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MINI-FOCUS ISSUE: HEART DISEASE IN WOMEN

ORIGINAL RESEARCH

Changes in Physical Activity and Cardiovascular Disease Risk in Cancer Survivors

A Nationwide Cohort Study

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ABSTRACT

BACKGROUND Cancer survivors face an elevated risk of cardiovascular disease, with physical inactivity after cancer treatment potentially worsening this risk.

OBJECTIVES The aim of this study was to investigate the association between physical activity before and after a cancer diagnosis and the risk for heart disease.

METHODS A nationwide cohort of 269,943 cancer survivors (mean age 56.3, 45.7% men) was evaluated for physical activity adherence 2 years before and after diagnosis. The primary outcomes were the incidence of myocardial infarction (MI), heart failure (HF), and atrial fibrillation. Subdistribution HRs (sHRs) and 95% CIs were calculated using Gray's method, accounting for death as a competing risk.

RESULTS Over a follow-up period of 1,111,329.28 person-years, compared with those who remained inactive, persistent physical activity was associated with a 20% reduction in MI risk (sHR: 0.80; 95% CI: 0.70-0.91) and a 16% reduction risk in HF risk (sHR: 0.84; 95% CI: 0.78-0.90). Initiating physical activity after a cancer diagnosis was linked to an 11% lower risk for MI (sHR: 0.89; 95% CI: 0.79-0.99) and a 13% lower risk for HF (sHR: 0.87; 95% CI: 0.82-0.93). Being active only before diagnosis was associated with a 20% lower risk for MI (sHR: 0.80; 95% CI: 0.71-0.91) and a 6% lower risk for HF (sHR: 0.94; 95% CI: 0.88-1.00). No association was observed between physical activity and atrial fibrillation risk. Associations varied by primary cancer site.

CONCLUSIONS These findings underscore the importance of maintaining physical activity for cardiovascular health in cancer survivors and suggest that physical activity before a diagnosis may offer enduring protection against ischemic heart disease and cardiac dysfunction. (JACC CardioOncol. 2024;6:879-889) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CKD = chronic kidney disease

DM = diabetes mellitus

HF = heart failure

ICD-10 = International Classification of Diseases-10th Revision

MI = myocardial infarction

NHIS = National Health Insurance Service

sHR = subdistribution HR

Advances in cancer therapy have significantly improved patient prognosis, resulting in a growing population of cancer survivors.[1] However, an unintended consequence of these treatments is their association with cardiotoxicity.[2-8] Some treatments can injure cardiomyocytes, cardiac fibroblasts, cardiac progenitor cells, and endothelial cells,[9-11] with these effects being worsened by pre-existing cardiovascular risk factors such as obesity, smoking, and physical inactivity.[12] This combination leads to an elevated risk for heart disease among cancer survivors.[13] Consequently, there is a critical need to address modifiable risk factors to prevent, reverse, and manage this cardiovascular burden.

Physical activity enhances the reserve capacity of the cardiovascular system.[14,15] However, adherence to physical activity among cancer survivors remains low. Only 10% of survivors maintain their activity levels during treatment, with this figure increasing only slightly to 20% to 30% after treatment.[16] This inactivity is due largely to the debilitating effects of treatments, which often lead to physical deconditioning and further declines in physical activity.[17-19] Despite these challenges, physical activity is both safe and beneficial for patients with cancer before, during, and after treatment. The American College of Sports Medicine and the American Cancer Society recommend 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity weekly for cancer survivors,[20] with the American College of Sports Medicine further emphasizing the safety of physical activity in this population.[21]

Much of the current research has focused on the benefits of physical activity in relation to overall or cancer-specific mortality.[22-26] However, most studies examining the cardiovascular benefits of physical activity before diagnosis,[27] during treatment,[28,29] and after diagnosis[29-31] have focused on patients with breast cancer.[27,30] Additionally, these studies are often limited by small sample sizes, which reduce their ability to achieve statistical significance for each cardiovascular outcome.

To address this research gap, this aim of this nationwide study was to investigate how changes in adherence to physical activity recommendations, before and after cancer diagnosis, are associated with the subsequent risk for heart diseases—specifically myocardial infarction (MI), heart failure (HF), and atrial fibrillation (AF)—in survivors of all cancer types.

METHODS

DATABASE SOURCE. The National Health Insurance Service (NHIS) is the sole insurer in Korea, covering approximately 97% of the population. It also administers medical aid to the remaining 3%, who fall within the lowest income levels. As a result, the NHIS provides health care services for the entire Korean population.

The NHIS compiles a comprehensive health information data set, linking sociodemographic, anthropometric, diagnostic, and medication data from both general health screenings and the medical treatment database. In Korea, the NHIS conducts biennial general health screenings. All individuals 40 years and older, as well as employees of any age, are eligible for these national general health examinations, which take place at medical institutions across the country.[32] These examinations include anthropometric measurements, questionnaires covering social and medical histories, and laboratory tests. A standardized questionnaire collects information on medical history and lifestyle behaviors, such as smoking, alcohol consumption, and physical activity.

