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ORIGINAL RESEARCH

Combined Associations of Physical Activity and Particulate Matter With Subsequent Cardiovascular Disease Risk Among 5-Year Cancer Survivors

Daein Choi, MD, MSc*; Seulggie Choi, MD*; Kyae Hyung Kim, MD, PhD; Kyuwoong Kim, PhD; Jooyoung Chang, MD; Sung Min Kim, BSc; Seong Rae Kim, MD; Yoosun Cho, MD, PhD; Gyeongsil Lee, MD, MSc; Joung Sik Son, MD, PhD; Sang Min Park, MD, MPH, PhD

BACKGROUND: The combined associations of physical activity and particulate matter (PM) with subsequent cardiovascular disease (CVD) risk is yet unclear.

METHODS AND RESULTS: The study population consisted of 18 846 cancer survivors who survived for at least 5 years after initial cancer diagnosis from the Korean National Health Insurance Service database. Average PM levels for 4 years were determined in administrative district areas, and moderate-to-vigorous physical activity (MVPA) information was acquired from health examination questionnaires. A multivariable Cox proportional hazards model was used to evaluate the risk for CVD. Among patients with low PM with particles ≤2.5 μm (PM2.5; (19.8–25.6 μg/m^3) exposure, ≥5 times per week of MVPA was associated with lower CVD risk (adjusted hazard ratio [aHR], 0.77; 95% CI, 0.60–0.99) compared with 0 times per week of MVPA. Also, a higher level of MVPA frequency was associated with lower CVD risk (*P* for trend=0.028) among cancer survivors who were exposed to low PM2.5 levels. In contrast, ≥5 times per week of MVPA among patients with high PM2.5 (25.8–33.8 μg/m^3) exposure was not associated with lower CVD risk (aHR, 0.98; 95% CI, 0.79–1.21). Compared with patients with low PM2.5 and MVPA ≥3 times per week, low PM2.5 and MVPA ≤2 times per week (aHR, 1.26; 95% CI, 1.03–1.55), high PM2.5 and MVPA ≥3 times per week (aHR, 1.34; 95% CI, 1.07–1.67), and high PM2.5 and MVPA ≤2 times per week (aHR, 1.38; 95% CI, 1.12–1.70) was associated with higher CVD risk.

CONCLUSIONS: Cancer survivors who engaged in MVPA ≥5 times per week benefited from lower CVD risk upon low PM2.5 exposure. High levels of PM2.5 exposure may attenuate the risk-reducing effects of MVPA on the risk of CVD.

Key Words: cancer survivor ■ cardiovascular disease ■ exercise ■ particulate matter ■ physical activity

The global number of cancer survivors has been continuously increasing. This is probably because of an increasing number of cancer diagnoses from an aging population, along with improved cancer prognosis attributable to early detection and treatment.[1] There are over 15.5 million cancer survivors in the United States as of January 1, 2016, and it is projected to reach over 20 million by 2026.[1] Therefore, there is a growing need for the management of cancer survivors after diagnosis and treatment for cancer. For these survivors, cardiovascular disease (CVD) is considered one of the most important causes of death. CVD-related death accounts for 11.3% of all-cause mortality among patients with cancer, which is 2 to 6 times higher than

Correspondence to: Sang Min Park, MD, MPH, PhD, Department of Biomedical Sciences and Family Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, South Korea. Email: smpark.snuh@gmail.com

*D. Choi and S. Choi contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- Engaging in physical activity under exposure to lower levels of particulate matter <2.5 μm was associated with decreased risk of cardiovascular risk among cancer survivors.
- The protective effect of physical activity was attenuated among those who were exposed to a higher concentration of particulate matter.

What Are the Clinical Implications?

- Cancer survivors engaging in physical activity in an environment with significant air pollution may benefit from adopting strategies to reduce exposure to particulate matter.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
MVPA	moderate-to-vigorous physical activity
NHIS	National Health Insurance Service
PA	physical activity
PM	particulate matter
PM2.5	PM with particles ≤2.5 μm
PM10	PM with particles <10 μm

that of the general population.[2] Cancer survivors are a high-risk population for CVD because of their lifestyle and cardiotoxicity related to cancer treatment.[2–5] Since CVD is a major cause of death and associated with various types of cancer,[6] it is important to manage cardiovascular risk factors among cancer survivors.

Meanwhile, a number of recent studies have reported the harmful effect of air pollutants such as particulate matter (PM) on CVD.[7,8] PM is defined as material suspended in the air in the form of minute solid particles or liquid droplets.[9] PM10, which consists of particles sized <10 μm in diameter, is further divided into PM2.5 to 10 (diameter 2.5–10 μm), PM2.5 (<2.5 μm), and ultrafine particle (<0.1 μm). Several studies have reported an association of PM with subclinical atherosclerosis as well as increased CVD morbidity and mortality risk.[10–12] A recent study also showed that PM2.5 exposure is associated with greater risk for CVD among cancer survivors,[13] and fine particles (PM2.5) seemed to have a stronger association than coarse particles (PM2.5–10), as they can reach the alveoli and enter the bloodstream more easily. On the other hand, the International Agency for Research on Cancer classified PM as a group 1 carcinogen, according to previous studies that reported the carcinogenic effect of PM on many different types of cancer.[9,10] Considering that PM is also associated with both cancer and CVD, cancer survivors would likely benefit from reducing their exposure to PM.

