Environmental Research 212 (2022) 113416

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Relationships among green space, ambient fine particulate matter, and cancer incidence in Taiwan: A 16-year retrospective cohort study

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ARTICLE INFO

Keywords:
Air pollution
$PM_{2.5}$
Green space
NDVI
Cancer incidence

ABSTRACT

Introduction: Green space and air pollution have been recognized as vital health determinants. There is a paucity of studies examining the interplay between green space, fine particulate matter ($PM_{2.5}$), and the incidence of specific cancers.

Objective: We aimed to explore the contributions of green space and ambient $PM_{2.5}$ to the risk of specific cancers in terms of the most common cancers based on incidence or mortality rate in Taiwan and to ascertain the interaction between green space and $PM_{2.5}$ and their role in cancer risk.

Materials and methods: This retrospective longitudinal cohort study included 407,415 participants. Data were obtained from the 2000–2015 Mei Jau Health Examination Database linked to the Taiwan Cancer Registry and Causes of Death datasets. All participants were aged ≥20 years and had no history of cancer. The environmental exposure were the normalized difference vegetation index (NDVI) and the 2-year average $PM_{2.5}$ at baseline. Multivariate adjusted hazard ratios (HRs) were calculated using Cox proportional hazards models. We adjusted for covariates including demographics, anthropometrics, comorbidities, health behaviors, biochemical data, and environmental factors.

Results: During a median follow-up of 10.37 years, 11,576 cancer cases were reported. $PM_{2.5}$ exposure increased the risk of all cancers (HR: 1.11, [95% CI: 1.06–1.15]), stomach cancer (HR: 1.27, [1.02–1.58]), endocrine gland cancer (HR: 2.13, [1.39–3.26]), breast cancer (HR: 1.12, [1.03–1.22]), and lung cancer (HR: 1.12, [1.01–1.24]). An increase in NDVI reduced the risk of prostate cancer (HR: 0.93, [0.88–0.99]) and lung cancer (HR: 0.95, [0.91–0.99]). NDVI influenced the incidence of prostate and all cancers by reducing $PM_{2.5}$ concentrations.

Conclusion: Long-term $PM_{2.5}$ exposure is associated with an increased risk of some types of cancers. In contrast, an increase in environmental green space exposure is associated with lowering of the risk of prostate and lung cancer.

1. Introduction

The urban environment is gradually being recognized as a crucial health determinant. Air quality and green space are vital constituents of the living environment. Considering the involuntary and ubiquitous nature of exposure, air pollution contributes to the risk of developing multiple illnesses. The association of long-term exposure to air pollution with increased risks of all-cause mortality (Beelen et al., 2014), cardiovascular disease (Cicoira, 2018), and specific types of cancers such as lung (Tseng et al., 2019), gastrointestinal, liver (Guo et al., 2020),

Abbreviations: NDVI, normalized difference vegetation index; $PM_{2.5}$, fine particulate matter; BMI, body mass index; PBF, percent body fat; HTN, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MET, metabolic equivalent of task; ALP, alkaline phosphatase; SGOT, serum glutamic oxaloacetic transaminase; UA, uric acid; TG, triglyceride; CHOL, total cholesterol; LDL-C, low-density lipoprotein cholesterol; AFP, alpha-fetoprotein; ICD, International Classification of Diseases; HR, hazard ratio; CI, confidence interval.

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https://doi.org/10.1016/j.envres.2022.113416
Received 14 December 2021; Received in revised form 27 April 2022; Accepted 30 April 2022
Available online 4 May 2022

kidney, bladder, and colorectal cancer (Turner et al., 2017) has been consistently demonstrated in several studies. Furthermore, outdoor air pollution and particulate matter from outdoor air pollution have been classified as Group 1 carcinogens (carcinogenic to humans) by the International Agency for Research on Cancer based on sufficient evidence of carcinogenicity in humans and experimental animals and strong mechanistic evidence (Loomis et al., 2013). In contrast, green space has beneficial effects on physical and mental health by reducing exposure to air pollutants, noise, and excessive heat and providing psychological relaxation and stress alleviation (Van den Berg et al., 2015). Systematic reviews have provided strong evidence of the inverse association of surrounding greenness with all-cause mortality and mortality associated with cardiovascular diseases (Gascon et al., 2016; Rojas-Rueda et al., 2019). In addition, higher neighborhood greenness exposure is linked to decreased risk of prostate cancer (Demoury et al., 2017; Iyer et al., 2020) and increased survival rate in lung cancer patients (Yang et al., 2021).

A large body of literature has focused on epidemiological evidence of individual health effects of green space and air pollution. Nevertheless, there is a paucity of research regarding the interplay between green space and air pollution considering the inseparable nature of these two environmental health determinants in the real world. Specifically, although green space coverages are reported to have an inverse correlation with $PM_{2.5}$ concentrations (Chen et al., 2019; Liu and Shen, 2014), the interaction between these two metrics and its health impact are yet to be comprehensively explored. Moreover, the extent to which they are associated with specific cancer types remains unclear. A semi-individual cohort study in Germany showed that higher ambient air pollution levels increased the risk of mouth, throat, and non-melanoma skin cancers and that residential green space level had a possible protective effect against non-melanoma skin cancers (Datzmann et al., 2018). However, comprehensive evidence regarding other types of cancer is still limited, particularly in the Asian population.

