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ORIGINAL ARTICLE
Cardiac Rehabilitation

Association Between Amount of Physical Activity and Clinical Outcomes After Treatment for Cardiovascular Disease in Cancer Survivors

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Background: The present study aimed to investigate the association between physical activity before the incidence of cardiovascular disease (CVD) and clinical outcomes in cancer survivors.

Methods and Results: We analyzed 904 cancer survivors (median age [interquartile range] 75 [68–80] years; 297 [32.9%] patients were female) who required hospitalization for treatment of CVD. The amount of physical activity 1 month before the admission was assessed using the 3-question (3Q) assessment tool, and categorized as minimal, low, adequate, and high according to physical activity level. The primary outcome was the composite events of all-cause death and/or rehospitalization for CVD up to 1 year after discharge. The total amount of physical activity was identified in 544 (60.2%) patients in the minimal group, 95 (10.5%) in the low group, 253 (28.0%) in the adequate group, and 12 (1.3%) in the high group. A total of 686 (75.9%) patients completed follow up, with 252 (27.9%) composite events occurring. Even after adjustment for various confounders, higher physical activity was significantly associated with a lower composite event rate (adjusted hazard ratio [95% confidence interval] 0.859 [0.833–0.900]).

Conclusions: High physical activity in cancer survivors was associated with a lower composite event rate after treatment for CVD. Assessment of prehospital physical activity using the 3Q score may be useful in their risk stratification.

Key Words: Cancer survivor; Cardio-oncology; Cardiovascular disease; Clinical outcome; Physical activity

The number of patients suffering from cancer is increasing worldwide and has become a serious public health concern.[1,2] Meanwhile, cancer treatment has made remarkable progress, and survival rates for cancer survivors are improving.[1] Although deaths due to primary cancer are decreasing, an increasing number of patients develop cardiovascular disease (CVD), which is linked to poor outcomes. Among cancer survivors, death from CVD rises as time passes from the diagnosis of the primary cancer and overlap for some typical cancers.[3] Several studies have previously reported that people with cancer have a higher risk of incident CVD.[4–6] To promote a good prognosis, previous studies have suggested the correction of lifestyle behaviors, including maintaining a high level of physical activity.[7–9] It has been reported that a high level of physical activity in cancer patients is beneficial in the prevention of CVD.[10,11] Thus, there are various benefits for cancer survivors who maintain physical activity levels. Although it is likely that maintaining high levels of physical activity is also associated with a favorable course after the development of any disease, including CVD, there is no knowledge of whether physical activity levels are even related to the outcomes after the incidence of CVD. We hypothesize that cancer survivors who maintain high levels of physical activity would have better outcomes after receving CVD treatment. Therefore, the purpose of the

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Table 1. Component of the 3Q Score Assessment

Three-question assessment	
1. How many times a week do you usually do 20 min or more of vigorous-intensity physical activity that makes you sweat or puff and pant (e.g., heavy lifting, digging, jogging, aerobics, or fast cycling)?	• ≥3 times a week • 1–2 times a week • None
2. How many times a week do you usually do 30 min or more walking (e.g., walking from place to place for exercise, leisure or recreation)?	• ≥5 times a week • 3–4 times a week • 1–2 times week • None
3. How many times a week do you usually do 30 min or more of moderate-intensity physical activity that increases your heart rate or makes you breathe harder than normal (e.g., carrying light loads, cycling at a regular pace, or playing doubles tennis)?	• ≥5 times a week • 3–4 times a week • 1–2 times week • None

3Q, 3-question.

Table 2. Classification of Physical Activity Levels Based on Brief Physical Activity Assessments

Category	Criteria†,‡
Walking and moderate activity	
0	0 sessions/week walking and 0 sessions/week moderate activity
1–2	1–2 sessions/week walking or 1–2 sessions/week moderate activity
3–4	3–4 sessions/week walking, or 3–4 sessions/week moderate activity, or 1–2 sessions/week walking plus 1–2 sessions/week
≥5	≥5 sessions/week walking, or ≥5 sessions/week moderate activity, or 3–4 sessions/week walking and ≥1–2 sessions/week walking and 3–4 se z ssions/week moderate activity
Vigorous activity	
0	0 sessions/week vigorous activity
1–2	1–2 sessions/week vigorous activity
≥3	≥3 sessions/week vigorous activity
Total activity	
0–2 (minimal)	0 sessions/week vigorous activity plus ≤1–2 sessions/week walking or moderate activity
3–4 (low)	1–2 sessions/week vigorous activity plus ≤1–2 sessions/week walking or moderate activity, or 0 sessions/week vigorous activity plus 3–4 sessions/week walking or moderate activity
5–7 (adequate)	≥3 sessions/week vigorous activity, or ≥5 sessions/week walking or moderate activity, or 1–2 sessions/week vigorous activity plus 3–4 sessions/week walking or moderate activity
≥8	≥3 sessions/week vigorous activity plus ≥3–4 sessions/week walking or moderate activity