However, an attempt to lower PM exposure becomes challenging when engaging in physical activity (PA). Although PA has been shown to reduce all-cause mortality and CVD,[14–16] outdoor PA could lead to increased exposure to PM. Furthermore, a higher tidal volume and higher breathing rate during exercise results in higher minute volume, which promotes the inhalation of PM and exacerbates the detrimental effects of PM.[17]

To date, the combined effects of both PA and air pollution on CVD are relatively unexplored, and there is not enough evidence to determine whether the beneficial effects of PA on CVD risk outweigh the harmful effects of increased PM exposure, particularly among cancer survivors. Therefore, we aimed to investigate the combined effects of PA and air pollution on CVD risk among cancer survivors by using a nationwide health claim database from the Korean National Health Insurance Service (NHIS).

METHODS

Following the NHIS's policy, the data cannot be provided to other researchers or third parties.

Study Population

The NHIS provides mandatory health insurance covering nearly all forms of health services to all citizens in South Korea.[18] Furthermore, the NHIS collects and maintains all information on insured health services for claims purposes. A part of the health claims data is provided for research purposes. The NHIS database includes sociodemographic information such as age, sex, insurance premium, and area of residence, as well as information on all outpatient and inpatient hospital visits such as diagnosis, blood laboratory examinations, pharmaceutical prescriptions, and diagnostic and surgical procedures. Moreover, all enrollees aged ≥40 years are eligible for a biannual health screening examination, which is composed of a self-reported questionnaire, anthropometric measurements such as height and weight, and blood laboratory examinations such as fasting serum glucose and total cholesterol.[19] The validity of the NHIS database is described in detail elsewhere, and a number of previous large-scale epidemiologic studies have used the NHIS.[18,20]

Among those diagnosed with cancer during 2006 residing in 3 metropolitan cities (Seoul, Incheon, and Busan) in South Korea, 20 954 patients who underwent health examinations during 2010 to 2011 survived until

at least 2011. Among them, we excluded 1079 participants with missing values for PM. Then, 1029 patients diagnosed with CVD before the index date of January 1, 2012, were excluded. The final study population of 18 846 five-year cancer survivors were then followed up for a total of 123 560 person-years, starting from January 1, 2012, until the date of the CVD event, death, or December 31, 2018, whichever came earliest.

Ethical Considerations

The Seoul National University Hospital Institutional Review Board approved this study (No. E-1905-148-1035). The requirement for informed consent was waived, as the NHIS database is anonymized according to strict confidentiality guidelines before distribution to researchers.

Key Variables

PA was determined by a self-reported questionnaire during the health screening examination. All participants were asked the frequency of moderate and vigorous PA in terms of times per week, which we defined as moderate-to-vigorous physical activity (MVPA).[21,22] Moderate PA was defined as exercising for at least 30 minutes of moderate-intensity PA that induces slight shortness of breath, such as brisk walking, tennis, bicycle riding, or cleaning. Vigorous PA was defined as exercising for at least 20 minutes of vigorous-intensity PA that induces shortness of breath, such as running, aerobics, high-speed cycling, or mountain hiking.[23] Then, all participants were divided into 0, 1 to 2, 3 to 4, or ≥5 times per week of MVPA. We used MVPA as a measure for PA in accordance with the *Physical Activity Guidelines for Americans, Second Edition*.[24]

PM data were obtained from the Air Korea database, which includes information on yearly average PM2.5 and PM10 levels for each administrative area district based on over 300 atmospheric monitoring sites distributed throughout South Korea.[22] There are >280 administrative area districts in South Korea, each of which ranges from 2.8 to 755.0 (average 55.1) km^2 in area. Within the Air Korea database, 3 metropolitan cities, including Seoul, Incheon, and Busan, have information on both PM2.5 and PM10 levels starting from 2008. All study subjects were then linked to yearly PM exposure levels according to the area of residence during 2008–2011. Then, a 4-year average PM2.5 and PM10 exposure was calculated, after which participants were stratified into being exposed to low (19.8–25.6 $\mu g/m^3$ for PM2.5 and 35.5–52.1 $\mu g/m^3$ for PM10) or high (25.8–33.8 $\mu g/m^3$ for PM2.5 and 52.4–61.9 $\mu g/m^3$ for PM10) levels of PM. The median (SD) PM2.5 value for each administrative region (Seoul, Incheon, and Busan) was 25.5 (1.4), 25.0 (4.6), and 31.0 (1.7) $\mu g/m^3$, respectively.

Diagnosis of cancer was defined as having a diagnosis code for cancer according to the *International Classification of Diseases, Tenth Edition* (*ICD-10*: C00-C99) and the critical condition code for cancer.[21] The primary outcome was CVD, which was defined as being hospitalized for coronary heart disease (CHD; *ICD-10*: I20–I25) or stroke (*ICD-10*: I60–I69) for ≥2 days, was derived from a previous study.[20] The secondary outcomes included CHD and stroke. The *ICD-10* codes used to define CVD, CHD, and stroke (both ischemic and hemorrhagic types) were in accordance with the American Heart Association guidelines.[25]

Upon multivariate analysis, the considered covariates included age (continuous; years), sex (categorical; men and women), household income (categorical; first, second, third, and fourth quartiles), smoking (categorical; never, past, and current smokers), alcohol intake (categorical; 0, 1–2, 3–4, and ≥5 times per week), body mass index (BMI; continuous; kg/m^2), systolic blood pressure (continuous; mm Hg), fasting serum glucose (continuous; mg/dL), total cholesterol (continuous; mg/dL), and Charlson comorbidity index (categorical). Household income was determined by the insurance premium, and BMI was calculated by dividing the weight in kilograms by height in meters squared.