The medical treatment database, which originates from reimbursed medical bills, can be cross-referenced with the health examination database. The NHIS database has been widely used in epidemiologic studies in Korea.[33-35] The data will be made available upon request and approval of a proposal by the NHIS database.

STUDY POPULATION. We identified 1,413,422 individuals newly diagnosed with cancer between January 1, 2010, and December 31, 2016. We excluded those who did not participate in general health screening examinations within 2 years before (n = 568,210) and after (n = 493,445) their cancer diagnosis, as well as 7,794 individuals with missing or erroneous examination data. Further exclusions included individuals younger than 20 years (n = 3) and those with histories of MI, ischemic stroke, HF, and AF (n = 67,177). To minimize the potential impact of pre-existing cardiovascular disease, we also

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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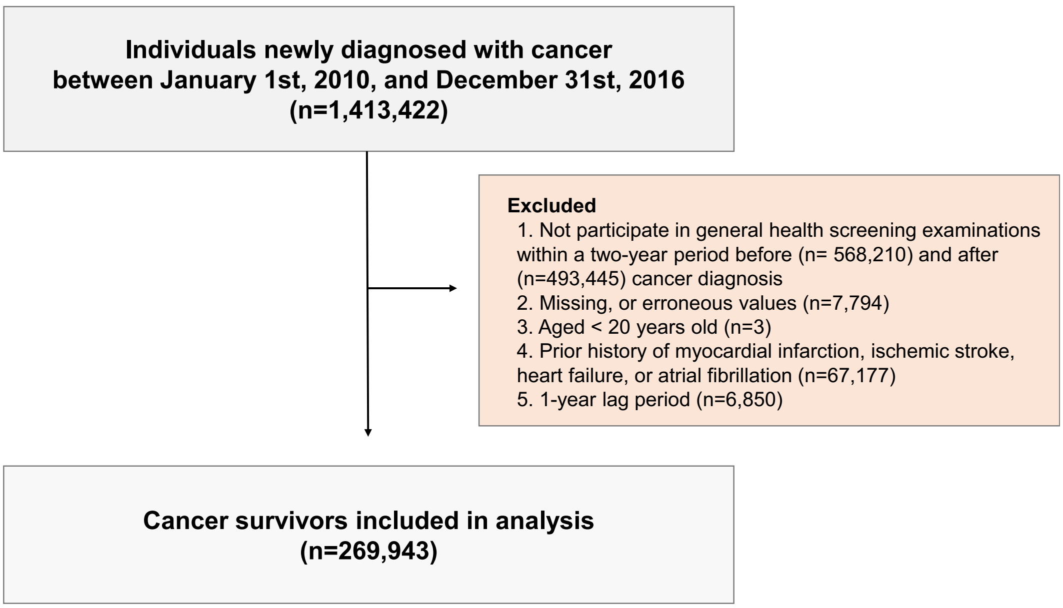
FIGURE 1 Flowchart of Study Population



This figure illustrates the selection process of participants included in the study.

excluded 6,850 cancer survivors diagnosed with MI, ischemic stroke, HF, and AF within 1 year after their cancer diagnoses. This resulted in a final analytical cohort of 269,943 cancer survivors (**Figure 1**).

CANCER ADJUDICATION. A cancer diagnosis was defined by the presence of both International Classification of Diseases, 10th Revision (ICD-10), codes beginning with "C" (Supplemental Table 1) and a cancer-specific insurance claim code (V193) in the patient's record. According to NHIS policy, patients with cancer are responsible for only 5% of their total medical bills for cancer-related care, which is covered by a special copayment reduction code (V193) that requires a physician-issued medical certificate. As a result, the cancer diagnoses in this study are considered highly reliable, with 97.9% sensitivity and 91.5% positive predictive value.[36] This dual-coding method has been validated and used in previous studies.[37,38]

ASCERTAINMENT OF PHYSICAL ACTIVITY. Physical activity data were collected from general health screenings conducted before and after cancer diagnosis using self-reported questionnaires (Supplemental Figure 1). Participants completed a short version of the International Physical Activity Questionnaire during their health screenings,[39] included 7 questions assessing the frequency and duration of physical activity over the previous 7 days. For this study, cancer survivors were categorized as either adherent to physical activity if they engaged in at least 30 minutes of moderate activity on 5 or more days per week or at least 20 minutes of strenuous activity on 3 or more days per week; otherwise they were categorized as nonadherent.[20] Four groups were then defined on the basis of changes in physical activity status with respect to cancer diagnosis: remained inactive, became inactive, became active, and remained active.

