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Association of Ambient Fine Particulate Matter ($PM_{2.5}$) with Elevated Fecal Hemoglobin Concentration and Colorectal Carcinogenesis: A Population-Based Retrospective Cohort Study

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Abstract

The roles of ambient fine particulate matter ($PM_{2.5}$) in the prevention of colorectal cancer (CRC) have been scarcely highlighted as there is short of empirical evidence regarding the influences of $PM_{2.5}$ on multistep carcinogenic processes of CRC. A retrospective cohort design with multistate outcomes was envisaged by linking monthly average $PM_{2.5}$ concentrations at 22 city/county level with large-scale cohorts of cancer-screened population to study the influences of $PM_{2.5}$ on short-term inflammatory process and multistep carcinogenic processes of CRC. Our study included a nationwide CRC screening cohort of 4,628,995 aged 50–69 years who attended first screen between 2004 and 2009 and continued periodical screens until 2016. We aimed to illustrate the carcinogenesis of $PM_{2.5}$ related to CRC by applying both hierarchical logistical and multistate Markov regression models to estimate the effects of air pollution on fecal immunochemical test (FIT) positive (a proxy of inflammatory marker) and pre-clinical and clinical states of CRC in the nationwide cohort. We found a significant association of high $PM_{2.5}$ exposure and FIT-positive by an increased risk of 11% [95% confidence interval (CI), 10–12]. $PM_{2.5}$ enhanced the risk of being preclinical state by 14% (95% CI, 10–18) and that of subsequent progression from pre-clinical to clinical state by 21% (95% CI, 14–28). Furthermore, the elevated risks for CRC carcinogenesis were significantly higher for people living in high $PM_{2.5}$ pollution areas in terms of yearly averages and the number days above 35 $\mu g/m^3$ than those living in low $PM_{2.5}$ pollution areas. We concluded that both short-term and long-term $PM_{2.5}$ exposure were associated with multistep progression of CRC, which were useful to design precision primary and secondary prevention strategies of CRC for people who are exposed to high $PM_{2.5}$ pollution.

Keywords

fine particulate matter, fecal hemoglobin concentration, colorectal cancer, carcinogenesis, cohort study

Introduction

Air pollution, especially fine particulate matter ($PM_{2.5}$), is a global problem with a significant impact on human health. In 2013, the International Agency for Research on Cancer (IARC) classified ambient air pollution as a group 1 carcinogen in humans, based on sufficient evidence from both humans and experimental animals.[1] Previous studies have shown that the effects of $PM_{2.5}$ exposure in outdoor pollution are mostly related to cancer mortality in multiple sites, including lung, colon, breast, liver, kidney, and genital cancers.[2–8] However, the association between $PM_{2.5}$ exposure and cancer incidence and carcinogenesis remains unclear for these cancers.

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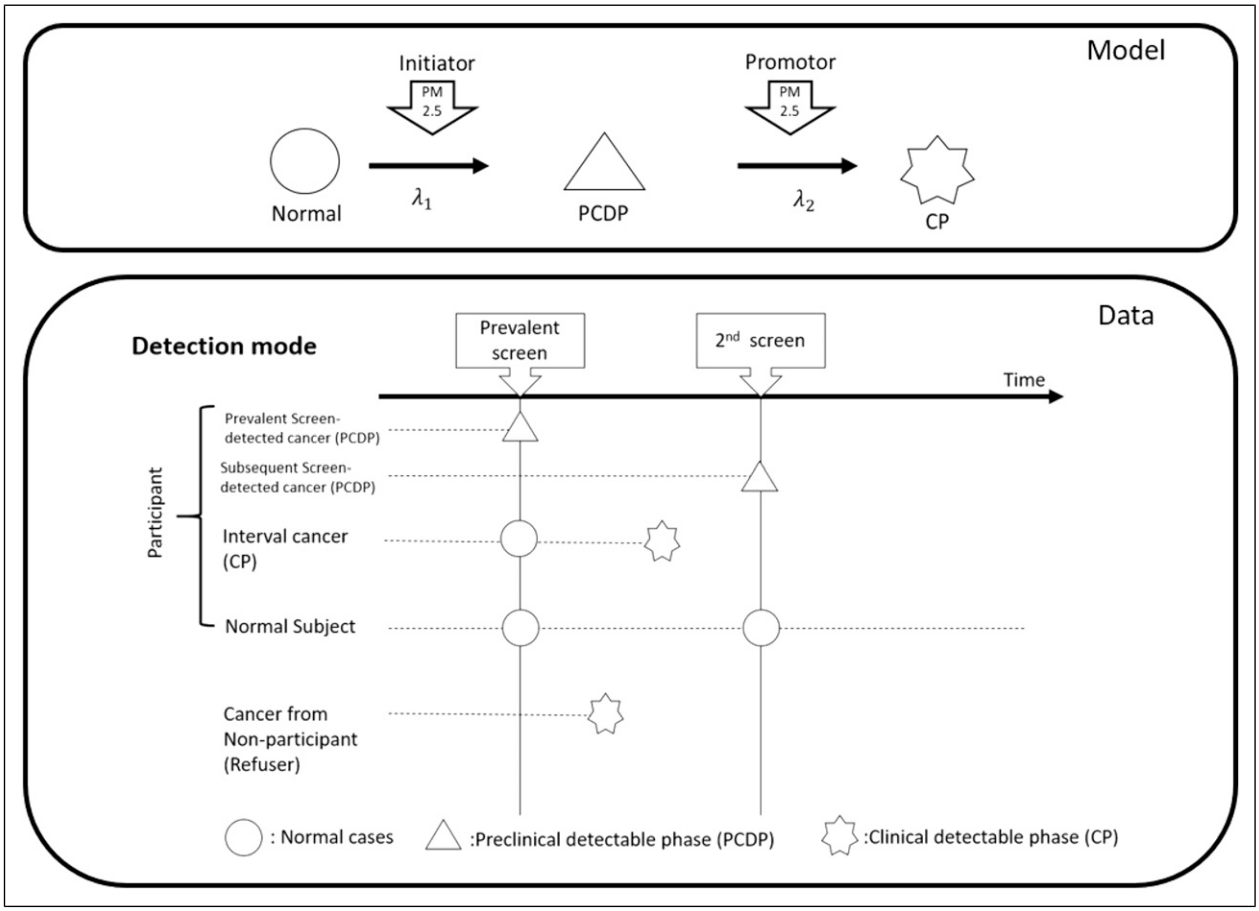