Statistical Analysis

The differences in distribution of descriptive characteristics according to MVPA frequency were determined by the chi-squared test for categorical variables and ANOVA for continuous variables. The adjusted hazard ratios (aHRs) and CIs for CVD according to PM2.5 and MVPA were calculated by multivariate Cox proportional hazards regression. The proportional hazards assumption was graphically tested and verified using the Schoenfeld residual method. *P* for interaction was calculated to determine whether the PM exposure was a significant factor in the association between BMI variability and the risk of CVD. The combined effects of PM2.5 and MVPA on future CVD risk among cancer survivors were determined. Stratified analysis on the association of PM2.5 and MVPA on CVD were conducted according to subgroups of age, sex, smoking, alcohol intake, BMI, and Charlson comorbidity index.

The risk for CVD according to PM10 and MVPA among cancer survivors was calculated, as well as the combined associations of PM10 and MVPA with CVD risk. The risk for CVD according to PM levels was determined, and the risk for CVD according to MVPA was also calculated. Finally, the combined associations of PM2.5 and MVPA with subsequent CVD risk among smoking-related, obesity-related, gastrointestinal, hepatobiliary, lung, breast, and thyroid cancer survivors were determined.

Statistical significance was determined as a *P* value of <0.05 in a 2-sided manner for primary outcome. Bonferroni correction was applied for secondary outcomes and subgroups analyses. All data collection and analysis were conducted with SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Table 1 depicts the descriptive characteristics of the study population. The number of cancer survivors with MVPA 0, 1 to 2, 3 to 4, and ≥5 times per week were 8360, 3024, 2738, and 4624, respectively. There was not a significant difference in PM2.5 levels according to MVPA frequency (*P* value=0.361). The mean (SD) age for those with MVPA 0, 1 to 2, 3 to 4, and ≥5 times per week were 60.6 (11.9), 56.1 (11.5), 57.9 (10.8), and 60.4 (10.5) years, respectively. Cancer survivors with more MVPA frequency tended to be men, have higher household income, have higher systolic blood pressure, have lower total cholesterol levels, and have more comorbidities (all *P* values <0.001).

The association of MVPA frequency with CVD risk according to PM2.5 levels are shown in Table 2. Among

Table 1. Descriptive Characteristics of the Study Population

	Moderate-to-vigorous physical activity, times/wk				
	0	1–2	3–4	≥5	*P* value
Follow-up period, y, mean (SD)	6.5 (1.5)	6.7 (1.2)	6.6 (1.3)	6.6 (1.3)	0.293
Number of participants	8460	3024	2738	4624	
PM2.5 range, μg/m^3	26.2 (3.1)	26.2 (2.9)	26.1 (3.1)	26.1 (3.0)	0.361
PM10 range, μg/m^3	51.5 (4.7)	51.6 (4.6)	51.4 (4.8)	51.5 (4.7)	0.809
Age, y, mean (SD)	60.6 (11.9)	56.1 (11.5)	57.9 (10.8)	60.4 (10.5)	<0.001
Sex, n (%)					
Male	2808 (33.2)	1194 (39.5)	1080 (39.4)	2100 (45.4)	<0.001
Female	5652 (66.8)	1830 (60.5)	1658 (60.6)	2524 (54.6)	
Household income, quartile, n (%)					
First (highest)	3438 (40.6)	1360 (45.0)	1264 (46.2)	2135 (46.2)	<0.001
Second	1933 (22.9)	671 (22.2)	575 (21.0)	990 (21.4)	
Third	1334 (15.8)	417 (13.8)	401 (14.7)	653 (14.1)	
Fourth (lowest)	1755 (20.7)	576 (19.1)	498 (18.2)	846 (18.3)	
Smoking, n (%)					
Never smoker	6563 (77.6)	2145 (70.9)	1962 (71.7)	3200 (69.2)	<0.001
Past smoker	1217 (14.4)	581 (19.2)	576 (21.0)	1117 (24.2)	
Current smoker	680 (8.0)	298 (9.9)	200 (7.3)	307 (6.6)	
Alcohol intake, times/wk, n (%)					
0	6649 (78.6)	2008 (66.4)	1886 (68.9)	3162 (68.4)	<0.001
1–2	1175 (13.9)	754 (24.9)	632 (23.1)	973 (21.0)	
3–4	357 (4.2)	182 (6.0)	159 (5.8)	305 (6.6)	
≥5	279 (3.3)	80 (2.7)	61 (2.2)	184 (4.0)	
Body mass index, kg/m^2, mean (SD)	23.5 (3.3)	23.3 (3.1)	23.4 (3.0)	23.5 (2.9)	0.004
Systolic blood pressure, mm Hg, mean (SD)	123.0 (15.9)	121.3 (15.2)	122.2 (15.3)	124.1 (15.2)	<0.001
Fasting serum glucose, mg/dL, mean (SD)	100.1 (23.3)	98.1 (19.7)	99.1 (20.2)	100.1 (22.0)	<0.001
Total cholesterol, mg/dL, mean (SD)	194.1 (40.1)	193.3 (36.6)	194.0 (36.8)	191.8 (38.5)	0.008
Charlson comorbidity index, n (%)					
≤1	2010 (23.8)	707 (23.4)	538 (19.7)	965 (20.9)	<0.001
2	2540 (30.0)	1016 (33.6)	941 (34.4)	1400 (30.3)	
≥3	3910 (46.2)	1301 (43.0)	1259 (46.0)	2259 (48.9)	

P values calculated by chi-squared test for categorical variables and ANOVA for continuous variables. PM2.5 indicates particulate matter with particles ≤2.5 μm; and PM10, particulate matter with particles <10 μm.