We investigated the association among green space, air pollution, and incidence of different types of cancers in a cohort of 407,415 adults in Taiwan who were followed up prospectively for up to 16 years. The cohort was linked to the Taiwan Cancer Registry (TCR) and Causes of Death (COD) datasets. We aimed to explore the contributions of green space and fine particulate matter ($PM_{2.5}$) to the risk of specific cancers in terms of the most common cancers based on incidence or mortality rate in Taiwan and to ascertain the interaction between green space and $PM_{2.5}$ and their role in cancer risk.

2. Material and methods

2.1. Study population and design

We conducted a retrospective longitudinal cohort study using data from the 2000–2015 Mei Jau (MJ) Health Examination Database, which is a large cohort in Taiwan that has been described in other publications (Wu et al., 2017). To obtain individual cancer and death records, this cohort was linked to the 2000–2015 TCR and COD datasets through encrypted personal identification by trained staff members from the Health and Welfare Data Science Center, Ministry of Health and Welfare.

Among the 466,543 participants with three complete datasets, 59,128 were excluded due to following reasons: cancer history before the health check-up from TCR and MJ (n = 2,692), date of primary cancer diagnosis or health check-up was after the date of death (n = 17), males patients with female genital cancer (n = 1), unavailability of cancer diagnosis data (n = 65), age <20 years (n = 14,392), and inadequate data regarding estimated glomerular filtration rate (eGFR), alkaline phosphatase (ALP), serum glutamic oxaloacetic transaminase (SGOT), triglyceride (TG), total cholesterol (CHOL), low-density

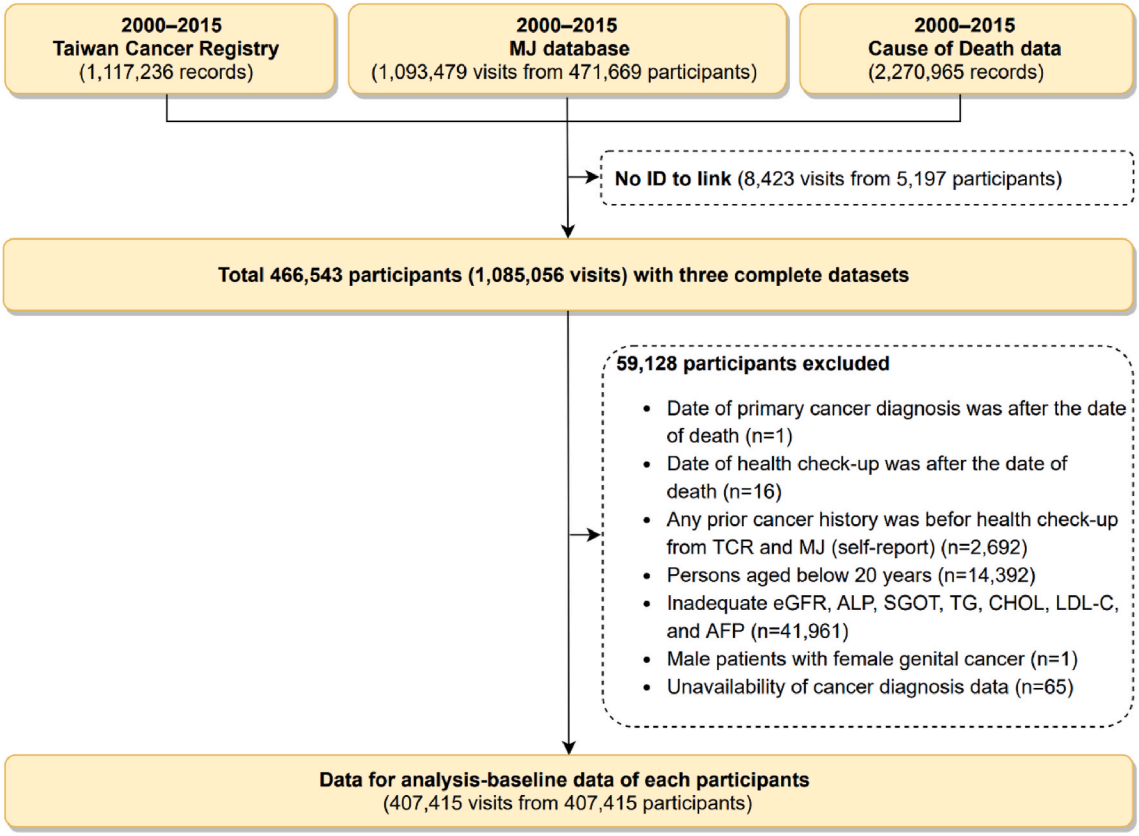

Fig. 1. Flowchart of the participants

Abbreviations: ID, personal identification; TCR, Taiwan Cancer Registry; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; SGOT, serum glutamic oxaloacetic transaminase; TG, triglyceride; CHOL, total cholesterol; LDL-C, low-density lipoprotein cholesterol; AFP, alpha-fetoprotein.

lipoprotein-cholesterol, and alpha-fetoprotein (AFP) (n = 41,961). Altogether, 407,415 participants were eligible for inclusion in the analyses. A flowchart of the study participants is depicted in Fig. 1. The follow-up period was defined as the duration from the baseline to the diagnosis of cancer, death, or the end of the follow-up period (December 31, 2015). Cancers were coded according to the International Classification of Diseases for Oncology, Third Edition in the TCR (http://tcr.cph.ntu.edu.tw/main.php?Page=N1). In the COD dataset, COD was coded using International Classification of Diseases (ICD)-9 before 2008 and ICD-10 from 2008.