†For calculation of number of sessions, the midpoint in the response category was used (e.g., 1.5 for a response of 1–2 sessions/week). ‡Total activity sessions/week = moderate sessions / week + (2 × vigorous sessions / week).

present study was to investigate the association between physical activity before the incidence of CVD, and clinical outcomes in cancer survivors who required treatment for CVD.

Methods

Study Population

This observational study included 1,206 cancer survivors aged ≥18 years who required hospitalization for treatment of CVD between January 2017 and December 2021. Those eligible included emergency hospitalization cases due to acute coronary syndromes and acute decompensated heart failure, as well as patients undergoing cardiac surgery, either emergency or planned. A cancer survivor was defined as one who had ever received a diagnosis of cancer, with or without any treatment for cancer. The exclusion criteria were as follows: need for assistance with activities of daily living before admission for CVD treatment; missing physical activity assessment; or in-hospital death. The study was conducted with the approval of our institute's clinical research review board (KMEO B22-143), and complied with the Declaration of Helsinki. All measures were evaluated in routine clinical practice. Information about the research was made public and patients could opt out, and therefore informed consent was waived. Patients could also withdraw from the study at any time by indicating their intention.

Measures

Information on patient characteristics, including age, sex, body mass index (BMI), blood pressure, heart rate, cause of admission, primary cancer,[12] comorbidities (hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, atrial fibrillation, and prior CVD), smoking status, left ventricular ejection fraction (LVEF), laboratory data (including hemoglobin, albumin, estimated glomerular filtration rate [eGFR], B-type natriuretic peptide [BNP], and C-reactive protein [CRP]), and medications (including angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], β-blocker, mineralocorticoid

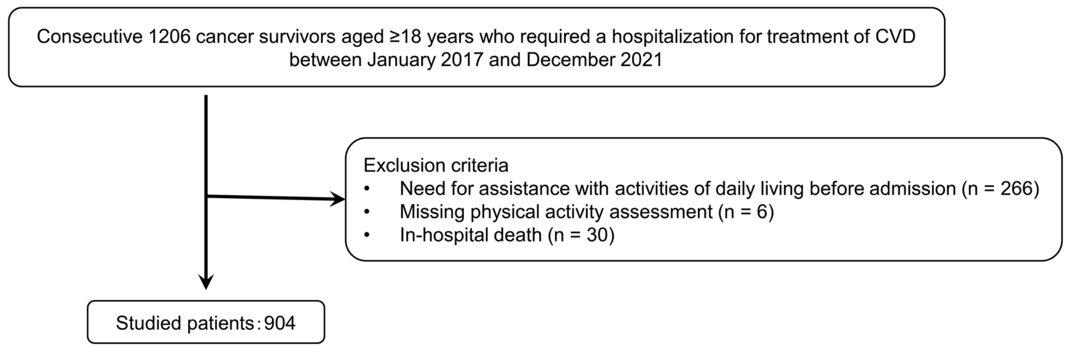

Figure 1. Flowchart of patient selection. CVD, cardiovascular disease.

receptor antagonist [MRA], and loop diuretics) were obtained from medical records at hospital discharge.

We also measured short physical performance battery (SPPB) at hospital discharge.[13] This is a comprehensive lower extremity function assessment battery consisting of a balance test, gait speed, and 5 chair-standing times, each scored from 0 to 4 points, with a total score ranging from 0 to 12 points. SPPB is a marker that has recently been focused on as a prognostic predictor and outcome in the region of CVD, such as heart failure.[14] In addition, we assessed frailty status using the Japanese version of the Cardiovascular Health Study (J-CHS) criteria[15] at discharge. The J-CHS criteria were developed by modifying the original CHS phenotype,[16] and consisted of 5 components (walking speed, handgrip strength, shrinking, exhaustion, and physical inactivity). The J-CHS scored 1 point for meeting the criteria for each item, with a range of 1–5 points, and defined as frail when ≥3 points were scored.