Figure 1. The multiple effects of $PM_{2.5}$ on three-state carcinogenesis model of CRC (Normal→ PCDP→ CP) captured by empirical data on various detection modes obtained from population-based screening for CRC. Note that while various detection modes were used for estimating incidence rate and progression rate, normal and screen-detected (prevalent and subsequent) CRCs captured information on the occurrence of PCDP, whereas interval cancer and cancers from non-participant provides information on subsequent progression to CP. A hierarchical Markov exponential regression model was then used to estimate the parameters of interest.

Research on colorectal cancer (CRC) by long-term exposure to $PM_{2.5}$ may shed light on this important scientific issue for the following reasons. First, ambient PM contains various carcinogenic components involved in DNA damage, such as polycyclic aromatic hydrocarbons (PAHs)[9] and reactive oxygen species (ROS) induced by transition metals.[10] In addition, long-term $PM_{2.5}$ has been found to cause excessive and continuous inflammation.[11,12] Chronic inflammation may initiate and promote tumorigenesis through the production of ROS and pro-inflammatory cytokines.[13] A study on the human colon adenocarcinoma cell line, Caco-2, showed that $PM_{2.5}$ exposure induced ROS and cell death in colonic epithelial cells in a dose-dependent manner.[14] Circulating inflammatory cytokines have been found to be involved in the development of colorectal adenomas, an asymptomatic precursor of CRC.[15] Inflammation is also known to affect carcinogenesis through the inactivation of tumor-suppressor genes, oncogene mutations, and production of angiogenic factors to promote cancer cell survival.[4,16–19] Thus, $PM_{2.5}$ may lead to colorectal tumorigenesis due to carcinogenic components and chronic inflammation. Second, CRC poses a great threat to public health in terms of incidence and leading causes of death among all cancers in Taiwan and in the world.[20,21] Previous studies have revealed that long-term exposure to $PM_{2.5}$ is associated with an increased risk for CRC mortality by 4–29%.[2,3,22–24] Among these, the study in the United States found a significantly higher risk (29%) for CRC mortality in every 10 $\mu g/m^3$ increase of $PM_{2.5}$ after considering age, sex, race/ethnicity, income, education, marital status, body mass index, smoking, urban/rural, census regions, and survey year.[24] Third, CRC prevention via chemoprevention, life-style modification, and early detection is more effective and cost-effective compared with other cancers.[25–27] In addition to hereditary factors, environmental risk factors are also found to be associated with the development of colorectal cancer.[28–30] $PM_{2.5}$ is an important environmental pollutant; therefore, it may play a role in CRC carcinogenesis in individuals living in polluted areas, including initiating the inflammatory process before the potential malignant transformation to CRC and the carcinogenesis processes of CRC, as shown in Figure 1. It is also possible that $PM_{2.5}$ exposure may affect the outcomes of

fecal immunochemical test (FIT), a widespread tool in screening programs to measure fecal hemoglobin concentration (f-HbC) for early-stage CRC detection. It is worthwhile to know whether $PM_{2.5}$ exposure affects all three stages of CRC carcinogenesis, that is, an elevated risk for malignant transformation of the alimentary lining cells (normal to pre-clinical detectable phase abbreviated as PCDP hereafter), the accelerated progression from asymptomatic lesions (PCDP), and symptomatic disease (clinical phase abbreviated as CP hereafter) with the presence of symptoms.

Using a population-based, human study in a large-scale, FIT-screening cohort with nationwide exposure data available in Taiwan, we aimed to quantify the effect of $PM_{2.5}$ on a possible inflammatory response from colorectal lining cells by using the proxy indicator of elevated f-HbC. We further attempted to characterize the effect of $PM_{2.5}$ on the occurrence of PCDP CRC and subsequent progression from PCDP to CP through the three-state carcinogenesis model of CRC.