2.2. Predictor variables: green space and air pollution exposure

The predictors assessed in this study were the normalized difference vegetation index (NDVI) and the 2-year average $PM_{2.5}$ at baseline. NDVI was used as an indicator of green space. The annual average NDVI data were computed and used for the year of the health checkup to link the data. Only the first health check-up data were linked to our exposure data. We extracted the mean values of NVDI within a radius of 500 m buffer of the participant's residential address (geocoded into latitude and longitude) from the Moderate Resolution Imaging Spectroradiometer vegetation index products at a high spatial resolution of 250 m × 250 m (Lin et al., 2019). For each buffer, we used the zonal statistic function from ArcGIS ArcMap 10.3.1 (ESRI, Redlands, CA, USA, http://www.esri.com/) to compute the average NDVI in the intersected area between the corresponding buffer and the raster data of NDVI. Higher values indicate greater greenness (range from −1 to +1), while negative values indicate blue space or water. The 2-year average $PM_{2.5}$ was used as an indicator of long-term exposure, which was the average of the exposure calculated from the calendar year of the health examination and the previous year. The details of the estimated $PM_{2.5}$ exposure have been published in other articles (Lin et al., 2015; Zhang et al., 2017). Briefly, $PM_{2.5}$ at each participant's reported address was estimated using a satellite-based spatiotemporal model based on the National Aeronautics and Space Administration aerosol optical depth data at a resolution of 1 km × 1 km.

2.3. Outcome variables

We selected the top ten cancer types based on the incidence or mortality rates in Taiwan from 2000 to 2015, with a total of 12 cancer types. Eight cancers (colon, female genital, liver, prostate, stomach, mouth, breast, and lung cancers) were in both the top ten cancer incidence and top ten cancer mortality rates. Four cancers were in either top ten cancer incidence (nasopharyngeal and endocrine gland cancers) or top ten cancer mortality (esophageal, and gallbladder and pancreatic cancers).

2.4. Covariates

The covariates were defined using baseline health examination data, which included variables such as (1) self-reported demographics: age, sex, education (senior high school and below or college and above), and region (stratified based on participants' residence coordinates (township): urban and rural); (2) anthropometrics: body mass index (<18.5, 18.5–24, or ≥24 kg/m^2) and percent body fat (TANITA body composition analyzer; Tanita Corp., Tokyo, Japan); (3) self-reported comorbidities: hypertension, diabetes mellitus, cardiovascular disease, and stroke; (4) level of kidney function: defined in terms of eGFR (≥90, 60–90, 45–60, or <45 mL/min/1.73 m^2) (HITACHI 7150; Tokyo, Japan (before 2005)/TOSHIBA C8000; Toshiba Corporation, Tokyo, Japan (since 2005)); (5) urine test: urine protein and occult blood (ROCHE Miditron or Cobas U411; F. Hoff-mann-La Roche Ltd., Basel, Switzerland); (6) self-reported history of diseases: asthma, nephritis, and gout; (7) self-reported long-term use of medications: uric acid (UA) medications, antihyperlipidemics, asthma medications, and steroids; (8) self-reported health behaviors: cigarette smoking, alcohol consumption, and physical activity; (9) biochemical values: ALP, SGOT, UA, TG, CHOL (HITACHI 7150; Tokyo, Japan (before 2005)/TOSHIBA C8000; Toshiba Corporation, Tokyo, Japan (since 2005)), and AFP (Abbott AxSYM or I2000; Abbott Park, Illinois, USA).

All variables had 5% or less missing data. For all models, the analysis results were restricted to individuals with complete information on all covariates.

2.5. Statistical analysis

Descriptive statistics were used to summarize the participants' baseline characteristics. The hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer incidence within the 16-year follow-up period according to NDVI and $PM_{2.5}$ were calculated using Cox proportional hazards models with a time-on-study scale. Since the dates of visits were available in the month-year format in the MJ database, we assumed the date as 15th of the month to obtain more precise estimates (Chuang et al., 2021; Woods et al., 2012). A confounder is a variable that influences both independent and dependent variables, and should be excluded from the causal pathway related to the two variables. The selection of covariates was based on common sociodemographic variables regardless of their significance levels and all possible confounders based on the following selection process. First, Spearman's rank correlation and analysis of variance (ANOVA) tests were used to analyze the relationship between confounders and independent variables. Second, mediation analysis was used to determine whether a confounder lies in the causal pathway between independent and dependent variables. Third, Cox proportional hazards models were used to analyze the relationship between confounders and dependent variables. Furthermore, we used the Change-in-Estimate (CIE) criterion with a 10% cut-off to check whether the model was affected by other unselected variables. The effect of interaction was also considered, and tested as multiplicative terms (independent variable × covariate) in the model. Furthermore, logistic regression was used for mediation analysis to explore the role of $PM_{2.5}$ on the association between NDVI and all or site-specific cancers. We used the following criteria to define a mediator: (a) a change in NDVI that significantly affected the changes in $PM_{2.5}$, and (b) $PM_{2.5}$ which was significantly associated with all or site-specific cancers (Valeri and VanderWeele, 2013). Total effect of exposure was decomposed into a natural direct effect (NDE) and a natural indirect effect (NIE). The NDE represents the effect of NDVI on all or site-specific cancers. NIE represents an association between NDVI and all or site-specific cancers, which could be explained by the association of NDVI with $PM_{2.5}$. To obtain valid estimates of NIE, we adjusted for potential NDVI–all or site-specific cancer confounders, NDVI–$PM_{2.5}$ confounders, and $PM_{2.5}$–all or site-specific cancer confounders, which included demographics, anthropometrics, comorbidities, health behaviors, biochemical data, and environmental factors. Screening for confounders followed the same rules. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Statistically significant consider as $p < 0.05$.