MI, HF, AND AF ADJUDICATION. The primary outcomes of this study were the incidences of MI, HF, and AF, identified using ICD-10 codes. Newly diagnosed MI was defined by ICD-10 code I21 or I22 during hospitalization.[40] HF was defined as the first hospitalization with a primary diagnosis of ICD-10 code I50, as used in previous studies.[41-43] AF was identified using ICD-10 codes I48.0 to I48.4 and I48.9.[44] The secondary outcome was all-cause mortality.

The cohort was followed for 1 year after the general health screening diagnosis, until the occurrence of incident MI, HF, and AF or until censoring because of events such as outmigration, death, or the end of the study period (December 31, 2019), whichever came first.

COVARIATES. Data on age, sex, income, and anthropometric measures were collected from general health

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screenings. Anthropometric measurements followed standard protocols during the screenings.[32] Obesity was defined according to the Asian-Pacific criteria, with a body mass index ≥25 kg/m^2 classified as obese.[45] Information on smoking status (current or no) and alcohol consumption (yes or no) was obtained from health screenings after cancer diagnosis.

Comorbid medical conditions were identified on the basis of laboratory results, claims data, and prescription records prior to the index date, as follows: hypertension (ICD-10 codes I10.x-I13.x and I15.x, use of antihypertensive medication, or blood pressure ≥140/90 mm Hg), diabetes mellitus (DM) (ICD-10 codes E11.x-E14.x with antidiabetic medications or fasting glucose ≥126 mg/dL), dyslipidemia (ICD-10 code E78.x with lipid-lowering medication or total cholesterol ≥240 mg/dL), and chronic kidney disease (CKD; glomerular filtration rate <60 mL/min/1.73 m^2, estimated using the MDRD [Modification of Diet in Renal Disease] equation).

STATISTICAL ANALYSES. General characteristics are presented as counts and percentages for categorial variables and as mean ± SD for continuous variables. To examine the significance of differences between 2 variables, chi-square tests were used for categorical variables, and 1-way analysis of variance was used for continuous variables.

We used the Fine-Gray proportional subdistribution hazards model to calculate subdistribution HRs (sHRs) and 95% CIs for risk for incident MI, HF, and AF, with death as a competing risk.[46] In this study, the reference group was "remained inactive," and sHRs with 95% CIs were calculated for each group in comparison with this reference group.

In the first model (model 1), unadjusted cause-specific HRs were estimated, with death treated as a censoring event. In the multivariable-adjusted models, potential confounders were identified a priori on the basis of previous research.[47] These models used sHRs, which account for individuals who die by considering them still at risk. Model 2 adjusted for age, sex, income, smoking status, alcohol consumption, obesity, hypertension, DM, dyslipidemia, and CKD. In the final step (model 3), we further adjusted for primary cancer sites. Gray's method for competing risks was used to estimate cumulative incidence curves on the basis of physical activity groups.

Additionally, exploratory analyses were conducted to refine our understanding of these associations. One analysis excluded participants who died within 1 year of baseline to reduce bias from early mortality, which may disproportionately affect those with more severe health conditions. Subgroup analyses were also conducted by primary cancer sites and by age (≥66 years vs <66 years, on the basis of the median year of cancer diagnosis in the United States) to assess whether the protective effects of physical activity differed by cancer type or age group.

All statistical analyses were performed using SAS version 9.4 (SAS Institute). *P* values were 2-sided, and a significance level of 0.05 was used.

ETHICS STATEMENT. This study was approved by the Institutional Review Board of Soongsil University (SSU-202303-HR-465-1). Because anonymized and deidentified data were used for the analyses, informed consent was not required.

RESULTS

GENERAL CHARACTERISTICS OF THE STUDY POPULATION. This study included 269,943 cancer survivors with a mean age of 56.3 ± 12.1 years, of whom 45.7% were men. The distribution of physical activity status after diagnosis was as follows: 62.0% remained inactive (n = 167,256), 11.4% became inactive (n = 30,649), 16.6% became active (n = 44,852), and 10.1% remained active (n = 27,186) (Table 1).

Those who became inactive were the oldest, with a mean age of 58.3 ± 11.7 years, while both the remained-inactive and became-active groups had a mean age of 55.9 years. Men were most prevalent in the remained-active group (56.7%) and least prevalent in the remained-inactive group (43.0%). The prevalence of obesity was lowest in the became-active group (30.0%) and highest in the became-inactive group (33.4%).

The became-active group also had the lowest prevalence of current smokers, alcohol consumers, and individuals with comorbid chronic conditions, including hypertension, DM, dyslipidemia, and CKD. This group also exhibited the most favorable clinical measurements, such as systolic and diastolic blood pressure, fasting glucose, and total cholesterol levels.

ASSOCIATION OF PHYSICAL ACTIVITY CHANGES WITH HEART DISEASE RISK IN CANCER SURVIVORS. During an average follow-up period of 4.1 years, covering 1,111,329.28 person-years, persistent physical activity was associated with a 20% reduction in MI risk (sHR: 0.80; 95% CI: 0.70-0.91) and a 16% decrease in HF risk (sHR: 0.84; 95% CI: 0.78-0.90) compared with those who remained inactive, after adjusting for age, sex, income, cardiovascular risk factors, and primary cancer site (Table 2).