Methods

Study Participants

This study was a retrospective, cohort study that included screening and disease status data from the nationwide CRC screening program in Taiwan. The data were used as a discovery phase to study the effects of $PM_{2.5}$ exposure on the inflammatory process and the three-state carcinogenesis model of CRC. A total of 4,628,995 individuals, aged 50–69 years, attended the first screening between 2004 and 2009 and also the continuation of subsequent screening with the confirmation and diagnosis of CRC until 2016, with 10 years of follow-up. Written informed consent was obtained from all of the participants before enrolling in the study. Data on age at screening, sex, family history of CRC, and residential area (city/county) were retrieved. The details of the program have been described elsewhere.[31] Only those free of colorectal cancer were eligible to participate in the screening program. The FIT-positive cases were referred for confirmatory diagnosis mainly using colonoscopy. Attendees with negative FIT results were invited to participate in the next screen for 2 years. The overall coverage of the eligible population from 2004 to 2016 reached almost 60% under the original goal of the gradual expansion of the covered population. During this period, 24,351 CRC cases were identified, including 13,141 screen-detected cancers and 11,210 interval cancers.

Colorectal Carcinogenesis Outcomes

In this study, FIT-positive results (f-HbC > 100 ng Hb/mL) obtained from the screening program were considered as a proxy indicator for the possible inflammatory response in colorectal lining cells, based on previous evidence that f-HbC was a quantitative, surrogate biomarker for early prediction of colorectal neoplasia. For long-term colorectal carcinogenesis, the diagnosis of CRC either during (screen-detected) or between screening (interval cancer), representing asymptomatic (PCDP) and symptomatic (CP) CRCs, was ascertained either from the periodic process of the CRC screening program or cancer registry.

Specifically, four detection modes are denoted in the three-state Markov model delineating the CRC carcinogenesis process (Figure 1). The normal subjects and screen-detected CRC are used to capture information on the rate of entering the PCDP; interval cancers and cancers from non-participants are used to capture additional information on the transition rate from PCDP to CP (Figure 1).

Fecal Hemoglobin Concentration Measurement

For nationwide colorectal cancer screening, f-HbC was measured by both OC-SENSOR (Eiken Chemical Company, Tokyo, Japan) and HM-Jack (Kyowa Medex Co. Ltd., Tokyo, Japan), both of which are ubiquitous methods for quantitative measurement of f-Hb. The quantitative values of f-HbC results were recorded in ng Hb/mL (5 ng Hb/mL = 1 μg Hb/g feces). The cut-off for identifying individuals as FIT-positive requiring further colonoscopy examination was 100 ng Hb/mL.[32]

Exposure Assessment of Fine Particulate Matter

Air pollution, especially fine particulate matter, has been a severe problem in Taiwan due to the rapid industrialization in the 1970s. Air monitoring stations have been installed since 1993 to ensure that air pollutant levels meet ambient air quality standards. Despite numerous efforts, the annual average level of $PM_{2.5}$ in Taiwan has not yet met the air quality standard (15 $\mu g/m^{3)}$. However, in the recent decades, a decreasing trend in $PM_{2.5}$ has been observed.

Air quality data measured by Taiwan's Environmental Protection Administration (TEPA) were used to estimate $PM_{2.5}$ for the study subjects of the nationwide screening program. TEPA established Taiwan Air Quality Monitoring Network (AQMN) including 73 air monitoring stations in 22 cities/counties to monitor nationwide air quality since 1993.[33] We obtained daily $PM_{2.5}$ concentrations at all monitoring stations in air quality management areas from 2004 to 2016 and classified them by city or county. Monthly averaged $PM_{2.5}$ concentrations over all monitoring sites in each city/county were aggregated in every one of the 22 cities/counties. These spatially averaged $PM_{2.5}$ data were chronologically matched by the study subjects' FIT measurements, clinical diagnoses, or screening dates to estimate their $PM_{2.5}$ exposures. We used the third quartile of the monthly average $PM_{2.5}$ Concentration of 22 cities/counties over 12 years (35 $\mu g/m^3$, Figure 2) to classify our study area