3. Results

3.1. Baseline characteristics

Baseline characteristics are listed in Table 1. The mean age was 39.5 ± 12.8 years. The proportion of female participants was slightly greater (53.5%) and the majority of the individuals had higher levels of education (63.0%). The mean NDVI and $PM_{2.5}$ were 0.35 ± 0.12 and 20.89 ± 5.74 μg/m^3, respectively.

During a median follow-up of 10.37 years (males: 10.45 years, females: 10.37 years), 11,576 participants were diagnosed with cancer at a mean age of 50.50 ± 14.10. The age-standardized incidence rate for all cancers was 244.91 per 100,000 population (males: 236.32 per 100,000

Table 1
Baseline characteristics.

	n	Total[a]	$PM_{2.5}$ (μg/m^3)	NDVI
n			407,033	407,415
Total			20.89 ± 5.74	0.35 ± 0.12
Age, years	407,415	39.5 ± 12.8	–	–
Sex	407,415			
Male	189,549	46.5	20.81 ± 5.81	0.35 ± 0.13
Female	217,866	53.5	20.95 ± 5.69	0.35 ± 0.12
Region				
Urban	371,419	91.6	21.74 ± 4.81	1.09 ± 3.38
Rural	33,980	8.38	11.22 ± 6.00	1.93 ± 4.48
Education	387,548			
Senior high school and below	143,473	37.0	19.74 ± 6.35	0.36 ± 0.14
College and above	244,075	63.0	21.51 ± 5.26	0.34 ± 0.12
BMI	407,285		–	–
<18.5	37,500	9.21	21.40 ± 5.42	0.34 ± 0.12
18.5–24	230,730	56.7	20.95 ± 5.68	0.35 ± 0.12
≥24	139,055	34.1	20.64 ± 5.91	0.35 ± 0.13
PBF	404,431	26.1 ± 6.92	–	–
HTN	404,148			
Yes	29,219	7.23	20.18 ± 0.62	0.36 ± 0.13
No	374,929	92.8	20.92 ± 5.71	0.35 ± 0.12
DM	404,185			
Yes	16,710	4.13	20.32 ± 6.20	0.36 ± 0.13
No	387,475	95.9	20.90 ± 5.73	0.35 ± 0.12
CVD	404,147			
Yes	12,358	3.06	20.32 ± 6.20	0.36 ± 0.13
No	391,789	96.9	20.90 ± 5.74	0.35 ± 0.12
Stroke	403,766			
Yes	1,460	0.36	19.84 ± 6.53	0.36 ± 0.13
No	402,306	99.6	20.93 ± 5.81	0.35 ± 0.12
eGFR	407,415		–	–
≥90	144,303	35.4	21.23 ± 5.52	0.34 ± 0.12
<90	263,112	64.6	20.69 ± 5.85	0.35 ± 0.13
Urine protein	387,998			
Yes	18,606	4.80	20.29 ± 6.45	0.35 ± 0.13
No	369,392	95.2	20.90 ± 5.72	0.35 ± 0.13
Occult blood	387,997			
Yes	295,966	76.3	20.88 ± 5.74	0.35 ± 0.12
No	92,031	23.7	20.82 ± 5.80	0.35 ± 0.12
History of asthma	404,149			
Yes	12,675	3.14	21.18 ± 5.51	0.35 ± 0.12
No	391,474	96.9	20.86 ± 5.76	0.35 ± 0.13
History of nephritis	404,147			
Yes	5,269	1.30	20.23 ± 5.95	0.36 ± 0.13
No	398,878	98.7	20.88 ± 5.75	0.35 ± 0.12
History of gout	323,147			
Yes	13,976	4.32	20.64 ± 5.95	0.35 ± 0.13
No	309,171	95.7	20.88 ± 5.75	0.35 ± 0.12
Long-term use of uric acid medications	404,154			
Yes	4,187	1.04	20.28 ± 6.11	0.36 ± 0.13
No	399,967	99.0	20.88 ± 5.75	0.35 ± 0.12
Long-term use of antihyperlipidemics	404,154			
Yes	4,066	1.01	20.62 ± 6.04	0.36 ± 0.13
No	400,088	99.0	20.87 ± 5.75	0.35 ± 0.12
Long-term use of asthma medications	404,154			
Yes	2,328	0.58	20.44 ± 6.11	0.36 ± 0.13
No	401,826	99.4	20.87 ± 5.75	0.35 ± 0.12
Long-term use of steroids	404,154			
Yes	1,920	0.48	20.08 ± 6.19	0.36 ± 0.14
No	402,234	99.5	20.87 ± 5.75	0.35 ± 0.12
Cigarette smoking	386,263			
No	288,126	74.6	20.88 ± 5.72	0.35 ± 0.12
Quit	22,301	5.77	20.49 ± 5.86	0.35 ± 0.13
Yes	75,836	19.6	20.84 ± 5.80	0.35 ± 0.13
Alcohol consumption	377,815			
No	315,783	83.6	20.94 ± 5.67	0.35 ± 0.13
Quit	10,205	2.70	20.03 ± 6.23	0.36 ± 0.14
Yes	51,827	13.7	20.50 ± 6.01	0.35 ± 0.13
Physical activity (MET-h/week)	407,415	0.68 ± 1.27	–	–
Light intensity (<7.5)	301,910	74.1	20.96 ± 5.73	0.35 ± 0.12
Moderate intensity (7.5<METs<21)	71,324	17.5	20.66 ± 5.81	0.35 ± 0.13
Vigorous intensity (≥21)	34,181	8.39	20.65 ± 5.71	0.35 ± 0.13
ALP, IU/L	395,435	95.9 ± 49.8	–	–
SGOT, IU/L	404,738	21.2 ± 6.00	–	–
UA, mg/dl	405,460	5.82 ± 1.58	–	–
TG, mg/dl	407,041	101 ± 54.2	–	–
<40	15,138	3.71	21.67 ± 5.52	0.34 ± 0.12
40–150	322,905	79.3	20.92 ± 5.71	0.35 ± 0.12
≥150	68,998	16.9	20.54 ± 5.91	0.35 ± 0.13
CHOL, mg/dl	407,183	190 ± 33.9	–	–
<120	3,268	0.80	20.93 ± 5.85	0.35 ± 0.13
120–200	257,308	63.2	20.95 ± 5.69	0.35 ± 0.12
≥200	146,607	36.0	20.77 ± 5.82	0.35 ± 0.13
AFP, ng/ml	391,061	2.75 ± 1.22	–	–