Physical activity before admission was determined by interview using the 3-question (3Q) assessment tool during hospitalization.[17] The 3Q assessment measures the frequency of vigorous-intensity exercise of ≥20 min per week, the frequency of walking of ≥30 min per week, and moderate-intensity physical activity of ≥30 min per week (**Table 1**). The amount of physical activity per week 1 month before admission was assessed, and classified as minimal, low, adequate, and high (**Table 2**).

The primary outcome was the composite events of all-cause death and/or rehospitalization for CVD events up to 1 year after discharge.

Statistical Analysis

Categorical variables are expressed as numbers (percentages) and continuous variables are expressed as medians (interquartile range [IQR]). We compared the patients' characteristics using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables in each group regarding physical activity levels.

The association between physical activity and composite events was examined using the Kaplan-Meier survival curves followed by log-rank tests for each physical activity level. In addition, we performed the multivariate Cox proportional hazard models adjusted for age, sex, BMI, systolic blood pressure, heart rate, cause of admission, comorbidities (hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, atrial fibrillation, and prior CVD), smoking status, LVEF, laboratory data (hemoglobin, albumin, eGFR, BNP, CRP), medications (ACEI or ARB, β-blocker, MRA, and loop diuretics), SPPB score, and frailty status.

Sensitivity analysis was performed using a Cox proportional hazard model with the same adjustment variables after excluding patients who had an event within 1 month. In addition, subgroup analyses were performed to verify the consistency of the results using the following criteria: age (≥65 years or <65 years), sex, cause of admission (acute decompensated heart failure [ADHF] or not), whether they had a history of CVD, and whether they were frail or not at the time of discharge.

Multiple imputation was used to address missing covariate data for the construction of multivariable Cox hazard models. Twenty datasets were generated using a chained-equations procedure. Parameter estimates were derived for each dataset and subsequently aggregated to yield an integrated result.

Statistical significance was defined as a 2-tailed P value of <0.05, indicating statistical significance. In subgroup analyses, a P value of <0.10 was considered statistically significant. Statistical analyses were performed using Stata version 15.1 (Stata Corp., College Station, TX, USA) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

After excluding patients who required assistance with activities of daily living (n=266), were missing a physical activity assessment (n=6), or who died in hospital (n=30), we analyzed 904 patients. A flowchart of patient selection is shown in **Figure 1**. Patient characteristics are shown in **Table 3**. The median age was 75 (IQR 68–80) years, and 297 (32.9%) patients were females. The most common cause of admission was heart failure in 337 (37.3%) patients, followed by cardiac surgery in 276 (30.5%) patients, and acute coronary syndrome in 98 (10.5%) patients. The total amount of physical activity was identified in 544 (60.2%) patients in the minimal group, 95 (10.5%) in the low group, 253 (28.0%) in the adequate group, and 12 (1.3%) in the high group.

The low physical group had significantly more female patients, higher rates of ADHF as the reason for hospitalization, more prior CVD, more often lung cancer as the

