{10-2.5}$
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_3	–	–	1.000	0.249*	0.141*	−0.083*	0.307*
PM_{10}	–	–	–	1.000	0.892*	0.495*	0.843*
$PM_{2.5}$	–	–	–	–	1.000	0.418*	0.508*
SO_2	–	–	–	–	–	1.000	0.446*
$PM_{10-2.5}$†	–	–	–	–	–	–	1.000

CO, carbon monoxide; NOx, nitrogen oxides; O_3, ozone; PM, particulate matter; SO_2, sulfur dioxide.
*$P < 0.05$.
†PM_{10}minus $PM_{2.5}$.

age, and betel quid chewing (table 4, Model 1). After a further adjustment including smoking (table 4, Model 2), the effect of $PM_{2.5}$ on oral cancer risk did not change. In both models, $PM_{10-2.5}$ and SO_2 had no significant association with oral cancer regardless of their concentrations. However, O_3, 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 $PM_{2.5}$ 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
$PM_{2.5}$			
$PM_{2.5}$<26.74	110 752 (23.02)	356 (22.02)	<0.0001*
26.74≤$PM_{2.5}$<32.37	152 790 (31.76)	432 (26.72)	
32.37≤$PM_{2.5}$<40.37	109 291 (22.72)	330 (20.41)	
$PM_{2.5}$≥40.37	108 209 (22.49)	499 (30.86)	
$PM_{10-2.5}$†			
$PM_{10-2.5}$<18.88	115 603 (24.03)	351 (21.71)	<0.0001*
18.88≤$PM_{10-2.5}$<23.66	141 381 (29.39)	408 (25.23)	
23.66≤$PM_{10-2.5}$<32.42	141 433 (29.4)	524 (32.41)	
PM_{10-25}≥32.42	82 625 (17.18)	334 (20.66)	
SO_2			
SO_2<2.96	74 999 (15.59)	269 (16.64)	<0.0001*
2.96≤SO_2<3.61	138 189 (28.73)	380 (23.5)	
3.61≤SO_2<4.43	134 173 (27.89)	497 (30.74)	
SO_2≥4.43	133 681 (27.79)	471 (29.13)	
O_3			
O_3<28.69	198 106 (41.18)	583 (36.05)	<0.0001*
28.69≤O_3<30.97	146 672 (30.49)	567 (35.06)	
30.97≤ O_3<33.79	74 951 (15.58)	235 (14.53)	
O_3≥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_2, sulfur dioxide.
*P<0.05.
†PM_{10}minus $PM_{2.5}$.

DISCUSSION

This study, with a large sample size, is the first to associate oral cancer with $PM_{2.5}$ using the aforementioned databases. After adjusting for the potential confounders, higher concentrations of $PM_{2.5}$ (≥40.37 µg/m^3) were significantly associated with oral cancer in Taiwanese men. These findings add to the growing evidence on the adverse effects of $PM_{2.5}$ on human health.[11–13] The adverse health effects of $PM_{2.5}$ 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.[16 17] Some of the components of $PM_{2.5}$ including metals like lead, cadmium, arsenic, chromium, and nickel, as well as organic compounds like polycyclic aromatic hydrocarbons (PAHs), among others[17–19] are carcinogenic. For instance, exposure to heavy metal pollutants like arsenic, nickel, and chromium has been associated with oral cancer risk.[8 9] Moreover, exposure to asbestos and PAHs adsorbed on $PM_{2.5}$ is reported to have increased the risk of oral cancer.[20] The carcinogenicity of $PM_{2.5}$ has been linked to oxidative DNA damage, metabolism of organic compounds as well as inflammatory injury.[16 18 21 22] Undetoxified carcinogenic substances and unrepaired damaged DNA, as well as replication of damaged DNA can aggravate carcinogenicity.[23 24]

In the current study, O_3 was significantly associated with an increased risk of oral cancer. The deleterious effects of ozone on the respiratory tract are well known.[25] Nonetheless, ozone was inversely associated with oral cancer risk though not statistically significant.[26] Besides O_3, smoking and betel quid chewing were associated with an increased risk of oral cancer in this study. Similar results have been previously reported.[4 5]