Abbreviations: NDVI, normalized difference vegetation index; PM2.5, fine particulate matter; BMI, body mass index; PBF, percent body fat; HTN, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MET, metabolic equivalent of task; ALP, alkaline phosphatase; SGOT, serum glutamic oxaloacetic transaminase; UA, uric acid; TG, triglyceride; CHOL, total cholesterol; AFP, alpha-fetoprotein.

[a] Data are presented as % or mean ± standard deviation.

population and females: 251.79 per 100,000 population). The incidence rates of all cancers and each type of cancer are shown in Table 2.

3.2. NDVI, $PM_{2.5}$, and the risk of cancers

Covariate-adjusted Cox proportional hazards models (Fig. 2) showed that the 2-year average $PM_{2.5}$ concentration with every 10 μg/m^3 increase at baseline was significantly associated with the incidence of stomach cancer (HR: 1.27, 95% CI: 1.02–1.58), endocrine gland cancer (HR: 2.13, 95% CI: 1.39–3.26), breast cancer (HR: 1.12, 95% CI: 1.03–1.22), lung cancer (HR: 1.12, 95% CI: 1.01–1.24), and all cancers (HR: 1.11, 95% CI: 1.06–1.15). NDVI at every 0.1-unit increase at baseline was significantly associated with the incidence of prostate cancer (HR: 0.93, 95% CI: 0.88–0.99) and lung cancer (HR: 0.95, 95% CI: 0.91–0.99). The results for other cancers (nonsignificant) are presented in Figs. A.1-A.2. The details of the multivariate model of all cancers and site-specific cancers are shown in Tables A.1-A.30.

We elucidated the relationship between NDVI, $PM_{2.5}$, and the risk of cancer via interaction tests and mediation analyses. There was no significant interaction effect for NDVI × $PM_{2.5}$ ($p > 0.05$). The results of mediation analysis showed that NDVI influenced the incidence of prostate and all cancers by reducing $PM_{2.5}$, with a natural indirect effect of 1.02 (95% CI: 1.01–1.02, full mediation), and 1.03 (95% CI: 1.00–1.05, partial mediation), respectively. Table A.31 demonstrates the demographics-adjusted mediation effects of mediators on the association between NDVI and lung and prostate cancer risks, and on the association between $PM_{2.5}$, and stomach and breast cancer risks.

We examined the interaction between environmental exposure and covariates (Table 3). We found that the effect of NDVI on prostate cancer varied with physical activity (p for interaction = 0.033). The effects of PM2.5 were shown as follows: on all cancer, they varied with cigarette smoking (p for interaction <0.001) and alcohol consumption (p for interaction = 0.006); on stomach cancer, they varied with education (p for interaction = 0.079, borderline significant) and alcohol consumption (p for interaction = 0.008); on endocrine gland and lung cancer, they varied with cigarette smoking (p for interactions were 0.039 and 0.077, respectively); on breast cancer, they varied with region (urban/rural) (p for interaction = 0.080, borderline significant). We further conducted stratified analysis using moderators to assess the association between environmental exposures and site-specific cancers, and the results are shown in Figure A.3.

Furthermore, given that education (as a proxy for socioeconomic status) and urban-rural differences could have potential implications in the association between environmental exposure and cancer incidence, we further performed a stratified analysis, although they were not statistically significant moderators (Table A.32-33).

4. Discussion

In this retrospective cohort study, we evaluated the associations between long-term environmental exposure to $PM_{2.5}$, green space exposure, and cancer incidence in Taiwan. We observed that $PM_{2.5}$ exposure was an independent risk factor for the incidence of all cancers, lung cancer, endocrine gland cancer, stomach cancer, and breast cancer. Green space exposure was a protective factor against the incidence of prostate cancer and lung cancers. And NDVI is an indirect protective factor for all cancer with the link being fully mediated by the $PM_{2.5}$ concentrations. This may imply that environmental greening is a practicable strategy to reduce the incidence of all cancer.