TABLE 1 General Characteristics of the Study Population Classified by Change in Physical Activity Status

	Total (N = 269,943)	Remained Inactive (n = 167,256)	Became Inactive (n = 30,649)	Became Active (n = 44,852)	Remained Active (n = 27,186)
Age at baseline, y	56.3 ± 12.1	55.9 ± 12.5	58.3 ± 11.7	55.9 ± 11.2	58.0 ± 10.9
Male	123,260 (45.7)	71,928 (43.0)	15,259 (49.8)	20,672 (46.1)	15,401 (56.7)
Income status, low	46,915 (17.4)	29,542 (17.7)	5,510 (18.0)	7,611 (17.0)	4,252 (15.6)
BMI, kg/m^2	23.7 ± 3.2	23.7 ± 3.3	23.9 ± 3.2	23.6 ± 3.1	23.8 ± 2.9
WC, cm	80.5 ± 9.2	80.5 ± 9.3	81.0 ± 8.9	79.9 ± 9.0	80.8 ± 8.6
Obesity, yes	86,589 (32.1)	54,227 (32.4)	10,227 (33.4)	13,439 (30.0)	8,696 (32.0)
Smoking, yes	21,104 (7.8)	14,461 (8.7)	2,227 (7.3)	2,715 (6.1)	1,701 (6.3)
Alcohol, yes	61,418 (22.8)	38,321 (22.9)	6,900 (22.5)	9,222 (20.6)	6,975 (25.7)
Hypertension, yes	92,209 (34.2)	55,701 (33.3)	11,595 (37.8)	14,823 (33.1)	10,090 (37.1)
DM, yes	37,226 (13.8)	22,228 (13.3)	4,913 (16.0)	5,933 (13.2)	4,152 (15.3)
Dyslipidemia, yes	67,129 (24.9)	41,253 (24.7)	8,061 (26.3)	10,744 (24.0)	7,071 (26.0)
CKD, yes	15,410 (5.7)	9,518 (5.7)	1,898 (6.2)	2,349 (5.2)	1,645 (6.1)
Height, cm	162.0 ± 8.4	161.6 ± 8.5	162.2 ± 8.2	162.4 ± 8.2	163.6 ± 8.0
Weight, kg	62.4 ± 10.9	62.1 ± 11.1	63.0 ± 10.7	62.3 ± 10.6	63.9 ± 10.4
SBP, mm Hg	121.8 ± 14.5	121.6 ± 14.6	122.7 ± 14.4	121.3 ± 14.2	122.8 ± 14.0
DBP, mm Hg	75.3 ± 9.5	75.3 ± 9.6	75.6 ± 9.5	75.0 ± 9.4	75.6 ± 9.3
Fasting glucose, mg/dL	100.3 ± 22.9	100.1 ± 23.2	101.7 ± 23.6	99.6 ± 21.6	101.1 ± 22.1
Total cholesterol, mg/dL	189.7 ± 37.5	190.3 ± 37.8	189.5 ± 37.5	188.3 ± 37.1	188.4 ± 36.7
eGFR, mL/min/1.73 m^2	91.1 ± 42.4	91.3 ± 40.9	90.2 ± 43.9	91.6 ± 43.6	90.0 ± 47.5
Cancer type					
Biliary	2,334 (0.9)	1,350 (57.8)	324 (13.9)	403 (17.3)	257 (11.0)
Bladder	6,189 (2.3)	3,731 (60.3)	817 (13.2)	944 (15.3)	697 (11.3)
Breast	28,988 (10.7)	16,673 (57.5)	2,811 (9.7)	6,786 (23.4)	2,718 (9.4)
Cervical	5,052 (1.9)	3,546 (70.1)	506 (10.0)	696 (13.8)	304 (6.0)
Colorectal	31,362 (11.6)	18,725 (59.7)	3,660 (11.7)	5,489 (17.5)	3,488 (11.1)
Corpus, uterine	3,244 (1.2)	2,074 (64.0)	348 (10.7)	557 (17.2)	265 (8.2)
Esophageal	1,056 (0.4)	603 (57.1)	148 (14.0)	173 (16.4)	132 (12.5)
Hodgkin	193 (0.1)	112 (58.0)	23 (11.9)	37 (19.2)	21 (10.9)
Kidney	6,271 (2.3)	3,816 (60.9)	736 (11.7)	1,000 (16.0)	719 (11.5)
Laryngeal	1,394 (0.5)	851 (61.1)	186 (13.3)	214 (15.4)	143 (10.3)
Leukemia	1,537 (0.6)	954 (62.1)	195 (12.7)	256 (16.7)	132 (8.6)
Liver	9,917 (3.7)	5,922 (59.7)	1,216 (12.3)	1,685 (17.0)	1,094 (11.0)
Lung	10,172 (3.8)	5,941 (58.4)	1,178 (11.6)	1,926 (18.9)	1,127 (11.1)
Lymphoma	3,509 (1.3)	2,099 (59.8)	439 (12.5)	592 (16.9)	379 (10.8)
Multiple myeloma	665 (0.3)	400 (60.2)	84 (12.6)	116 (17.4)	65 (9.8)
Nerves	1,875 (0.7)	1,261 (67.4)	196 (10.5)	283 (15.1)	135 (7.2)
Oral cavity	2,865 (1.1)	1,728 (60.4)	391 (13.7)	436 (15.2)	310 (10.8)
Ovarian	2,121 (0.8)	1,304 (61.5)	204 (9.6)	435 (20.5)	178 (8.4)
Pancreatic	1,016 (0.4)	603 (59.4)	102 (10.0)	196 (19.3)	115 (11.3)
Prostate	15,036 (5.6)	8,125 (54.1)	2,194 (14.6)	2,483 (16.5)	2,234 (14.9)
Skin	6,835 (2.5)	4,623 (67.6)	790 (11.6)	778 (11.4)	644 (9.4)
Stomach	34,858 (12.9)	21,023 (60.3)	4,176 (12.0)	5,788 (16.6)	3,871 (11.1)
Testicular	412 (0.2)	268 (65.0)	47 (11.4)	54 (13.1)	43 (10.4)
Thyroid	84,394 (31.3)	56,106 (66.5)	8,843 (10.5)	12,204 (14.5)	7,241 (8.6)
Others	8,648 (3.2)	5,418 (62.7)	1,035 (12.0)	1,321 (15.3)	874 (10.1)