Table 2. Interactions for PM2.5 and Physical Activity on the Risk of Cardiovascular Disease Among 5-Year Cancer Survivors

	Moderate-to-vigorous physical activity, times/wk					
	0	1–2	3–4	≥5	P_{trend}	$P_{interaction}$
Cardiovascular disease						0.041
Low PM2.5						
Events	220	52	49	92		
Person-y	27 561	10 021	9204	15 485		
aHR (95% CI)	1.00 (reference)	0.91 (0.67–1.23)	0.82 (0.60–1.13)	0.77 (0.60–0.99)	0.028	
High PM2.5						
Events	247	62	60	138		
Person-y	27 283	10 128	8957	14 921		
aHR (95% CI)	1.00 (reference)	0.88 (0.66–1.17)	0.86 (0.64–1.14)	0.98 (0.79–1.21)	0.711	
Coronary heart disease						0.281
Low PM2.5						
Events	93	31	23	48		
Person-y	27 561	10 021	9204	15 485		
aHR (95% CI)	1.00 (reference)	1.27 (0.79–2.04)*	0.88 (0.52–1.49)*	0.91 (0.61–1.36)*	0.472	
High PM2.5						
Events	106	37	27	77		
Person-y	27 283	10 128	8957	14 921		
aHR (95% CI)	1.00 (reference)	1.22 (0.79–1.89)*	0.89 (0.55–1.45)*	1.26 (0.89–1.77)*	0.229	
Stroke						0.078
Low PM2.5						
Events	127	21	26	44		
Person-y	27 561	10 021	9204	15 485		
aHR (95% CI)	1.00 (reference)	0.64 (0.37–1.09)*	0.78 (0.48–1.27)*	0.67 (0.45–0.99)*	0.020	
High PM2.5						
Events	141	25	33	61		
Person-y	27 283	10 128	8957	14 921		
aHR (95% CI)	1.00 (reference)	0.63 (0.39–1.03)*	0.84 (0.54–1.30)*	0.76 (0.53–1.08)*	0.090	

aHR calculated by Cox proportional hazards regression after adjustments for age, sex, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index. PM2.5 range: low, 19.8–25.6 μg/m^3; high, 25.8–33.8 μg/m^3. MVPA determined by adding the frequency of moderate PA and vigorous PA per week, each ranging between 0–7 times per week. aHR indicates adjusted hazard ratio; MVPA, moderate-to-vigorous physical activity; and PM2.5, particulate matter with particles ≤2.5 μm.

*95% CI calculated after Bonferroni correction (*P*<0.025 for significance).

patients exposed to low PM2.5 levels, MVPA of ≥5 times per week was associated with lower risk for CVD (aHR, 0.77; 95% CI, 0.60–0.99) and stroke (aHR, 0.67; 95% CI, 0.45–0.99) compared with MVPA 0 times per week. Moreover, increased frequency of MVPA was associated with lower CVD (*P* for trend=0.028) and stroke (*P* for trend=0.020) risk among those exposed to low PM2.5 levels. In contrast, MVPA ≥5 times per week was not associated with lower risk for CVD (aHR, 0.98; 95% CI, 0.79–1.21) or stroke (aHR, 0.76; 95% CI, 0.53–1.08) among patients exposed to high PM2.5 levels.

Table 3 shows the combined associations of PM2.5 and MVPA with subsequent CVD risk among cancer survivors. Compared with those with low PM2.5 and MVPA ≥3 times per week, low PM2.5 and MVPA ≤2 times per week (aHR, 1.26; 95% CI, 1.03–1.55), high PM2.5 and MVPA ≥3 times per week (aHR, 1.34; 95% CI, 1.07–1.67), and high PM2.5 and MVPA ≤2 times per week (aHR, 1.38; 95% CI, 1.12–1.70) was associated with higher CVD risk. Finally, compared with low PM2.5 and MVPA ≥3 times per week, patients with high PM2.5 and MVPA ≤2 times per week (aHR, 1.46; 95% CI, 1.05–2.04) had lower risk for stroke. There was a tendency toward increased risk for CHD among participants exposed to high PM2.5 and MVPA ≥3 times per week (aHR, 1.39; 95% CI, 0.98–1.98), and increased risk for stroke among participants on low PM2.5 and MVPA ≤2 times per week (aHR, 1.35; 95% CI, 0.97–1.87), but the association was not statistically significant after multiplicity adjustment.

Stratified analysis on the association of PM2.5 and MVPA with CVD risk according to subgroups of age, sex,

Table 3. Hazard Ratios for Cardiovascular Disease According to PM2.5 and Physical Activity Among 5-Year Cancer Survivors

	Low PM2.5 and MVPA ≥3 times/wk	Low PM2.5 and MVPA ≤2 times/wk	High PM2.5 and MVPA ≥3 times/wk	High PM2.5 and MVPA ≤2 times/wk
Cardiovascular disease				
Events	141	272	198	309
Person-y	24 690	37 578	23 877	37 411
aHR (95% CI)	1.00 (reference)	1.26 (1.03–1.55)	1.34 (1.07–1.67)	1.38 (1.12–1.70)
Coronary heart disease				
Events	71	124	104	143
Person-y	24 690	37 578	23 877	37 411
aHR (95% CI)	1.00 (reference)	1.17 (0.83–1.64)*	1.39 (0.98–1.98)*	1.30 (0.93–1.82)*
Total stroke				
Events	70	148	94	166
Person-y	24 690	37 578	23 877	37 411
aHR (95% CI)	1.00 (reference)	1.35 (0.97–1.87)*	1.28 (0.89–1.83)*	1.46 (1.05–2.04)*

aHR calculated by Cox proportional hazards regression after adjustments for age, sex, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index. PM2.5 range: low, 19.8–25.6 μg/m^3; high, 25.8–33.8 μg/m^3. MVPA determined by adding the frequency of moderate PA and vigorous PA per week, each ranging between 0 and 7 times per week. aHR indicates adjusted hazard ratio; CI, confidence interval; MVPA, moderate-to-vigorous physical activity; and PM2.5, particulate matter with particles ≤2.5 μm.