Airborne particulate matter, a complex mixture containing various carcinogens and endocrine disrupting chemicals, adversely affects cellular health via several mechanisms such as oxidative stress and inflammation, thus increasing the risk of cancer (Loomis et al., 2013; Valavanidis et al., 2008). The hormone properties of the pollutants may induce aberrant endocrine stimulation (Darbre, 2018), corresponding to the increased risk of endocrine gland cancer with high $PM_{2.5}$ exposure in our study. Several epidemiological studies have shown that higher $PM_{2.5}$ exposure is associated with an increased risk of lung cancer (Yu et al., 2021). A consistent result was obtained in our study. Given the strong relationship between cigarette smoking and lung cancer risk, evidence that $PM_{2.5}$ is associated with lung cancer incidence in never-smokers

Table 2
Incidence of cancers among participants from the 2000–2015 MJ Health Examination (n = 407,415).

Type of cancer	ICD-9/10 code	No. of cases	Mean age at diagnosis (median)	Follow-up time in years mean (median)	Age-standardized incidence rates[a] (per 100,000 population)		
					Total	Male	Female
All cancers	140–199, C00–C80	11,576	50.50 ± 14.10 (51)	9.90 ± 4.40 (10.37)	244.91	236.32	251.79
Colon cancer	153–154, C18–C21	2088	54.02 ± 13.62 (55)	9.98 ± 4.38 (10.46)	48.45	58.60	39.92
Liver cancer	155, C22	720	55.63 ± 13.11 (58)	10.00 ± 4.38 (10.54)	16.41	24.37	9.53
Lung cancer	162, C33–C34	1663	56.63 ± 12.94 (58)	9.99 ± 4.38 (10.54)	41.06	47.07	35.20
Stomach cancer	151, C16	408	57.33 ± 13.32 (58)	10.00 ± 4.38 (10.54)	10.86	13.08	8.80
Mouth cancer	140–141, 143–146, 148–149, C00–C06, C09–C10, C12–C14	436	50.26 ± 12.58 (50)	10.00 ± 4.38 (10.54)	8.45	15.09	2.80
Nasopharyngeal cancer	147, C11	216	41.63 ± 11.52 (39)	10.00 ± 4.38 (10.54)	3.30	4.78	1.99
Endocrine gland cancer	193–194, C73–C75	155	37.53 ± 10.42 (35)	10.00 ± 4.38 (10.54)	2.27	1.55	2.86
Esophageal cancer	150, C15	88	55.59 ± 13.33 (56)	10.00 ± 4.38 (10.54)	2.29	3.85	1.85
Gallbladder and pancreatic cancer	156–157, C23–C25	103	54.75 ± 12.67 (56)	10.00 ± 4.38 (10.54)	2.19	2.20	2.20
Breast cancer	174–175, C50	2917	44.17 ± 11.35 (42)	9.97 ± 4.38 (10.46)	47.92	0.16	90.19
Female genital cancer	179–184, C51–58	1412			–	–	43.25
Cervical Cancer	180, C53	951	40.19 ± 12.86 (37)	9.99 ± 4.38 (10.54)	–	–	28.39
Corpus uteri cancer	179, 182, C54-55	277	45.91 ± 11.25 (45)	10.00 ± 4.38 (10.54)	–	–	8.77
Ovary and other uterine adnexal cancer	183, C56, C570–C574	176	43.75 ± 12.07 (41)	10.00 ± 4.38 (10.54)	–	–	5.76
Prostate cancer	185, C61	732	61.24 ± 9.35 (61)	10.00 ± 4.38 (10.54)	–	41.08	–

Abbreviations: ICD, International Classification of Diseases.

[a] Age-standardized rates were calculated using the 2000 World Health Organization World Standard Population.