Table 3. Patient Characteristics

	Missing data	Overall (n=904)	Physical activity status				P value
			Minimal (n=544)	Low (n=95)	Adequate (n =253)	High (n=12)	
Age (years)	6	75 [68–80]	76 [68–81]	74 [69–79]	74 [67–80]	70 [54–77]	0.113
Female	0	297 (32.9)	194 (35.7)	34 (35.8)	64 (25.3)	5 (41.7)	0.026
BMI (kg/m²)	8	21.5 [19.3–23.8]	21.5 [19.1–23.8]	21.7 [20.1–23.9]	21.3 [19.3–23.8]	23.2 [20.8–24.3]	0.206
Cause of admission	0						
ACS		98 (10.8)	54 (9.9)	9 (9.5)	31 (12.3)	4 (33.3)	0.059
ADHF		337 (37.3)	233 (42.8)	24 (25.3)	77 (30.4)	3 (25.0)	<0.001
Surgery		276 (30.5)	155 (28.5)	30 (31.6)	88 (34.8)	3 (25.0)	0.334
SBP (mmHg)	2	116 [102–130]	115 [100–130]	119 [108–132]	116 [106–131]	124 [104–133]	0.082
DBP (mmHg)	2	67 [58–77]	66 [58–77]	70 [59–78]	67 [60–76]	71 [63–79]	0.194
HR (beats/min)	115	75 [65–87]	76 [66–89]	75 [66–84]	74 [62–85]	74 [57–90]	0.111
LVEF (%)	121	57 [41–67]	55 [40–66]	54 [40–64]	56 [40–66]	52 [26–70]	0.929
Primary cancer	0						
Lung		89 (9.8)	70 (12.9)	7 (7.4)	12 (4.7)	0 (0.0)	0.031
Breast		80 (8.8)	38 (7.0)	9 (9.5)	32 (12.6)	1 (8.3)	0.481
Stomach		92 (10.2)	58 (10.7)	9 (9.5)	24 (9.5)	1 (8.3)	0.801
Liver		58 (6.4)	41 (7.5)	6 (6.3)	11 (4.3)	0 (0.0)	0.089
Gallbladder/bile duct		14 (1.5)	8 (1.5)	2 (2.1)	4 (1.6)	0 (0.0)	0.799
Pancreas		16 (1.8)	9 (1.7)	4 (4.2)	3 (1.2)	0 (0.0)	0.694
Colon		117 (12.9)	64 (11.8)	14 (14.7)	37 (14.6)	2 (16.7)	0.556
Rectum		22 (2.4)	12 (2.2)	4 (4.2)	6 (2.4)	0 (0.0)	0.704
Kidney		50 (5.5)	32 (5.9)	6 (6.3)	11 (4.3)	1 (8.3)	0.643
Bladder		30 (3.3)	16 (2.9)	6 (6.3)	7 (2.8)	1 (8.3)	0.701
Uterus		9 (1.0)	5 (0.9)	2 (2.1)	2 (0.8)	0 (0.0)	0.904
Prostate		125 (13.8)	71 (13.1)	10 (10.5)	42 (16.6)	2 (16.7)	0.855
Skin		9 (1.0)	3 (0.6)	2 (2.1)	3 (1.2)	1 (8.3)	0.886
Lymphoma/ hematopoietic organ		74 (8.2)	51 (9.4)	7 (7.4)	15 (5.9)	1 (8.3)	0.101
Other		119 (13.2)	66 (12.1)	7 (7.4)	44 (17.4)	2 (16.7)	0.555
Comorbidities	0						
Hypertension		514 (56.9)	306 (56.3)	55 (57.9)	146 (57.7)	7 (58.3)	0.976
Dyslipidemia		278 (30.8)	161 (29.6)	25 (26.3)	87 (34.4)	5 (41.7)	0.326
Diabetes		290 (32.1)	190 (34.9)	23 (24.2)	72 (28.5)	5 (41.7)	0.08
COPD		57 (6.3)	40 (7.4)	4 (4.2)	13 (5.1)	0 (0.0)	0.375
AF		256 (28.3)	166 (30.5)	27 (28.4)	62 (24.5)	1 (8.3)	0.141
Prior CVD		472 (52.2)	308 (56.6)	47 (4.9)	116 (45.8)	1 (8.3)	<0.001
Current smoker	0	146 (16.3)	93 (17.1)	8 (8.4)	43 (17.0)	2 (16.7)	
Laboratory data							
Hemoglobin (g/dL)	2	11.3 [9.9–12.7]	11.2 [9.8–12.6]	11.1 [9.8–12.6]	11.6 [10.2–13.1]	12.7 [11.8–14.1]	0.003
Albumin (g/dL)	13	3.4 [3.0–3.8]	3.4 [3.0–3.8]	3.4 [2.9–3.8]	3.5 [3.0–3.9]	3.4 [3.2–3.7]	0.127
eGFR (mL/min/1.73 m²)	3	50 [34–64]	46 [32–63]	49 [32–61]	56 [40–67]	65 [54–71]	<0.001
Medication	0						
ACEI/ARB		492 (54.4)	297 (54.6)	50 (52.6)	138 (54.5)	7 (58.3)	0.977
β-blocker		536 (59.3)	324 (59.6)	61 (64.2)	147 (58.1)	4 (33.3)	0.215
Diuretic		510 (56.4)	323 (59.4)	52 (54.7)	129 (51.0)	6 (50.0)	0.153
MRA		219 (24.2)	136 (25.0)	26 (27.4)	53 (20.9)	4 (33.3)	0.438
SPPB score	206	12 [10–12]	11 [9–12]	12 [10–12]	12 [11–12]	12 [12–12]	<0.001
Frailty	250	308 (34.1)	201 (36.9)	45 (47.4)	61 (24.1)	1 (8.3)	<0.001

Data are presented as n (%), or median [IQR]. Patient characteristics were compared using the chi-square test for categorical valuables and the Kruskal-Wallis test for continuous variables in each group regarding physical activity levels. ACS, acute coronary syndrome; ACEI, angiotensin-converting enzyme inhibition; ADHF, acute decompensated heart failure; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SPPB, short physical performance battery.