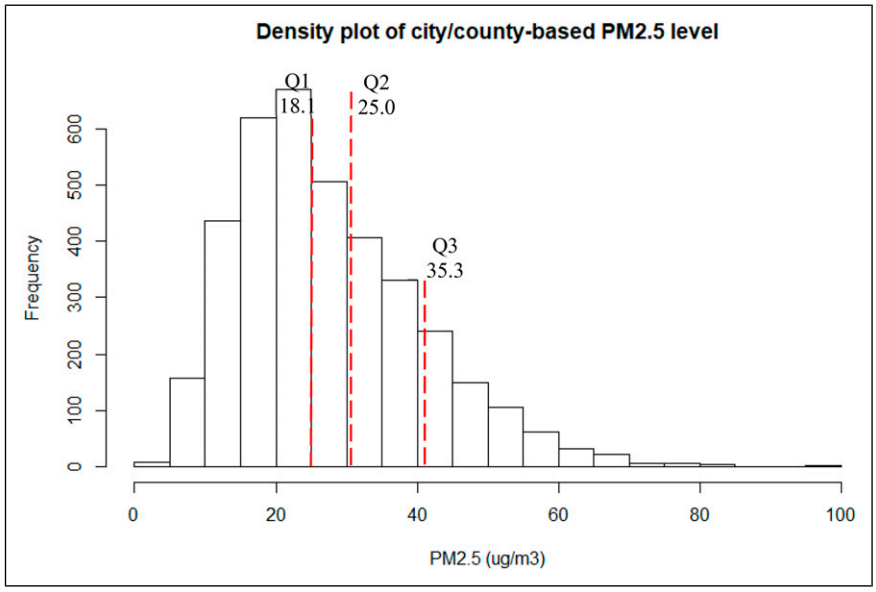

Figure 2. Density plot of 22 city/county-based $PM_{2.5}$ level from 2004 to 2016.

as high (>35 μg/m^3) and low (≦35 μg/m^3) $PM_{2.5}$ exposure. According to the air quality standards of TEPA, 35 μg/m^3 is also the cut-off point for regulating 24-h running mean concentration. $PM_{2.5}$ exposures included monthly and yearly averaged concentrations, as well as the number of days above 35 μg/m^3 in one month.

Statistical Analysis

Kruskal–Wallis tests were used to compare the $PM_{2.5}$ levels between the four detection modes. A multilevel logistic random-effect regression model was applied to investigate the association between $PM_{2.5}$ exposure at the city/county level and individuals with FIT-positive results, as adjusted for age (≥60 vs < 60 years), sex (male vs female), and family history of CRC (yes vs no), using the data from a nationwide CRC screening program.

To evaluate the role of $PM_{2.5}$ exposure on the evolution of colorectal neoplasm through the states of PCDP and CP stemming from the nationwide CRC screening program, a three-state Markov model was applied.[34,35] Two transition rates, the occurrence of PCDP from the state of free of CRC (λ_1), and the progression of PCDP to CP (λ_2), were used to depict this process. The effects of personal attributes (age, sex, and family history of CRC) at the individual level and $PM_{2.5}$ exposure at the regional level on this three-state process of CRC evolution were assessed using a series of hierarchical Markov regression models.[34,35] An exponential hazards regression form was thus used to associate $PM_{2.5}$ at the city/county level with the incidence of PCDP and the transition from PCDP to CP, making allowance for the individual factors of age (≥60 vs < 60 years), sex (male vs female), and family history of CRC (FH, yes vs no).

Specifically, the incidence rate of PCDP for *the* i_{th} subject in region j (λ_{1ij}) is expressed as follows

$$\begin{aligned}
&\lambda_{1ij}(t) = \lambda_{01j}(t) \times \exp[\beta_{11} \times Age_i + \beta_{12} \times Sex_i + \beta_{13} \times FH_i + r_{1i}] \\
&\lambda_{01j}(t) = \lambda_{010} \times \exp[\beta_{14} \times PM_{2.5}\ level_j + r_{1j}] \\
&r_{1i} \sim N(0, \sigma_1^2) \\
&r_{1j} \sim N\left(0, \sigma_{\lambda_{01}}^2\right)
\end{aligned} \tag{1}$$

where the effects of personal attributes for the i_{th} subject on the occurrence of PCDP of CRC were captured by the coefficients, β_{11}, β_{12}, and β_{13}, of the individual-level regression model. Regarding the impact of $PM_{2.5}$ exposure on the risk of PCDP for the j_{th} region, the effect was captured by the β_{14} coefficient of the regional level regression model. Following this rationale, the hierarchical regression model for the rate of transition from PCDP to CP (λ_{2ij}) is written as follows

$$\begin{aligned}
&\lambda_{2ij}(t) = \lambda_{02j}(t) \times \exp[\beta_{21} \times Age_i + \beta_{22} \times Sex_i + \beta_{23} \times FH_i + r_{2i}] \\
&\lambda_{02j}(t) = \lambda_{020} \times \exp[\beta_{24} \times PM_{2.5}\ level_j + r_{2j}] \\
&r_{2i} \sim N(0, \sigma_2^2) \\
&r_{2j} \sim N\left(0, \sigma_{\lambda_{02}}^2\right)
\end{aligned} \tag{2}$$

where the β_{24} regression coefficient represents the impact of $PM_{2.5}$ exposure on the progression from PCDP to CP CRC, considering individual characteristics. Thus, the exponent of the regression coefficients represents the ratio of hazards for the occurrence of PCDP (β_{11}, β_{12}, β_{13}, and β_{14}) and that of the progression from PCDP to CP (β_{21}, β_{22}, β_{23}, and β_{24}). All statistical analyses were performed using the SAS software (version 9.4).

Table 1. Demographic Characteristics and $PM_{2.5}$ Exposure Levels of Study Population by Detection Modes of Colorectal Cancer.