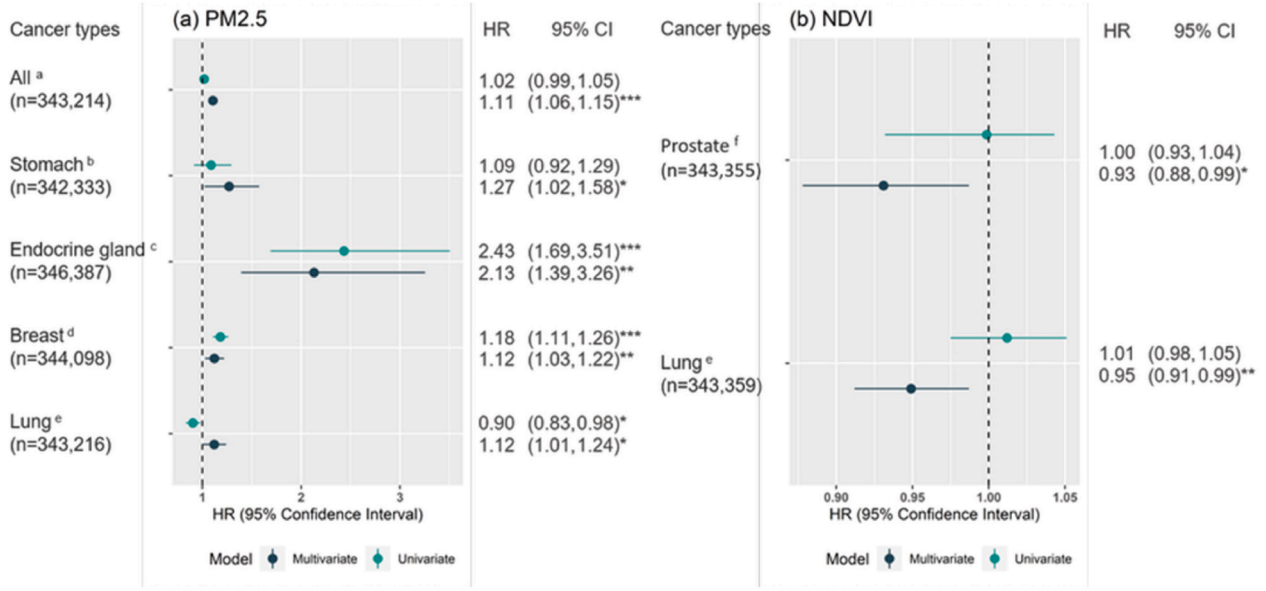

Fig. 2. Hazard ratios for cancer incidence within the 16-year follow-up period according to each 0.1-unit increase in contemporaneous NDVI and each 10 μg/m^3 increase in 2-year average $PM_{2.5}$

n denotes the number of participants included in the multivariate model.

[a] Adjusted for age, sex, region, education, DM, history of nephritis, long-term use of UA medication, urine protein, cigarette smoking, alcohol consumption, ALP, SGOT, UA, and AFP

[b] Adjusted for age, sex, region, education, alcohol consumption, physical activity, and ALP

[c] Adjusted for age, sex, region, education, PBF, and ALP

[d] Adjusted for age, sex, region, education, PBF, HTN, history of nephritis, long-term use of UA medication, cigarette smoking, alcohol consumption, physical activity, occult blood, UA, ALP, SGOT, and AFP

[e] Adjusted for age, sex, region, education, history of asthma, history of gout, cigarette smoking, UA, ALP, and AFP

[f] Adjusted for age, region, education, cigarette smoking, alcohol consumption, physical activity, occult blood, ALP, SGOT, and AFP.

Abbreviations: NDVI, normalized difference vegetation index; $PM_{2.5}$, fine particulate matter; HR, hazard ratio; CI, confidence interval; PBF, percent body fat; HTN, hypertension; DM, diabetes mellitus; UA, uric acid; ALP, alkaline phosphatase; SGOT, serum glutamic oxaloacetic transaminase; AFP, alpha-fetoprotein

***$p < 0.0001$

**$p < 0.01$

*$p < 0.05$

Table 3
Interaction test between environmental exposures and covariates.

Variables		p for interaction					
		All cancer	Stomach cancer	Endocrine gland cancer	Breast cancer	Lung cancer	Prostate cancer
$PM_{2.5}$	Education	0.985	0.079	0.453	0.996	0.704	–
	Region	0.628	0.249	0.429	0.080	0.852	–
	Alcohol consumption	0.006	0.008	0.606	0.619	0.183	–
	Cigarette smoking	<0.001	0.742	0.039	0.917	0.077	–
	Physical activity	0.193	0.753	0.700	0.603	0.634	
NDVI	Education	–	–	–	–	0.189	0.216
	Region	–	–	–	–	0.855	0.473
	Alcohol consumption	–	–	–	–	0.282	0.611
	Cigarette smoking	–	–	–	–	0.455	0.626
	Physical activity					0.391	0.033

may be more convincing. Our study observed and obtained consistent results in never-smokers. In addition, we found that long-term exposure to $PM_{2.5}$ increased stomach cancer risk, which were in accordance with prior research. Specifically, a previous study showed an increase of 5.0 μg/m^3 $PM_{2.5}$ increased gastric cancer risk by 38% (Nagel et al., 2018). In addition, the Cancer Prevention Study II demonstrated a significant positive associations of near-source $PM_{2.5}$ and stomach cancer mortality (Turner et al., 2017). The bioaccumulation of air pollutants in the gastrointestinal tract through inhalation and pulmonary absorption, or intaking through mucociliary clearance may give rise to genomic instability and elevated stomach cancer risk. In recent years, the association between air pollution and breast cancer incidence has attracted attention. Previous research has shown that exposure to $PM_{2.5}$-bound polycyclic aromatic hydrocarbon is associated with breast cancer due to its estrogenic characteristics and DNA damage response to oxidative stress (Chen et al., 2013; White et al., 2019). However, the results from some studies are not consistent. A nationwide prospective cohort study conducted in the US found that $PM_{2.5}$ exposure was associated with the incidence of breast cancer, but it varied according to geographic location (White et al., 2019). Nevertheless, another cohort study (Nurses' Health Study II) from the US found no significant evidence to support this hypothesis (Hart et al., 2016). A study involving 15 cohorts from nine European countries found only suggestive evidence of an association between $PM_{2.5}$ and the incidence of postmenopausal breast cancer (HR: 1.08, 95% CI: 0.77–1.51) (Andersen et al., 2017). Our study supports the hypothesis that higher $PM_{2.5}$ exposure increases the risk of

breast cancer.