*95% CI calculated after Bonferroni correction (*P*<0.025 for significance).

smoking, alcohol intake, BMI, and Charlson comorbidity index are shown in Table 4. Compared with low PM2.5 and MVPA ≥3 times per week, high PM2.5 and MVPA ≤2 times per week was associated with lower CVD among those aged <60 years (aHR, 2.38; 95% CI, 1.32–4.31). High PM2.5 and MVPA ≤2 times per week was associated with higher CVD risk (aHR, 1.58; 95% CI, 1.07–2.33) among women. Compared with low PM2.5 and MVPA ≥3 times per week, high PM2.5 and MVPA ≤2 times per week was associated with lower CVD among never or past smokers (aHR, 1.32; 95% CI, 1.03–1.69).

Among patients exposed to low PM10 levels, MVPA ≥5 times per week was associated with lower stroke risk (aHR, 0.66; 95% CI, 0.44–0.98) compared with those with MVPA 0 times per week (Table S1). High PM10 and MVPA ≤2 times per week was associated with higher CVD risk (aHR, 1.26; 95% CI, 1.03–1.54) compared with low PM10 and MVPA ≥3 times per week (Table S2). High PM2.5 levels were associated with higher CVD risk (aHR, 1.18; 95% CI, 1.03–1.36) compared with low PM 2.5 levels (Table S3). Patients with MVPA of ≥3 times per week had a tendency toward lower stroke risk (aHR, 0.82; 95% CI, 0.66–1.02) compared with those with MVPA ≤2 times per week, although the association was not statistically significant after multiplicity adjustment (Table S4). Compared with patients with low PM2.5 and MVPA ≥3 times per week, those with low PM2.5 and MVPA ≤2 times per week (aHR, 1.43; 95% CI, 1.06–1.91), high PM2.5 and MVPA ≥3 times per week (aHR, 1.40; 95% CI, 1.04–1.88), and high PM2.5 and MVPA ≤2 times per week (aHR, 1.71; 95% CI, 1.28–2.23) had higher risk for CVD among survivors of obesity-related cancer (Table S5).

DISCUSSION

In this nationwide population-based study among 18 846 cancer survivors, we found that MVPA ≥5 times per week of with exposure to a lower concentration of PM2.5 was associated with a lower risk of CVD (aHR, 0.77; 95% CI, 0.60–0.99), and there was a tendency toward decreased risk of CVD with increased frequency of MVPA among those exposed to lower PM2.5 levels (*P* for trend=0.028). Either participating in a lower frequency of MVPA or exposure to a higher concentration of PM2.5 was associated with increased risk of CVD among cancer survivors, compared with those who participated in high-frequency MVPA with lower exposure to PM2.5. To our knowledge, this was the first study to determine the combined associations of PA and PM with subsequent CVD among cancer survivors.

Previous studies noted the challenge of balancing the beneficial effect of PA along with the detrimental effects PM[17,26] and suggested strategies to minimize the health effect of air pollutant exposure. Results from 2 studies suggested that the beneficial effect of exercise might outweigh the adverse effects of air pollution,[27,28] but the combined association of PA and PM is unexplored, specifically among CVD high-risk populations such as cancer survivors.

It was noted in earlier studies that exposure to ambient PM increases the risk of CVD through systemic inflammation,[29–31] oxidative stress,[32] endothelial dysfunctions,[30,31] elevated fibrinogen,[33] and atherosclerotic changes.[32] Furthermore, short-term exposure to PM2.5 is associated with autonomic dysfunction, which

Table 4. Stratified Analysis on the Combined Associations of PM2.5 and MVPA With Cardiovascular Disease Risk According to Subgroups of Age, Sex, Smoking, Alcohol, Body Mass Index, and Charlson Comorbidity Index

	Low PM2.5 and MVPA ≥3 times/wk	Low PM2.5 and MVPA ≤2 times/wk	High PM2.5 and MVPA ≥3 times/wk	High PM2.5 and MVPA ≤2 times/wk	$P_{interaction}$
Age, y					0.426
<60	1.00 (reference)	2.12 (1.17–3.84)*	2.37 (1.28–4.40)*	2.38 (1.32–4.31)*	
≥60	1.00 (reference)	1.19 (0.92–1.54)*	1.16 (0.88–1.53)*	1.27 (0.98–1.65)*	
Sex					0.789
Male	1.00 (reference)	1.08 (0.80–1.46)*	1.17 (0.85–1.61)*	1.30 (0.96–1.76)*	
Female	1.00 (reference)	1.56 (1.07–2.28)*	1.68 (1.10–2.56)*	1.58 (1.07–2.33)*	
Smoking					0.566
Never or past	1.00 (reference)	1.20 (0.94–1.53)*	1.32 (1.02–1.71)*	1.32 (1.03–1.69)	
Current	1.00 (reference)	2.16 (0.93–5.00)*	1.61 (0.63–4.10)*	2.25 (0.96–5.26)*	
Alcohol intake					0.815
No	1.00 (reference)	1.42 (1.07–1.89)*	1.52 (1.11–2.08)*	1.46 (1.09–1.96)*	
Yes	1.00 (reference)	0.92 (0.60–1.42)*	1.04 (0.68–1.60)*	1.28 (0.85–1.93)*	
Body mass index, kg/m^2					0.758
<25	1.00 (reference)	1.42 (1.07–1.89)*	1.27 (0.92–1.75)*	1.43 (1.07–1.91)*	
≥25	1.00 (reference)	0.96 (0.64–1.45)*	1.41 (0.93–2.14)*	1.27 (0.85–1.90)*	
Charlson comorbidity index					0.798
≤2	1.00 (reference)	1.59 (1.10–2.30)*	1.50 (1.00–2.25)*	1.57 (1.80–2.27)*	
≥3	1.00 (reference)	1.05 (0.77–1.43)*	1.22 (0.89–1.68)*	1.25 (0.92–1.70)*	