	Normal (n = 5,546,794)	Screen-detected cancer (n = 13,141)	Interval cancer (n = 11,210)	Refuser (n = 46,374)
Age, mean (SD), y	60 (5.1)	61 (4.9)	62 (5.6)	65 (7.6)
		Sex, n (‰)		
Female	3,272,690	5426 (1.6)	5298 (1.6)	18,365 (5.5)
Male	2,274,104	7715 (3.3)	5912 (2.5)	28,009 (11.9)
		Family history of CRC		
No	5,295,005	12,140 (2.3)	10,700 (2.0)	—
Yes	251,789	1001 (4.0)	510 (2.0)	—
		$PM_{2.5}$, median (IQR), μg/m^3		
[1]Yearly average	28.3 (9.8)	27.1 (8.6)	30.1 (10.2)	29.7 (10.6)
[2]Monthly average	26.3 (13.1)	24.9 (12.8)	27.0 (15.8)	28.2 (16.1)
[3]Num. of days >35	6 (11)	5 (12)	7 (13)	8 (12)

[1,2,3] Kruskal–Wallis tests for all analysis between groups were statistically significant (P<.05).

Table 2. The Distribution of FIT-Positive Result by Demographic Factors and Exposure Levels of $PM_{2.5}$

	f-Hb>100(ng/Ml)/Total (n)	Positive rates	*P* value
Total	403,067/4,628,995	8.7	
Age (years old)			<.0001
<60	237,211/3,034,964	7.8	
≧60	165,856/1,594,031	10.4	
Sex			<.0001
Female	207,609/2,765,401	7.5	
Male	195,458/1,863,594	10.5	
Family history of CRC			<.0001
No	382,404/4,424,704	8.6	
Yes	20,663/204,291	10.1	
$PM_{2.5}$ (μg/m^3) (monthly)			<.0001
≦35	300,567/3,589,359	8.4	
>35	102,500/1,039,636	9.9	

Results

Demographic Characteristics and $PM_{2.5}$ Levels by CRC Detection Modes

A total of 5,546,843 normal results, 24,351 CRC cases, and 46,374 refusers were documented during 10 years of follow-up in the national CRC screening program (Table 1). The mean (SD) ages of normal, screen-detected CRC, interval CRC, and refusers were 60 (5.1), 61 (4.9), 62 (5.6), and 65 (7.6) years, respectively. Men accounted for a larger proportion than women for all detection modes, except for those with normal results. Table 1 also illustrates the monthly and yearly averaged $PM_{2.5}$ level, as well as the number of days above 35 μg/m^3 in each month by detection modes available from the CRC screening program, corresponding to the current date of screening or cancer diagnosis time. The monthly averaged $PM_{2.5}$ level was significantly higher in interval cancer (median [IQR]: 27.0 [15.8] μg/m^3) or refusers (median (IQR): 28.2 (16.1) μg/m^3), than in screen-detected cancer (median [IQR]: 24.9 [12.8] μg/m^3) or normal individuals (median [IQR]: 26.3 [13.1] μg/m^3). Similarly, a higher level of $PM_{2.5}$ in interval cancer or refuser than in screen-detected cancer was also observed in the yearly averaged $PM_{2.5}$ levels. A similar contrast in $PM_{2.5}$ between disease status was also shown by using the number of days above 35 μg/m^3 in a month as an exposure indicator.

Effects of $PM_{2.5}$ on FIT-Positive Individuals

We included 4,628,995 individuals with information on FIT levels in the analysis. The distribution of positive rates by demographic characteristics (age, sex), family history of CRC, and $PM_{2.5}$ exposure groups is presented in Table 2. Older age, men, and those with a family history of CRC exhibited higher FIT-positive rates. Individuals in the high $PM_{2.5}$-exposure group showed higher FIT-positive rates as than those in the low exposure group (9.9% vs 8.4%). Results showed a positive association between monthly averaged $PM_{2.5}$ concentrations at the city/county level and the FIT-positive

Table 3. Association Between $PM_{2.5}$ and FIT-Positive Outcomes.

Variables	Crude model OR (95%CI)	Model[1] aOR (95%CI)	Model[2] aOR (95%CI)
Age (≧60 vs <60 year)	1.33 (1.32, 1.34)	1.30 (1.30, 1.31)	1.30 (1.29, 1.31)
Sex (male vs female)	1.37 (1.36, 1.38)	1.35 (1.34, 1.36)	1.35 (1.34, 1.36)
Family history of CRC	1.14 (1.12, 1.15)	1.18 (1.16, 1.20)	1.18 (1.16, 1.20)
$PM_{2.5}$ (>35 vs ≦35 μg/m^3)	1.11 (1.10, 1.12)	1.11 (1.10, 1.12)	—
$PM_{2.5}$ (Num. of days >35 μg/m^3 per month)	1.009 (1.008, 1.009)	—	1.009 (1.008, 1.009)

Multi-level logistic random-effect regression analyses for FIT-positive outcome.
[1]Dichotomous $PM_{2.5}$ was used as main variable, adjusted for age, sex, and family history. The random effect of $PM_{2.5}$ between city and county was estimated by .07 (.03–.11).
[2]Number of days above 35 μg/m^3 per month was used as main variable, adjusted for age, sex, and family history. The random effect of $PM_{2.5}$ between city and county was estimated by .09 (.05–.13).