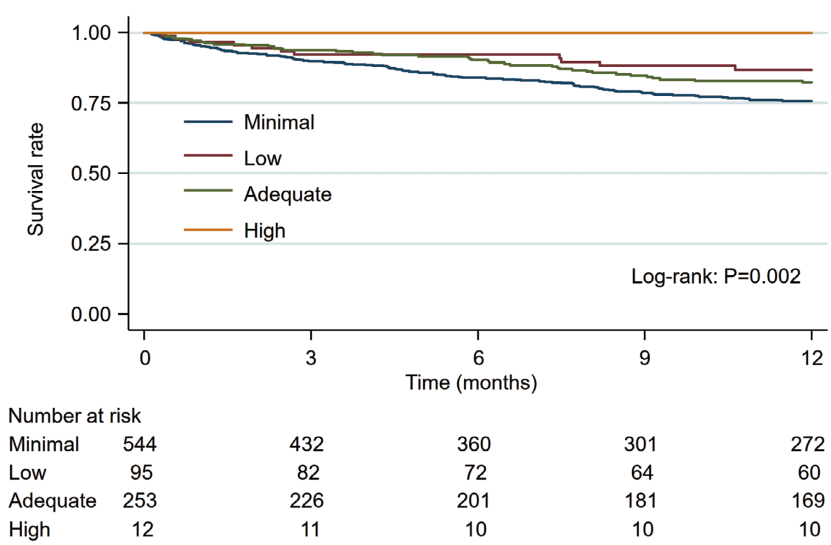

Figure 2. Kapan-Meier survival curve for composite events according to physical activity levels. A higher physical activity was associated with a lower rate of composite events.

Table 4. Results of the Cox Proportional Hazard Model

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Physical activity	0.693 (0.672–0.714)	<0.001	0.859 (0.833–0.900)	<0.001

Multivariate cox proportional hazard model was adjusted for age, sex, body mass index, systolic blood pressure, heart rate, cause of admission (hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, atrial fibrillation, and prior cardiovascular disease), smoking status, left ventricular ejection fraction, laboratory data (hemoglobin, albumin, and estimated glomerular filtration rate), medications (angiotensin-converting enzyme inhibition or angiotensin receptor blocker, β-blocker, mineralocorticoid receptor antagonist, and loop diuretics), short physical performance battery score, and frailty status. CI, confidence interval; HR, hazard ratio.

primary cancer, lower hemoglobin and eGFR, lower SPPB score, and higher rates of frailty.

A total of 686 (75.9%) patients completed follow up to 1 year after discharge, with 252 (27.9%) composite events occurring during the period. The results of the Kaplan-Meier survival analysis are shown in **Figure 2**, and the results of the Cox proportional hazard model are shown in **Table 4**. Even after adjustment for confounders, higher physical activity was significantly associated with a lower composite event rate (P<0.001). A sensitivity analysis excluding the 33 cases that had an event within 1 month after discharge yielded consistent results (adjusted hazard ratio 0.833; 95% confidence interval 0.798–0.880). In addition, the results of the subgroup analysis are shown in the **Figure 3**. Although there were interactions in several subgroups, higher physical activity was consistently associated with a lower rate of composite events (**Figure 3**).

Discussion

We examined the association between pre-admission physical activity and prognosis in cancer survivors who required treatment for CVD. Our main findings were as follows: (1) a higher level of physical activity before admission was associated with a lower composite event rate after CVD treatment; (2) cancer survivors were more likely to be inactive; and (3) higher physical activity was consistently associated with better outcomes, even with interactions in several subgroups. These findings suggest that the amount of physical activity assessed using the 3Q score is a useful predictor of outcomes. We believe these results support our hypothesis that a higher physical activity level among cancer survivors is associated with better outcomes after CVD treatment. The 3Q score is a valid, safe, and easy-to-use measure of physical activity that can be easily adapted to clinical practice. Therefore, the results of this study are likely to be helpful and widely used in daily clinical practice.