Values are mean ± SD or n (%). Analysis of variance and chi-square tests across groups were all significant ($P < 0.001$). Four groups were constructed on the basis of changes in physical activity status with respect to cancer diagnosis: remained inactive, became inactive, became active, and remained active. For this study, participants were categorized as either being adherent to physical activity, defined as engaging in a minimum of 30 minutes of moderate-intensity activity at least 5 days a week or at least 20 minutes of high-intensity activity at least 3 days a week, or nonadherent to physical activity.

BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; WC = waist circumference.

Individuals who became active had an 11% lower risk for MI (sHR: 0.89; 95% CI: 0.79-0.99) and a 13% lower risk for HF (sHR: 0.87; 95% CI: 0.82-0.93) compared with those who remained inactive. Among those who became inactive, the risk for MI was reduced by 20% (sHR: 0.80; 95% CI: 0.71-0.91), and the risk for HF also decreased (sHR: 0.94; 95% CI: 0.88-1.00) compared with the group that remained

TABLE 2 Association of Change of Physical Activity Status With the Risk for Cardiovascular Disease in Cancer Survivors

		N	No. of Events	Duration, Person-Years	IR per 1,000 Person-Years	Model 1 (Unadjusted): HR (95% CI)	Model 2: sHR (95% CI)	Model 3: sHR (95% CI)
Myocardial infarction	Remained inactive	167,256	1,764	691,420.14	2.55	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Became inactive	30,649	400	126,139.73	2.32	0.91 (0.80-1.03)	0.80 (0.71-0.91)	0.80 (0.71-0.91)
	Became active	44,852	293	183,668.85	2.18	0.86 (0.77-0.96)	0.88 (0.79-0.99)	0.89 (0.79-0.99)
	Remained active	27,186	243	110,100.56	2.21	0.87 (0.76-1.00)	0.79 (0.69-0.91)	0.80 (0.70-0.91)
Heart failure	Remained inactive	167,256	5,965	686,363.11	8.69	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Became inactive	30,649	1,169	124,941.86	9.36	1.07 (1.01-1.14)	0.94 (0.88-1.00)	0.94 (0.88-1.00)
	Became active	44,852	1,337	182,582.35	7.32	0.85 (0.80-0.90)	0.88 (0.83-0.93)	0.87 (0.82-0.93)
	Remained active	27,186	867	109,357.18	7.93	0.92 (0.86-0.99)	0.84 (0.78-0.90)	0.84 (0.78-0.90)
Atrial fibrillation	Remained inactive	167,256	1,528	691,871.90	2.21	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Became inactive	30,649	310	126,142.36	2.46	1.11 (0.98-1.25)	0.95 (0.84-1.07)	0.95 (0.84-1.08)
	Became active	44,852	346	183,802.53	1.88	0.86 (0.76-0.96)	0.90 (0.80-1.01)	0.90 (0.80-1.01)
	Remained active	27,186	262	110,096.85	2.38	1.09 (0.95-1.24)	0.96 (0.84-1.09)	0.97 (0.85-1.11)

Model 2 was adjusted for age, sex, income, smoking, alcohol consumption, obesity, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease. Model 3 was adjusted for the variables used in model 2 and additionally for primary site of cancer.