Adjusted hazard ratios calculated by Cox proportional hazards regression after adjustments for age, sex, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index. PM2.5 range: low, 19.8–25.6 μg/m^3; high, 25.8–33.8 μg/m^3. MVPA determined by adding the frequency of moderate PA and vigorous PA per week, each ranging between 0–7 times per week. MVPA indicates moderate-to-vigorous physical activity; PA, physical activity; and PM, particulate matter.

*95% CI calculated after Bonferroni correction (P<0.025 for significance).

provokes dysrhythmia.[7,34] The pathogenic effect of PM for CVD is likely explained by PM2.5, rather than PM2.5 to 10 and PM10 concentration, which is likely attributable to the fact that fine particles may reach further into smaller airways and subsequently have systemic effects via the bloodstream.[7,34–36] Given that PM2.5 to 10 concentration was not associated with CVD after adjustment of PM2.5, it is likely that the PM2.5 component of PM10 accounted for the harmful cardiovascular effect.[37–39]

On the other hand, a number of studies reported that engaging in PA is not only safe among cancer survivors but also associated with multiple health benefits, including improved cardiorespiratory fitness, improved immune function, minimization of functional decline, and decreased mortality.[40–43] Several mechanisms have been proposed for these associations, and it is suggested that the reduction of adipose tissues through exercise, in turn, decreases the production of inflammatory cytokines, improves insulin resistance, and enhances immune function.[43–46] Moreover, PA directly reduces systemic inflammation, improves glycemic control, and improves insulin sensitivity, which are intermediate risk factors for CVD.[46]

The suggested mechanism that explains the benefits of PA on CVD exactly counteracts the mechanism of the detrimental effect of PM. This trade-off between the potentially harmful effects of PM and health benefits of PA is even more challenging since higher tidal volume and high breathing frequency during PA promotes the inhalation of PM, which might augment the hazardous impact of PM.[17] The results of our study showed that MVPA was associated with decreased risk for CVD, while the protective effect was attenuated among participants who were exposed to a higher level of PM2.5. This result implies that participating in PA in an environment with various measures to reduce air pollutants might be recommended for cancer survivors who are exposed to severe ambient pollution.

The results from the stratified analysis (Table 4) imply that the risk-elevating effect upon exposure to a higher concentration of PM or engaging in less MVPA was more pronounced among participants who are middle-aged, women, current smokers, nondrinkers, not obese, and with fewer comorbidities. This effect was also prominent among patients with obesity-related cancer, especially among breast cancer survivors (Table S5), which may in part explain the higher effect among women. Similar results were reported on previous studies, in that women[47] and breast cancer survivors[13,48] were more susceptible to PM exposure. It seems that women

are more vulnerable to CHD possibly because of the smaller size of coronary vessels with more atherosclerosis.[49] Further studies would be warranted to explore the PM-susceptible subgroups noted in our study.

There are several limitations to be considered in this study. First, the stage of cancer and severity were not considered in the analysis. Also, the treatment options for cancer were not considered. Future studies focused on the cancer severity and measure of treatment would be needed to validate our findings. Second, other air pollutants such as ozone, nitrogen dioxide, or sulfur dioxide were not considered in our study. This study also investigated the impact of long-term exposure to PM, and the association of short-term exposure to PM on the risk of CVD among cancer survivors might be different. Therefore, future studies investigating the short-term impact of various air pollutants will be needed. Third, a direct comparison with the noncancer population was not performed in this study, and it is unclear whether cancer survivors are even more susceptible to the interaction of PM exposure and PA. Further investigations with a direct comparison of cancer survivors with the noncancer population would be merited. Finally, there is no study to date that has evaluated the questionnaires of the NHIS health examination through the doubly labeled water method. Although the questionnaire has detailed examples of PA and the questionnaire's use has been validated through numerous previous studies, future studies would need to validate the NHIS questionnaire with the doubly labeled water method. Despite these limitations, there are a number of strengths in our study. A large sample of cancer survivors with an adjustment of a wide range of potential confounders for CVD enhances the generalizability of our findings. The results from various subgroup analyses also showed a similar trend toward the increased risk of CVD upon higher PM2.5 levels and engaging in less MVPA, which reinforces the reliability of the study.

In conclusion, engaging in MVPA under exposure to lower PM2.5 levels was associated with decreased risk of CVD among cancer survivors. The protective effect of MVPA tended to be attenuated among those who were exposed to a higher concentration of PM2.5. Various measures of lowering PM levels might be recommended to cancer survivors participating in PA in an environment with severe air pollution.

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Affiliations

Department of Medicine, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai, New York, NY (D.C.); Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, South Korea (S.C., J.C., S.M.K., G.L., S.M.P.); Department of Family Medicine (K.H.K., G.L., S.M.P.) and Department of Dermatology (S.R.K.), Seoul National University Hospital, Seoul, South Korea; Division of Cancer Control and Policy, National Cancer Control Institute, National Cancer Center, Goyang, South Korea (K.K.); Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea (Y.C.); and Department of Family Medicine, Korea University Guro HospitalSouth Korea, (J.S.S.).