In cancer survivors, higher physical activity has been reported to be associated with several favorable outcomes in previous studies. Among breast cancer patients, Aune et al. showed that their higher physical activity was associated with better health-related quality of life in a meta-analysis,[18] and Fortner et al. reported that higher physical activity reduced all-cause mortality.[19] In addition, López-Bueno et al. found that higher Life's Essential 8 scores, which are recommended by the American Heart Association and include physical activity as one of the components, were associated with lower all-cause mortality and suggested a dose-response relationship.[7] In addition, high levels of physical activity in cancer survivors have been reported to be associated with lower incidence of CVD.[10,11] Thus, the significance of maintaining a high physical activity level in cancer survivors has been highlighted in a number of previous studies. Accordingly, a multidisciplinary discipline of cardio-oncology has been developed to appropriately

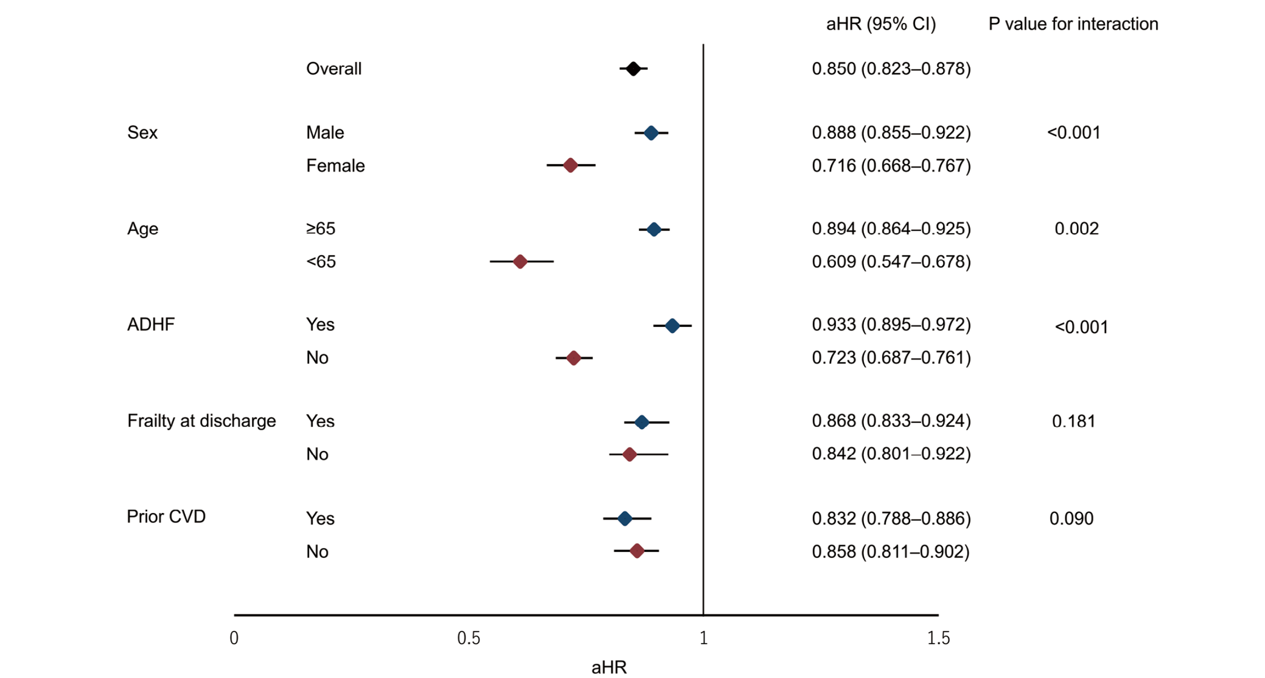

Figure 3. Results of the subgroup analysis for the Cox proportional hazard model. High physical activity was consistently associated with a lower rate of composite events. ADHF, acute decompensated heart failure; CVD, cardiovascular disease.

manage cancer and CVD.[20,21] However, there are no reports examining the association between physical activity and prognosis after the treatment for CVD in cancer survivors, and this is the first report. The finding that physical activity is independently associated with outcomes in cancer survivors who required treatment for CVD, even after adjusting for various confounders, may provide a new recommendation to encourage cancer survivors to maintain a high levels of physical activity.