IR = incidence rate; sHR = subdistribution HR.

inactive. These associations remained consistent after excluding patients who died within 1 year of baseline (Supplemental Table 2).

No significant change in AF risk was observed in any of the physical activity groups. Cumulative incidence curves showing the estimated probability of MI, HF, and AF over time are presented in **Figure 2**.

SUBGROUP ANALYSES AND SECONDARY OUTCOME. We investigated associations on the basis of various cancer types (Supplemental Table 3) and found varied results. Survivors of thyroid, colorectal, bladder, breast, and prostate cancers generally showed a marginally decreased risk for MI, HF, and AF. However, no significant interactions were identified by cancer group (Supplemental Table 4). Similarly, there were no significant interactions by age (Supplemental Table 5).

In our analysis of the secondary outcome, all-cause mortality, we observed that cancer survivors who became active after diagnosis had an 11% lower risk for all-cause mortality (sHR: 0.89; 95% CI: 0.86-0.93), while those who remained active had a 23% lower risk (sHR: 0.77; 95% CI: 0.73-0.82) (Supplemental Table 6). Interestingly, survivors who became inactive after diagnosis still experienced a 9% reduction in all-cause mortality.

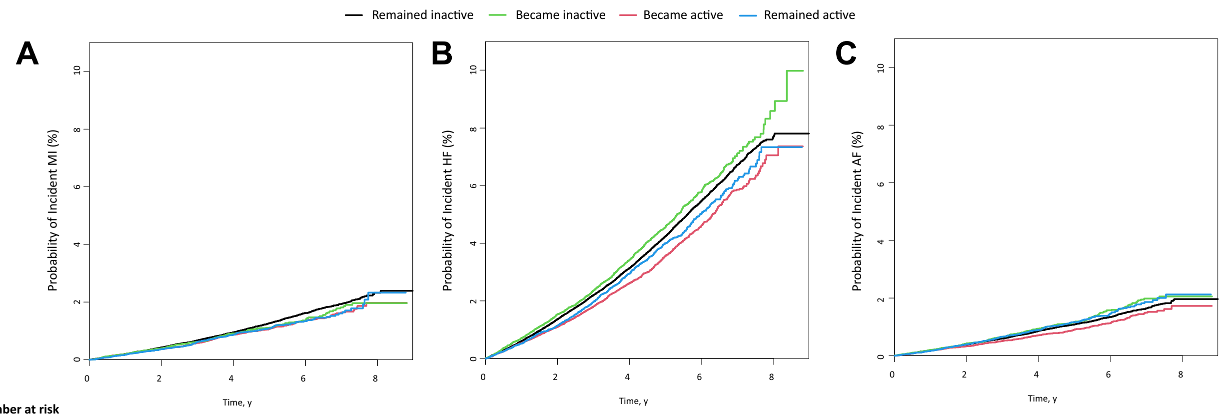
DISCUSSION

To our knowledge, this is the first large-scale cohort study to comprehensively examine the association between changes in physical activity and the risk for Cardiovascular disease among survivors of various cancer types. In this cohort of 269,943 cancer survivors, maintaining physical activity, as well as being active before or after diagnosis, was associated with a reduced risk for MI and HF compared with remaining inactive (**Central Illustration**). Notably, the greatest risk reduction was observed in survivors who engaged in regular physical activity both before and after diagnosis. However, physical activity had no significant effect on the risk for AF.

We observed that physical activity, both before and after diagnosis, was linked to reductions in incident MI and HF events in cancer survivors. This aligns with findings from studies on the general population, in which continuous physical activity is linked to cumulative cardiovascular benefits.[48,49] The risk for MI and HF is particularly significant for cancer survivors, as cardiovascular disease mortality is rising in this group because of improvements in cancer survival and the aging population.[50] Although the cardiotoxic effects of certain cancer treatments may contribute to future MI and HF risk, predicting this risk early on remains challenging. Our findings suggest that engaging in physical activity could serve as a preventive strategy to mitigate these detrimental effects.

Regular physical activity over time improves endothelial function,[51] enhances myocardial contractility,[52] and is associated with lower systemic inflammatory markers,[53,54] reduced blood pressure,[55] and ultimately decreased risk for MI and HF. Moreover, over time, regular physical activity may stabilize atherosclerotic plaques, reducing their likelihood of triggering MI[56] and fostering cardiac remodeling.[57] Additionally, physical activity may modulate the expression of specific genes involved in inflammation and thrombosis, offering further cardioprotection.[58] Although our findings emphasize the protective

FIGURE 2 **Estimated Incidence Probability of Cardiovascular Disease**



Number at risk

A

Remained inactive	167256	163685	140085	113945	88157	60900	37026	15239	1838
Became inactive	30649	29936	25645	20702	15870	11138	6716	2681	302
Became active	44852	43963	37277	30057	23324	16124	9781	3959	462
Remained active	27186	26710	22483	18072	13766	9501	5609	2201	246