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Supplemental Material

Tables S1–S5

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Supplemental Material

Table S1. Interactions for PM10 and physical activity on the risk of cardiovascular disease among 5-year cancer survivors.

	Moderate-to-vigorous physical activity, times/week					
	0	**1-2**	**3-4**	**≥5**	p_{trend}	$p_{interaction}$
Cardiovascular disease						0.428
Low PM10						
Events	228	53	54	98		
Person-years	27,415	9,783	8,934	15,056		
aHR (95% CI)	1.00 (reference)	0.88 (0.65-1.19)	0.91 (0.67-1.23)	0.81 (0.64-1.03)	0.089	
High PM10						
Events	239	61	55	132		
Person-years	27,429	10,367	9,227	15,351		
aHR (95% CI)	1.00 (reference)	0.90 (0.67-1.20)	0.77 (0.58-1.04)	0.94 (0.76-1.17)	0.385	
Coronary heart disease						0.858
Low PM10						
Events	99	30	26	55		
Person-years	27,415	9,783	8,934	15,056		
aHR (95% CI)	1.00 (reference)	1.14 (0.71-1.84)*	0.99 (0.60-1.64)*	1.00 (0.68-1.46)*	0.979	
High PM10						
Events	100	38	24	70		
Person-years	27,429	10,367	9,227	15,351		
aHR (95% CI)	1.00 (reference)	1.33 (0.86-2.06)*	0.80 (0.48-1.34)*	1.18 (0.82-1.69)*	0.561	
Stroke						0.635
Low PM10						
Events	129	23	28	43		
Person-years	27,415	9,783	8,934	15,056		
aHR (95% CI)	1.00 (reference)	0.67 (0.40-1.12)*	0.85 (0.53-1.37)*	0.66 (0.44-0.98)*	0.021	
High PM10						
Events	139	23	31	62		
Person-years	27,429	10,367	9,227	15,351		
aHR (95% CI)	1.00 (reference)	0.59 (0.35-0.99)*	0.76 (0.48-1.19)*	0.77 (0.54-1.09)*	0.082	

Adjusted hazard ratios calculated by Cox proportional hazards regression after adjustments for age, sex, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
* 95% CI calculated after Bonferroni correction ($p<0.025$ for significance).

PM10 range: low, 35.5-52.1 μg/m^3; high, 52.4-61.9 μg/m^3.
MVPA determined by adding the frequency of moderate PA and vigorous PA per week, each ranging between 0-7 times per week.
Acronyms: MVPA, moderate-to-vigorous physical activity; PM, particulate matter; aHR, adjusted hazard ratio; CI, confidence interval.

Table S2. Hazard ratios for cardiovascular disease according to PM10 and physical activity among 5-year cancer survivors.

	Low PM10 and MVPA≥3 times/week	Low PM10 and MVPA≤2 times/week	High PM10 and MVPA≥3 times/week	High PM10 and MVPA≤2 times/week
Cardiovascular disease				
Events	152	281	187	300
Person-years	23,890	37,193	24,577	37,795
aHR (95% CI)	1.00 (reference)	1.18 (0.96-1.44)	1.15 (0.93-1.43)	1.26 (1.03-1.54)
Coronary heart disease				
Events	81	129	94	138
Person-years	23,890	37,193	24,577	37,795
aHR (95% CI)	1.00 (reference)	1.04 (0.72-1.50)*	1.12 (0.75-1.67)*	1.15 (0.78-1.69)*
Acute myocardial infarction				
Events	16	34	14	22
Person-years	23,890	37,193	24,577	37,795
aHR (95% CI)	1.00 (reference)	1.39 (0.63-3.05)*	0.81 (0.31-2.13)*	0.87 (0.35-2.13)*
Total stroke				
Events	71	152	93	162
Person-years	23,890	37,193	24,577	37,795
aHR (95% CI)	1.00 (reference)	1.33 (0.91-1.93)*	1.20 (0.79-1.82)*	1.38 (0.94-2.02)*
Ischemic stroke				
Events	37	84	49	93
Person-years	23,890	37,193	24,577	37,795
aHR (95% CI)	1.00 (reference)	1.42 (0.85-2.37)*	1.16 (0.65-2.06)*	1.47 (0.87-2.48)*
Hemorrhagic stroke				
Events	12	25	12	16
Person-years	23,890	37,193	24,577	37,795
aHR (95% CI)	1.00 (reference)	1.27 (0.50-3.20)*	0.85 (0.29-2.52)*	0.78 (0.28-2.18)*

Adjusted hazard ratios calculated by Cox proportional hazards regression after adjustments for age, sex, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
* 95% CI calculated after Bonferroni correction ($p<0.01$ for significance).

PM10 range: low, 35.5-52.1 μg/m^3; high, 52.4-61.9 μg/m^3.
MVPA determined by adding the frequency of moderate PA and vigorous PA per week, each ranging between 0-7 times per week.
Acronyms: PM, particulate matter; MVPA, moderate-to-vigorous physical activity; aHR, adjusted hazard ratio; CI, confidence interval.

Table S3. Hazard ratios for cardiovascular disease according to particulate matter.