Table 4. Estimated Effects of $PM_{2.5}$ on CRC as an Initiator and a Promotor Based on Hierarchical CRC Evolution Models.

		Estimate/RR	95% CI	Estimate/aRR	95% CI
		Normal to PCDP (initiators)			
	Incidence rate (baseline)	1.33×10^{-3}	(1.31×10^{-3}, 1.35×10^{-3})	$6.9\times10^{-4*}$	(6.4×10^{-4}, 7.3×10^{-4})
Age	(≥60 vs <60 years old)	2.04	(1.98, 2.1)	2.07*	(2.01, 2.13)
Sex	(Male vs female)	1.68	(1.64, 1.73)	1.58*	(1.53, 1.63)
Family history	(Yes vs No)	1.24	(1.16, 1.33)	1.31*	(1.22, 1.39)
$PM_{2.5}$ (yearly)	(>35 vs ≦35 μg/m^3)	1.18	(1.14, 1.23)	1.22	(1.17, 1.26)
$PM_{2.5}$ (monthly)	(>35 vs ≦35 μg/m^3)	1.15	(1.10, 1.19)	1.14	(1.10, 1.18)
$PM_{2.5}$	(Num. of days >35 μg/m^3 per month)	1.005	(1.003, 1.007)	1.004	(1.002, 1.006)
		PCDP to CP (promoters)			
	Progression rate (baseline)	.38	(.37, .40)	.36*	(.33, .38)
Age	(≥60 vs <60 years old)	1.07	(1.03, 1.11)	1.16*	(1.11, 1.21)
Sex	(Male vs female)	.83	(.80, .86)	.83*	(.79, .86)
Family history	(Yes vs No)	.66	(.62, .72)	.71*	(.74, .77)
$PM_{2.5}$ (yearly)	(>35 vs ≦35 μg/m^3)	1.20	(1.14,1.28)	1.21	(1.15, 1.28)
$PM_{2.5}$ (monthly)	(>35 vs ≦35 μg/m^3)	1.23	(1.16, 1.30)	1.21	(1.15, 1.28)
$PM_{2.5}$	(Num. of days >35 μg/m^3 per month)	1.011	(1.008, 1.014)	1.009	(1.006, 1.012)

Estimated sensitivity: Crude model: .75 (.73–.77); Adjusted model: .73 (.71–.76). Note that the estimated sensitivity is to capture false negative CRCs occurring after the first year of time since last negative screen
*The estimated baseline incidence rate, progression rate, aRR of age and sex were based on the multivariable model using monthly averaged $PM_{2.5}$ as main exposure indicator. The random effect of $PM_{2.5}$ between city and county was estimated by .14 (.10–.18).

outcome, with an odds ratio (OR) of 1.11·(95%CI, 1.10–1.12) in the univariate analysis and adjusted odds ratio (aOR) of 1.11 (95%CI, 1.10–1.12) in the multivariate analysis after adjustment for age and sex (Table 3) between the high and low $PM_{2.5}$ exposure groups. A similar association was found by using the number of days above 35 μg/m^3 in 1 month as another exposure indicator both in the univariate and multivariate analyses (OR, 1.009; 95%CI, 1.008–1.009; aOR, 1.009; 95%CI, 1.008–1.009) (Table 3).

Exposure Effect of $PM_{2.5}$ on the Carcinogenesis of CRC

The overall screen-detected cancer rate was 2.9 and 1.7 per 1000 person-times for prevalent and subsequent screening, respectively, whereas that for interval cancers was 4.4 per 1000 person-time. In general, individuals aged over 60 years (9.3 ‰), men (6.2 ‰), and higher $PM_{2.5}$ exposure groups (5.6 ‰) exhibited higher interval cancer rates than their counterparts.

As shown in Figure 1, we hypothesize that $PM_{2.5}$ may exert initiation (λ_1) and/or promotion (λ_2) in the three-state carcinogenesis model of CRC. Our nationwide screening data showed that the baseline estimated annual incidence of PCDP CRC was 1.33 per 1000 persons (95%CI, 1.31–1.35) and that the baseline progression rate was .38 (95%CI, .37–.40) with the incorporation of screening sensitivity, as shown in Table 4. Exposure to $PM_{2.5}$, using yearly and monthly averages above 35 μg/m^3 and the number of days $PM_{2.5}$ above 35 μg/m^3 as indicators, were associated with significantly increased risk ratios (RR) on the disease progression of CRC, as compared to low $PM_{2.5}$ exposures in both models of treating $PM_{2.5}$ as both an initiator and promoter. For example, high monthly exposures to $PM_{2.5}$ were significantly associated with an increased risk for entering the PCDP as both an initiator (RR, 1.15; 95%

CI, 1.10–1.19) and promoter (RR, 1.23; 95%CI, 1.16–1.30) than low monthly exposures of $PM_{2.5}$.