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

Table 4 Association of oral cancer with PM2.5 in Taiwanese men

	Model 1			Model 2		
Variables	OR	95% CI	P values	OR	95% CI	P values
$PM_{2.5}$						
$PM_{2.5}$<26.74	1	–	–	1	–	–
26.74≤$PM_{2.5}$<32.37	0.91	0.75 to 1.10	0.332	0.91	0.75 to 1.11	0.342
32.37≤$PM_{2.5}$<40.37	1.00	0.84 to 1.20	0.964	1.01	0.84 to 1.20	0.955
$PM_{2.5}$≥40.37	1.42	1.17 to 1.73	0.001*	1.43	1.17 to 1.74	<0.0001*
$PM_{10-2.5}$†						
$PM_{10-2.5}$<18.88	1	–	–	1	–	–
18.88≤$PM_{10-2.5}$<23.66	0.95	0.80 to 1.11	0.511	0.95	0.81 to 1.12	0.517
23.66≤$PM_{10-2.5}$<32.42	1.06	0.91 to 1.25	0.451	1.07	0.91 to 1.25	0.447
$PM_{10-2.5}$≥32.42	1.10	0.89 to 1.37	0.367	1.10	0.89 to 1.36	0.373
SO_2						
SO_2<2.96	1	–	–	1	–	–
2.96≤SO_2<3.61	0.82	0.67 to 1.01	0.064	0.83	0.67 to 1.02	0.070
3.61≤SO_2<4.43	0.92	0.75 to 1.14	0.454	0.93	0.75 to 1.14	0.464
SO_2≥4.43	0.86	0.70 to 1.07	0.171	0.86	0.70 to 1.07	0.174
O_3						
O_3<28.69	1	–	–	1	–	–
28.69≤O_3<30.97	1.26	1.12 to 1.42	<0.0001*	1.26	1.11 to 1.42	<0.0001*
30.97≤O_3<33.79	0.94	0.79 to 1.11	0.472	0.94	0.80 to 1.11	0.480
O_3≥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
Betel chewing						
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*		
Smoking						
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 $PM_{10-2.5}$, SO_2, O_3, age, and betel quid chewing.
Model 2: adjusted for $PM_{10-2.5}$, SO_2, O_3, age, betel quid chewing, and smoking.
*P<0.05.
†PM_{10} minus $PM_{2.5}$.
O_3, ozone; PM, particulate matter; SO_2, sulfur dioxide.

Table 5 Correlation of particulate matter 2.5 (PM2.5) 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 $PM_{2.5}$ 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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Air pollution may be linked to heightened mouth cancer risk

High levels of fine particulate matter and to lesser extent, ozone, may be key

High levels of air pollutants, especially fine particulate matter ($PM_{2.5}$) and to a lesser extent, ozone, may be linked to a heightened risk of developing mouth cancer, suggests the first study of its kind, published online in the ***Journal of Investigative Medicine.***

The number of new cases, and deaths from, mouth cancer is increasing in many parts of the world. Known risk factors include smoking, drinking, human papilloma virus, and in parts of South East Asia, the chewing of betel quid ('paan'), a mix of ingredients wrapped in betel leaf.

Exposure to heavy metals and emissions from petrochemical plants are also thought to be implicated in the development of the disease, while air pollution, especially $PM_{2.5}$, is known to be harmful to respiratory and cardiovascular health.

To find out if air pollutants might have a role in the development of mouth cancer, the researchers mined national cancer, health, insurance, and air quality databases.

They drew on average levels of air pollutants (sulphur dioxide, carbon monoxide, ozone, nitrogen monoxide, nitrogen dioxide, and varying sizes of fine particulate matter), measured in 2009 at 66 air quality monitoring stations across Taiwan.

In 2012-13, they checked the health records of 482,659 men aged 40 and older who had attended preventive health services, and had provided information on smoking/betel quid chewing.

Diagnoses of mouth cancer were then linked to local area readings for air pollutants taken in 2009.

In 2012-13, 1617 cases of mouth cancer were diagnosed among the men. Unsurprisingly, smoking and frequent betel quid chewing were significantly associated with heightened risk of a diagnosis.

But so too were high levels of $PM_{2.5.}$ After taking account of potentially influential factors, increasing levels of $PM_{2.5}$ were associated with an increasing risk of mouth cancer.

When compared with levels below 26.74 ug/m^3, those above 40.37 ug/ m^3 were associated with a 43 per cent heightened risk of a mouth cancer diagnosis.

A significant association was also observed for ozone levels below 28.69-30.97 parts per billion.

This is an observational study, and as such, can't establish cause. And there are certain caveats to consider, say the researchers. These include the lack of data on how much $PM_{2.5}$ enters the mouth, or on long term exposure to this pollutant.

Nor is it clear how air pollutants might contribute to mouth cancer, they acknowledge, and further research would be needed to delve further into this.

But some of the components of $PM_{2.5}$ include heavy metals, as well as compounds such as polycyclic aromatic hydrocarbons–known cancer causing agents–they say.

And the smaller diameter, but larger surface area, of $PM_{2.5}$ means that it can be relatively easily absorbed while at the same time potentially wreaking greater havoc on the body, they suggest.

"This study, with a large sample size, is the first to associate oral cancer with $PM_{2.5...}$These findings add to the growing evidence on the adverse effects of $PM_{2.5}$ on human health," they conclude.