	PM2.5		PM10	
	Low PM	**High PM**	**Low PM**	**High PM**
Cardiovascular disease				
Events	413	507	433	487
Person-years	62,272	61,289	61,188	62,373
aHR (95% CI)	1.00 (reference)	1.18 (1.03-1.36)	1.00 (reference)	1.10 (0.96-1.26)
Coronary heart disease				
Events	195	247	210	232
Person-years	62,272	61,289	61,188	62,373
aHR (95% CI)	1.00 (reference)	1.21 (0.96-1.52)*	1.00 (reference)	1.11 (0.88-1.40)*
Stroke				
Events	218	260	223	255
Person-years	62,272	61,289	61,188	62,373
aHR (95% CI)	1.00 (reference)	1.16 (0.93-1.45)*	1.00 (reference)	1.09 (0.87-1.36)*

Adjusted hazard ratios calculated by Cox proportional hazards regression after adjustments for age, sex, physical activity, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
* 95% CI calculated after Bonferroni correction ($p<0.025$ for significance).

PM2.5 range: low, 19.8-25.6 $\mu g/m^3$; high, 25.8-33.8 $\mu g/m^3$.
PM10 range: low, 35.5-52.1 $\mu g/m^3$; high, 52.4-61.9 $\mu g/m^3$.
Acronyms: PM, particulate matter; aHR, adjusted hazard ratio; CI, confidence interval.

Table S4. Hazard ratios for cardiovascular disease according to physical activity.

	Moderate-to-vigorous physical activity, times per week	
	≤2	**≥3**
Cardiovascular disease		
Events	581	339
Person-years	74,988	48,567
aHR (95% CI)	1.00 (reference)	0.89 (0.77-1.02)
Coronary heart disease		
Events	267	175
Person-years	74,988	48,567
aHR (95% CI)	1.00 (reference)	0.97 (0.78-1.21)*
Stroke		
Events	314	164
Person-years	74,988	48,567
aHR (95% CI)	1.00 (reference)	0.82 (0.66-1.02)*

Adjusted hazard ratios calculated by Cox proportional hazards regression after adjustments for age, sex, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
* 95% CI calculated after Bonferroni correction ($p<0.025$ for significance).

MVPA determined by adding the frequency of moderate PA and vigorous PA per week, each ranging between 0-7 times per week.
Acronyms: aHR, adjusted hazard ratio; CI, confidence interval.

Table S5. Hazard ratios for cardiovascular disease according to PM2.5 and physical activity among 5-year cancer survivors by cancer type.

	Low PM2.5 and MVPA≥3 times/week	**Low PM2.5 and MVPA≤2 times/week**	**High PM2.5 and MVPA≥3 times/week**	**High PM2.5 and MVPA≤2 times/week**
Smoking-related cancer (N=7,943)				
Number of participants	1,761	2,218	1,731	2,233
Events, N (%)	129 (7.3)	149 (6.7)	126 (7.3)	120 (5.4)
aHR (95% CI)	1.00 (reference)	1.17 (0.91-1.51)	1.17 (0.92-1.50)	1.18 (0.91-1.54)
Obesity-related cancer (N=10,742)				
Number of participants	2,321	2,934	2,439	3,048
Events, N (%)	124 (5.3)	113 (3.9)	107 (4.4)	80 (2.6)
aHR (95% CI)	1.00 (reference)	1.43 (1.06-1.91)	1.40 (1.04-1.88)	1.71 (1.28-2.23)
Gastrointestinal cancer (N=5,636)				
Number of participants	1,249	1,589	1,243	1,555
Events, N (%)	88 (7.1)	104 (6.5)	89 (7.2)	83 (5.3)
aHR (95% CI)	1.00 (reference)	1.14 (0.84-1.54)	1.18 (0.88-1.59)	1.16 (0.84-1.59)
Hepatobiliary cancer (N=613)				
Number of participants	146	177	122	168
Events, N (%)	13 (8.9)	10 (5.7)	9 (7.4)	5 (3.0)
aHR (95% CI)	1.00 (reference)	2.26 (0.71-7.19)	1.37 (0.44-4.25)	2.74 (0.92-8.12)
Lung cancer (N=356)				
Number of participants	83	95	73	106
Events, N (%)	7 (8.5)	5 (5.3)	4 (5.5)	8 (7.6)
aHR (95% CI)	1.00 (reference)	0.85 (0.23-3.09)	0.76 (0.23-2.55)	1.28 (0.41-4.00)
Breast cancer (N=3,062)				
Number of participants	663	835	682	882
Events, N (%)	38 (5.7)	26 (3.1)	25 (3.7)	12 (1.4)
aHR (95% CI)	1.00 (reference)	2.22 (1.10-4.46)	2.37 (1.18-4.76)	3.52 (1.80-6.89)
Thyroid cancer (N=3,703)				
Number of participants	789	1,012	834	1,068
Events, N (%)	23 (2.9)	29 (2.9)	25 (3.0)	22 (2.1)
aHR (95% CI)	1.00 (reference)	1.27 (0.71-2.27)	1.13 (0.63-2.02)	1.04 (0.56-1.94)

Smoking related cancer includes cancer from head and neck, esophagus, stomach, colorectum, liver, pancreas, larynx, trachea, bronchus and lung, bladder, kidney, and acute myeloid leukemia.
Obesity related cancer includes cancer from thyroid, esophagus, breast, multiple myeloma, liver, kidney, gallbladder, stomach, pancreas, endometrium, colorectum, and ovary.
Adjusted hazard ratios calculated by Cox proportional hazards regression after adjustments for age, sex, household income, area of residence, smoking, alcohol intake, body mass index, systolic blood pressure, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
PM2.5 range: high, 25.8-33.8 $\mu g/m^3$; low, 19.8-25.6 $\mu g/m^3$.
MVPA determined by adding the frequency of moderate PA and vigorous PA per week, each ranging between 0-7 times per week.
Acronyms: PM, particulate matter; MVPA, moderate-to-vigorous physical activity; aHR, adjusted hazard ratio; CI, confidence interval.