After further considering both roles as initiator and promoter for $PM_{2.5}$, age, and sex, Table 4 shows that high $PM_{2.5}$ exposure (monthly) enhanced the risk for entering the PCDP phase by 14% (95%CI, 10–18) and the risk for faster disease progression by 21% (95%CI, 14–28). Using the number of days of $PM_{2.5}$ above 35 $\mu g/m^3$, similar results (initiator: .4%; 95%CI, .2–.6; promoter: .9%; 95%CI, .6–1.2) were observed. Furthermore, a significant risk for higher incidence was observed in men than in women (adjusted risk ratio [aRR], 1.58; 95%CI, 1.54–1.63); and women had relatively faster disease progression than men by 17% (aRR, .83; 95%CI, .80–.87). Those with a family history of CRC also showed a significantly higher risk for greater incidence rate (aRR, 1.31; 95% CI, 1.22–1.39), but not disease progression.

Table 4 also illustrates the exposure effect of $PM_{2.5}$ on CRC carcinogenesis by using the yearly averaged concentration as an exposure indicator, after adjusting for individual factors related to age and sex. Moreover, $PM_{2.5}$ exposure significantly elevated the risk for progression when entering the PCDP phase by approximately 22%, as compared to low $PM_{2.5}$ exposure (RR, 1.22; 95%CI, 1.17–1.26). Additionally, on a monthly basis, the figure is higher than the given exposure (RR, 1.14; 95%CI, 1.10–1.18). An elevated risk of 21% (95% CI, 15–28%) was found by using yearly averaged $PM_{2.5}$ exposures, which was comparable to the effect of using monthly averaged exposures in the model treating $PM_{2.5}$ exposure as a promoter.

Discussion

Our findings not only fill the knowledge gap on the health effects of $PM_{2.5}$ through the evolution of CRC, but also provide evidence of the relationship between $PM_{2.5}$ exposure, short-term inflammatory processes, and the subsequent occurrence and progression of colorectal cancer. Thanks to the longitudinal follow-up study design of the screening program in Taiwan, the carcinogenic effect of $PM_{2.5}$ on CRC can be assessed by comparing the exposure level between detection modes, including symptomatic CRC, such as interval cancer, refuser, asymptomatic screen-detected CRC, and normal individuals. The carcinogenic effect of $PM_{2.5}$ on CRC is strongly suggested by the high levels of $PM_{2.5}$ among patients with symptomatic CRC, as compared with asymptomatic CRC and normal individuals (Table 1). This finding may support the hypothesis that the reason why symptomatic CRC patients possess worse clinicopathologic features than asymptomatic CRC patients may be because of living in an area with higher $PM_{2.5}$ exposures, compared to asymptomatic CRC or normal cases. This finding is also consistent with the detailed exploration of the mechanism of CRC using a hierarchical CRC evolution model.

Previous studies based in the United States, Taiwan, and China,[2,22–24] as well as a meta-analysis on various similar studies,[3] have reported a significantly increased risk for CRC mortality due to higher $PM_{2.5}$ exposure. Additionally, studies on the association between $PM_{2.5}$ and CRC incidence revealed a significant effect of $PM_{2.5}$ exposure on CRC incidence in Thailand and the United States[36,37] Our study provides new information on the potential effect of $PM_{2.5}$ exposure on CRC carcinogenesis, in addition to the association between $PM_{2.5}$ and CRC incidence.

Previous studies indicated that gastrointestinal (GI) tracts can be exposed to $PM_{2.5}$ through direct ingestion of food and water contaminated by air pollutants or via mucociliary clearance of $PM_{2.5}$ from the lungs.[38,39] Other studies also proposed that $PM_{2.5}$ exposure may alter microbial compositions in the intestines and consequently change redox lipids, leading to higher permeability, impaired gut barrier, inflammatory cell infiltration, and systematic inflammation.[39,40] Therefore, it can be inferred that the underlying mechanism between $PM_{2.5}$ exposure and CRC carcinogenesis may be through systemic inflammation induced by $PM_{2.5}$, a well-established mechanism for $PM_{2.5}$ exposure on the cardiopulmonary system.[41] Furthermore, based on epidemiologic findings, $PM_{2.5}$ is proven to be involved in the process of inflammation; longer $PM_{2.5}$ exposure was accompanied by elevated C-reactive protein (CRP) levels at the population level,[42] consistent with the conclusion from a meta-analysis suggesting an activated systematic inflammatory state upon exposure and supported by a strong association between $PM_{2.5}$ and CRP.[43] Both studies investigating the inflammatory responses of $PM_{2.5}$ exposures at the individual and molecular levels also revealed that increased blood proinflammatory activity (TNFα-EQ) and significantly elevated mRNA and protein levels of interferon (IFN)-γ, interleukin (IL)-10, IL-17, and IL-21 production was demonstrated in the $PM_{2.5}$ treatment group.[44,45] As a result, we assume that both short-term and long-term exposure to $PM_{2.5}$ may contribute to the disease progression of CRC through such an inflammatory pathway.

FIT is not only a non-invasive, sensitive, and widely used tool for CRC screening, but also a surrogate for predicting CRC.[46,47] The underlying biological mechanism of our finding in the short-term inflammatory effect is supported by a recent study on the bidirectional temporal relationship between metabolic syndrome (MetS) and FIT-positive results, which suggests that MetS precedes elevated f-Hb concentration through the hypothesized pathway of chronic inflammation[48] and insulin-like growth factor signaling.[49] This pathway leading to FIT positivity may also be linked with cardiovascular disease through various inflammatory factors (such as TNF-α), as shown in Figure 3. The inflammatory effect of $PM_{2.5}$, independent of other potential risk factors, was further validated by other community-based screening data. The magnitude was equivalent to MetS or smokers, but slightly less than the drinking status.