B

Remained inactive	167256	163200	139280	112987	87215	60057	36389	14929	1802
Became inactive	30649	29819	25448	20484	15638	10935	6554	2614	289
Became active	44852	43861	37105	29868	23125	15928	9628	3872	454
Remained active	27186	26629	22377	17944	13624	9367	5505	2146	245

C

Remained inactive	167256	163735	140168	114054	88235	60981	37093	15238	1844
Became inactive	30649	29949	25657	20716	15876	11125	6699	2663	294
Became active	44852	43983	37305	30089	23362	16136	9786	3949	460
Remained active	27186	26715	22484	18079	13771	9490	5607	2189	250

This figure presents cumulative incidence curves calculated using Gray's method for competing risks, showing the estimated incidence probability of (A) myocardial infarction (MI), (B) heart failure (HF), and (C) atrial fibrillation (AF) on the basis of changes in physical activity after cancer diagnosis. Numbers at risk are displayed below each curve.

benefits of physical activity on MI and HF risk in cancer survivors, we acknowledge that unmeasured confounders may have influenced these associations, as beneficial changes in cardiovascular risk factors among physically active cancer survivors could not be fully captured.

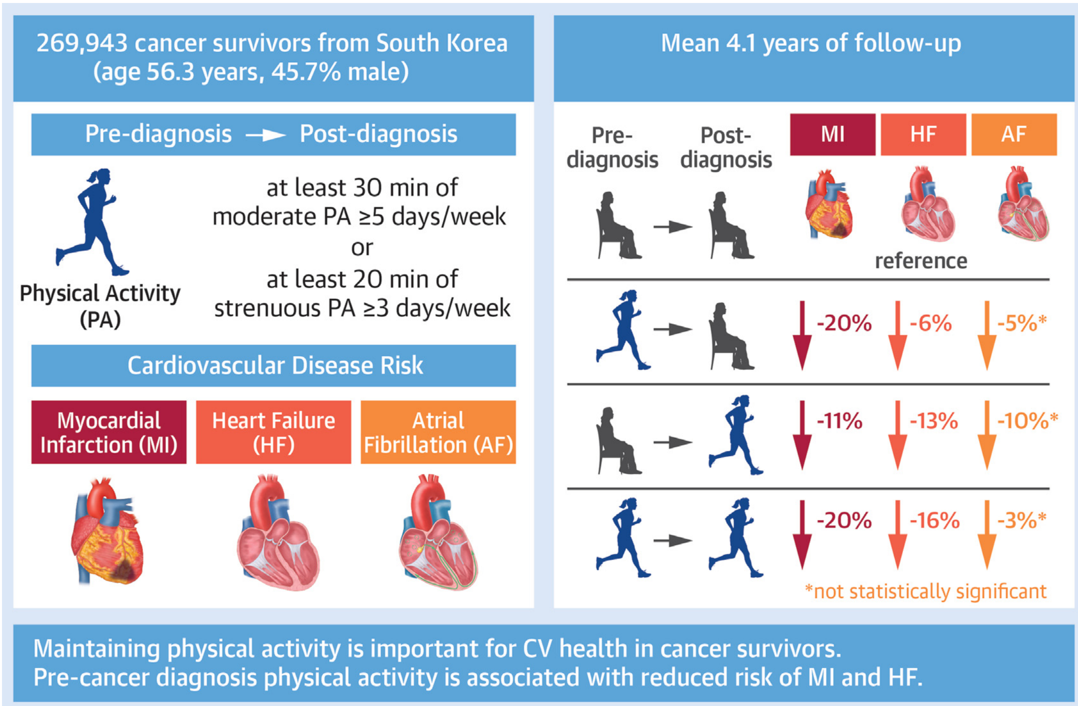
Intriguingly, we observed that even cancer survivors who became inactive after their cancer diagnoses showed 20% and 6% lower risk for MI and HF, respectively. This raises questions about the enduring protective effects of previous physical activity. Cancer survivors are often more likely to become sedentary after their cancer diagnoses,[16] possibly because of the debilitating effects of cancer treatments.[17-19] In our exploratory analysis, both insufficient and sufficient physical activity before diagnosis were associated with a lower risk for MI and HF (Supplemental Table 7). This suggests that physical activity before diagnosis might confer certain enduring cardiovascular benefits after diagnosis.