Our results also showed that the amount of physical activity was low among cancer survivors. This could be due to cancer-related fatigue or because they were discouraged from going out to prevent complications such as infections.[22] Despite the large amount of missing data, 34.1% of patients had frailty at the time of discharge. Reduced physical activity is a component of the definition of frailty.[16] The prevalence of frailty has been reported to be approximately 10–50% in cancer survivors[23–27] and 20–60% in patients with CVD.[28–33] In this study, 52.2% of patients had a history of CVD, and it is possible that some patients had frailty before admission, resulting in low physical activity. However, a subgroup analysis of patients with or without frailty at hospital discharge, which is associated with an impact on the prognosis of patients with CVD, showed no interaction, and consistently high physical activity was associated with a low composite event rate. Therefore, it is important to maintain physical activity regardless of the presence or absence of frailty.

As this is an observational study, the mechanisms are unclear. However, it has been reported that maintaining a high level of physical activity is associated with a reduction in coronary risk factors and atherosclerosis, preservation of physical function including exercise tolerance, and prevention of frailty.[34–38] These are all comorbidities, including hypertension, associated with a prognosis of CVD, and their improvement may be associated with improved prognosis. We also reported that a history of cancer combined with low physical function was associated with higher mortality in patients with CVD,[39] and it may be that physical activity levels are also important for maintaining physical function. Furthermore, exercise therapy such as aerobic exercise has been reported to have an antitumor effect,[40] so high physical activity may have contributed to a better course of primary cancer. In addition, Feeney et al. suggested that higher physical activity before surgery for esophageal cancer decreases postoperative pulmonary complications.[41] As this study included patients who had undergone surgery, it is possible that high physical activity levels also contributed to the prevention of postoperative complications. Such benefits of maintaining high physical activity may be associated with a better course of both cancer and CVD, and with improved outcomes. Further studies, including basic research, are needed to clarify the mechanisms.

The strength of this study is that physical activity assessed using the 3Q score, a method that can be used for evaluation after hospitalization, was shown to be useful in predicting composite events in cancer survivors who required treatment for CVD. The method is extremely simple, inexpensive, validated, and easy to use in daily clinical practice. Although it is not feasible to measure physical activity in all cancer survivors using an accelerometer, the 3Q score can be assessed by interview, making it highly applicable and useful information for risk stratification after the onset of CVD.

Study Limitations

The present study has several limitations. First, this is a single-center observational study using the Kitasato cohort and selection bias is a concern. Although the Kitasato cohort is a dataset that has been used for validation as well as original research in several studies,[42–47] we cannot exclude the possibility that the facility-specific treatment environment or patient population may have influenced the results. In addition, the number of valuables that could be used was limited, and confounders may have been insufficient in the multivariate analysis. There were also many missing values, although multiple imputation was performed. Further studies, such as prospective observational studies and multicenter registry studies, are required in the future. Second, the study included patients who were diagnosed with cancer with or without treatment, and did not consider treatment history or duration since diagnosis of the cancer. Depending on the stage of the cancer, metastases, and treatment, it is likely that walking was difficult due to a variety of symptoms, including fatigue, or that walking may have been restricted to prevent infection. These may have affected outcomes as well as the amount of physical activity. Third, the method used to assess physical activity was a questionnaire, and although the usefulness of the 3Q score has been reported,[17,48] it is less objective than instrumental methods of measuring physical activity. Given the recent development of smartphones and wearable devices such as smartwatches, it may be desirable to use electronic devices to assess physical activity.

Conclusions

The large number of cancer survivors who developed CVD had low levels of physical activity prior to hospitalization. Meanwhile, maintaining high levels of physical activity among cancer survivors was associated with favorable outcomes after the onset of CVD. If cancer survivors require treatment for CVD, assessment of prehospital physical activity using the 3Q score may be beneficial in risk stratification after discharge from hospital.

Acknowledgments

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Disclosures

K.K., J.A. are members of *Circulation Reports*' Editorial Team. All authors declare that there is no conflict of interest.

IRB Information

The present study was approved by our institute's clinical research review board (KMEO B22-143). Written informed consent was waived because all measures were evaluated in routine clinical practice. Information about the study was made public and patients could opt out, and could also withdraw from the study at any time by notifying us.

Data Availability

Individual deidentified participant data will not be shared.

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