Regarding the biological plausibility for supporting the increased risk for $PM_{2.5}$ as initiators and promoters using a three-state carcinogenesis model, $PM_{2.5}$ exposure has been

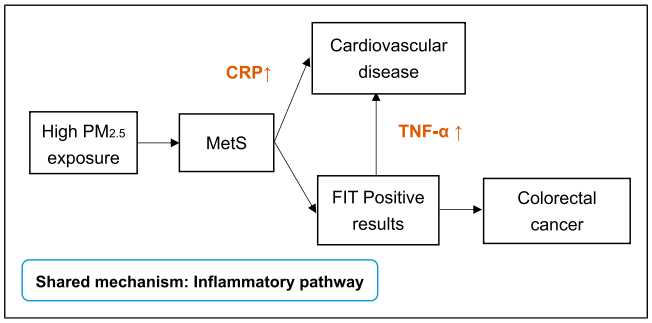

Figure 3. The potential mechanism of health effect of PM2.5 exposure in the early carcinogenesis of colorectal cancer pertaining to the inflammatory pathway in the relationship between metabolic syndrome and cardiovascular diseases.

found to induce genetic mutations and epigenetic changes linked to tumor-suppressor gene inactivation, oncogene mutations, resistance to cell death, production of angiogenetic factors, and metastasis during cancer continuum.[1,17,50–52] We speculate that the higher exposure effect as a promoter, as compared to being an initiator, may be attributed to accumulated oxidative stress, inflammation, and the induction of epithelial–mesenchymal transition that is linked to tumor progression and metastasis from sustained chronic $PM_{2.5}$ exposure.[53]

The novelty of this study is that we developed a precision model to demonstrate that $PM_{2.5}$ exposure acts as an initiator and a promoter in a continuous spectrum of multistep CRC processes. Additionally, this model shows the inflammatory effect of long-term $PM_{2.5}$ exposure in patients with invasive CRC. Moreover, individual data needed for the model presented in this study was collected by combining large, population-based cohort data with community-level $PM_{2.5}$ data in a multi-level study. This precision model has also elucidated the causal relationships between $PM_{2.5}$ exposure, short-term inflammatory processes, and the occurrence and subsequent progression of CRC. High levels of $PM_{2.5}$ among patients with symptomatic CRC, as compared with those with asymptomatic CRC and normal individuals, may support the postulate that living in an area with higher $PM_{2.5}$ concentrations may have caused poor clinicopathologic features in symptomatic CRC patients (Figure 1).

This study has a few limitations. Other potential individual factors, such as alcohol consumption and cigarette smoking, should also be considered. However, this is a longitudinal cohort study with a large sample size in consideration of time in each state (normal, pre-clinical, or clinical). Drinking and smoking, although not included in our analysis, would not bias our findings because county-specific rates of neither of these factors are positively correlated with county-specific $PM_{2.5}$ concentrations.[54] Regardless, the potential risk for $PM_{2.5}$ by city/county should still be noted. Additionally, these findings pertained to ambient $PM_{2.5}$, without considering exposure to indoor $PM_{2.5}$ or other ambient air pollutants. However, such undocumented exposure is more likely to be nondifferential and may underestimate the polluting effects of $PM_{2.5}$, as possible exposure misclassifications tend to bias our findings toward the null hypothesis. Lastly, the $PM_{2.5}$ exposure reported in this study cannot be treated as a threshold level of pollution effects on carcinogenesis, as our study was bound by the exposure levels we observed in Taiwan. More studies are needed to elucidate the exposure-response relationship for CRC carcinogenesis by $PM_{2.5}$ exposure at lower levels.

Conclusions

In conclusion, our findings of both short-term and long-term $PM_{2.5}$ exposure associated with multistep progression of CRC are useful for designing primary and secondary prevention strategies for patients with CRC who are exposed to high environmental $PM_{2.5}$ concentrations. The role of $PM_{2.5}$ as an initiator suggests that governments must strengthen $PM_{2.5}$ monitoring to improve air quality. Moreover, the role of $PM_{2.5}$ as a promoter for CRC also suggests that environmental screening for people living in polluted areas can act as a secondary preventive measure in order to provide early diagnosis and treatment to those with CRC at the pre-clinical detectable phase.

Appendix

Abbreviations

CP	clinical phase
CRC	colorectal cancer
FIT	fecal immunochemical test
f-HbC	fecal hemoglobin concentration
PCDP	pre-clinical detectable phase
$PM_{2.5}$	fine particulate matter

Declaration of Conflicting Interests

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Ethics Approval

The research ethics committee of National Taiwan University Hospital approved this project and granted a waiver for informed consent (202002091W) pursuant to the regulations of the institutional review board. The study protocol was reviewed and approved by the Health Promotion Administration of Taiwanese government.

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Notes

An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org

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