These findings are consistent with a prospective study of 4,015 breast cancer survivors, which linked exercise before diagnosis to a reduced risk for cardiovascular events.[27] The data indicate that cardiometabolic fitness before diagnosis might reduce the chances of MI and HF after cancer diagnosis, potentially because of improvements in cardiovascular risk factors such as atherosclerosis, hypertension, and DM from regular physical activity.[59] However, this also raises the possibility that unmeasured confounders, such as social determinants of health (eg, built environment, psychosocial stressors), could be contributing to these unexpected findings.[60]

Another unique finding of our study is that the risk reduction among cancer survivors who became active after diagnosis was comparable with those who remained consistently active. This underscores the idea that it is never too late for cancer survivors to gain cardiovascular benefits from physical activity. A previous study suggested an association between increased exercise after diagnosis and a gradual decrease in cardiovascular events, but significant associations for specific outcomes such as MI and HF were not observed, possibly because of the small sample size (n = 2,973).[30] In contrast, our analysis of 269,943 cancer survivors likely provided sufficient power to detect statistical significance. Although the beneficial effects of physical activity on cardiovascular disease risk have been established in findings in the general population,[48,49] these benefits may not extend to sedentary cancer survivors. Our finding that physical activity has cardioprotective effects, even when initiated after a cancer diagnosis, highlights the importance of remaining active after diagnosis.

In our study, we observed variations in how physical activity patterns influenced cardiovascular

CENTRAL ILLUSTRATION Changes in PA and Cardiovascular Disease Risk in Cancer Survivors



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The findings indicate that maintaining physical activity (PA) after a cancer diagnosis is associated with a reduced risk for myocardial infarction (MI) and heart failure (HF), highlighting the cardiovascular (CV) benefits of continued exercise. Furthermore, cancer survivors who were physically active before diagnosis experienced a modest reduction in risk, even if their activity decreased afterward, indicating a residual protective effect of previous PA. AF = atrial fibrillation.

disease risk across different groups of cancer survivors. Although our findings for individual cancer sites and specific cancer types did not reveal significant differences in outcome risks, our comprehensive analysis offers a broader understanding of the relationship between physical activity and cardiovascular disease after cancer diagnosis. Differences in cardiovascular pathophysiological mechanisms may be related to the type of cancer treatments used such as thoracic radiotherapy in lung cancer compared with no radiotherapy in colorectal cancer.

Additionally, our main results likely reflect the cancer types that made up the majority of our study population—thyroid, colorectal, and breast cancer—all of which have higher incidence and survival rates in Korea.[61] These cancers are also linked to obesity, making the marginal decrease in MI and HF particularly plausible given the well-established benefits of physical activity in managing body weight and improving cardiovascular health. Further prospective studies with detailed clinical information on cancer stages and treatments are warranted to confirm these observations.

Our findings emphasize the importance of staying active to lower the risk for cardiovascular disease in cancer survivors. Cancer survivorship programs offer an ideal setting to promote and support healthy behaviors in this population.[62] Increasing evidence confirms that physical activity is safe during cancer treatment and highlights its role in improving physical function and quality of life.[63] Furthermore, patients undergoing chemotherapy or radiation are encouraged to stay as active as possible, with a gradual increase in physical activity recommended after treatment.[21,63]

STUDY LIMITATIONS. First, as this was an observational study, we cannot establish causal relationships. Second, physical activity was assessed through self-reported questionnaires during 2 general health examinations, which may have introduced information bias, potentially resulting in underestimation or overestimation of the true associations. Moreover, cancer survivors with serious health conditions may have been excluded from the study. Future research could benefit from more frequent assessments or the use of pedometers for more accurate tracking.

Third, because of the high incidence and excellent survival rates of thyroid cancer in Korea, about one-third of our cohort consisted of thyroid cancer patients. As thyroid cancer is a highly curable and typically has minimal impact on lifestyle, this may have influenced the overall association, although stratified analysis showed no significant interaction.

Fourth, the lack of data for some cancers (eg, Hodgkin's lymphoma, ovarian cancer, testicular cancer), likely because of the small number of participants or absence of events, highlights the need for larger, cancer-specific studies to draw more definitive conclusions. Fifth, detailed clinical information, such as cancer stage, pathology, and treatment, was not available in this cohort.

Finally, caution should be exercised when generalizing these findings to other races, ethnicities, or health care systems, given potential differences in cancer epidemiology and cardiovascular risk factors.[64,65]

CONCLUSIONS

Our findings indicate that staying physically activity after a cancer diagnosis is linked to a reduced risk for MI and HF, underscoring the cardiovascular benefits of continued exercise for cancer survivors. Even for survivors who were active before diagnosis, a decrease in physical activity afterward was still associated with a modest reduction in risk, indicating a residual protective effect from prior activity. These results highlight the importance of maintaining physical activity for cardiovascular health in cancer survivors and suggest that being physically active before a cancer diagnosis may provide lasting protection against ischemic heart disease and cardiac dysfunction.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Cancer survivors who engage in regular physical activity, whether continuously or only before or after diagnosis, have a reduced risk for MI and HF compared with those who remained inactive prior to and after diagnosis.

TRANSLATIONAL OUTLOOK: Intervention studies are necessary to confirm these findings and further validate the cardioprotective benefits of physical activity in cancer survivors.

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KEY WORDS atrial fibrillation, cancer survivor, cardiovascular disease, heart failure, myocardial infarction, physical activity

APPENDIX For supplemental tables and the figure, please see the online version of this paper.