Green space has potential beneficial effects on human mental and physical health through three possible pathways (Markevych et al., 2017). (1) The high density of trees and vegetation decreases noise, heat, and air pollutant concentrations. (2) Living in areas with more green spaces might increase the motivation for physical activity. (3) Exposure to green spaces improves and restores psychophysiological health. In recent years, several studies have suggested that living in areas with high greenness is associated with a decrease in adverse health effects such as all-cause mortality, incidence of cardiovascular and respiratory diseases and associated mortality, and mortality associated with breast, prostate, skin, lung, and all cancers (Coleman et al., 2021; Fong et al., 2018; Gascon et al., 2016). However, a limited number of studies have evaluated the association between green space exposure and cancer incidence. A 27-year follow-up cohort study (the GAZEL study involving employees of the French National Utility for Energy Production and Distribution recruited in 1989) found that the risks of all cancers increased with an increase in green space (NDVI at 100 m), but green space was a protective factor against breast cancer (Zare Sakhvidi et al., 2021). A population-based, multi-centric, case-control study in Spain (the MCC-Spain study) suggested that living in urban green spaces within a 300 m buffer was associated with a reduced risk of breast cancer whereas living in agricultural areas within a 300 m buffer was associated with an increased risk of breast cancer (O'Callaghan-Gordo et al., 2018). A cohort study in Germany reported the protective effects of green space against mouth and throat cancer and non-melanoma skin cancers (Datzmann et al., 2018). Nevertheless, we have no evidence to support the association between green space and the incidence of breast or mouth cancer. The results are inconsistent, perhaps due to differences in the study designs, exposure assessment methods, and geographical contexts of the studies. However, our study is one of the few large population-based cohort studies that focused on the association between greenness and cancer incidence and provided evidence that greenness has a protective effect against the incidence of cancer, especially lung and prostate cancer. The mitigating effect of green space on lung cancer risk is mainly a reduction in air pollution. With less inhaled toxicants reaching the lung tissue, the burden of genetic and epigenetic responses leading to tumorigenesis is curtailed (Shahadin et al., 2018). Our findings corroborate those of a population-based case-control study conducted by Demoury et al. suggesting that men living in greener areas had a lower risk of prostate cancer (Demoury et al., 2017). There is unclear evidence of how green space influences prostate cancer; however, our mediation analysis indicated that percent body fat and uric acid may play important mediating roles in this association. Previous studies have shown an association between visceral obesity evaluated using computed tomography (CT) and prostate cancer risk (Von Hafe et al., 2004). The mechanisms of adipocytokine secretion by visceral fat cells, steroid hormone disturbances, and elevated insulin levels may account for this association (Gann et al., 1996; Stattin et al., 2001). Interestingly, serum uric acid levels were positively correlated with visceral fat (Rospleszcz et al., 2020), highlighting the importance of further exploration of uric acid metabolism, body fat distribution, and carcinogenesis.

Our study has several limitations. First, the $PM_{2.5}$ exposure and NDVI were calculated based on the residential locations of patients; as a result, information regarding exposure during daily activities or occupations was not available. Second, our study consisted of participants with a higher socioeconomic status due to the self-paid nature of the health checkup. However, this cohort is representative of the general population of Taiwan in terms of the prevalence of risk factors, incidence, and mortality rates of cancer (Wu et al., 2017). Third, the extrapolation of short-term or recent air pollution data to long-term PM exposure has proven to be valid in previous studies due to the strong correlation in annual exposure among different geographical locations (Brook et al., 2010). This claim was supported by our sensitivity analysis (Figure A.4–5). We calculated cumulative environmental exposure for all participants during follow-up as a predictor of site-specific cancer incidence. However, it is of concern that 55% of participants only have one visit (baseline); therefore, we needed to assume that they did not move so as to calculate the cumulative environmental exposure. Fourth, due to the limitations of secondary data, it is difficult for us to control for every possible confounder, such as reproductive factors and social cohesion, in the Cox proportional hazards models and mediation analysis.

Finally, NDVI, a large-scale green space indicator, could not accurately estimate greenness if the participants had small gardens or their houses were adjacent to certain large green spaces. Therefore, to clarify the health benefits of greening, it is necessary to further investigate the effect of greening on cancer using small-scale indicators or greening types such as street trees, private planting, parks, and farmland.

5. Conclusions

Long-term $PM_{2.5}$ exposure is a possible risk factor for the incidence of all cancers and four site-specific cancers: endocrine gland cancer, stomach cancer, breast cancer, and lung cancer. Green space may play a protective role against the incidence of lung cancer and prostate cancer. Furthermore, higher green space exposure is associated with a lowering risk of all cancers by diluting the direct health impacts of $PM_{2.5}$. Increasing access to green spaces in residential neighborhoods may provide positive health outcomes and improve public health.

Author contributions

TCC conceived and designed the study. TCC acquired the health data. YJH and LCC drafted the manuscript. PHL performed the statistical analyses. BCL processed the green space data. CL processed the $PM_{2.5}$ data. TCC obtained funding and supervised the study. All authors have critically revised the manuscript. All authors have read and approved the final manuscript.

Funding

This research was supported by a grant from the Ministry of Science and Technology, Taiwan (MOST- 108-2628-M-001-008-MY3).

Ethics statement

Informed consent was obtained to authorize data processing and analysis. Ethical review was approved by the Institutional Review Board (IRB) of Biomedical Science Research, Academia Sinica (AS-IRB-BM-17044). Data identifying individuals were removed and anonymized throughout the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The data that support the findings of this study are available from the MJ Health Research Foundation and Ministry of Health and Welfare, Taiwan. However, restrictions apply to the availability of these data, which are under approval for the current study and thus, are not publicly available. The linked datasets used in this study had to be analyzed in person at the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.envres.2022.113416.

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