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RAPID COMMUNICATIONS

Changes in physical activity and incident cardiovascular events in cancer survivors

Hyeok-Hee Lee [1,2,3†], Hokyou Lee [1,2,3†], Deepak L. Bhatt [4], Danbee Kang [5,6], Jong-Chan Youn [7], Dong Wook Shin [5,8,9], Juhee Cho [5,6,9,10], and Hyeon Chang Kim [1,2,3*]

[1]Department of Preventive Medicine, Yonsei University College of Medicine,Seoul, Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [3]Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Korea; [4]Mount Sinai Heart, Icahn School of Medicine at Mount Sinai Health System, NewYork, NY, USA; [5]Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea; [6]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University, Seoul, Korea; [7]Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, Catholic Research Institute for Intractable Cardiovascular Disease, College of Medicine, The Catholic University of Korea, Seoul, Korea; [8]Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [9]Department of Digital Health, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea; and [10]Departments of Epidemiology and Medicine, and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA

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Introduction

In the rapidly growing population of cancer survivors worldwide, cardiovascular disease (CVD) is the leading cause of non-cancer mortality.[1] Promoting a healthy lifestyle is crucial in this population. Yet, little is known regarding the association of physical activity (PA), particularly post-diagnosis changes, with CVD among cancer survivors.

Methods

We utilized a nationwide, single-provider database of the Korean National Health Insurance Service, which covers the entire Korean population, to identify 515 261 adults aged ≥20 newly diagnosed with cancer [having International Classification of Disease, 10th revision (ICD-10) codes C00–C97 and critical condition code V193] in 2011–13.[2] Among 371 184 (72.0%) ≥3-year survivors, 162 543 underwent health examinations each within 2 years before and within 3 years after a cancer diagnosis. We excluded 1228 participants with missing data on covariables, 4294 who had myocardial infarction or stroke before the 3-year survival date (index date; *Figure 1A*), and 6588 with <2 years of follow-up, yielding a final cohort of 150 433 participants. This study was approved by the Institutional Review Board of Severance Hospital (Y-2021-0052) with a waiver of informed consent.

Physical activity was assessed using a modified International PA Questionnaire in each health examination.[3] For light, moderate, and vigorous PA, we calculated the weekly minimum energy expenditure by multiplying frequency (days/week) by session duration (30 min for light and moderate, 20 min for vigorous), and weighting by standardized energy costs [2.9, 4.0, and 7.0 metabolic equivalent of task (MET), respectively].[4,5] The total weekly energy expenditure was estimated by summing these values across all PA intensities.

Pre-diagnosis PA was assessed during the last health examination within 2 years before cancer; post-diagnosis PA was assessed during the last health examination within 3 years after cancer (*Figure 1A*). Using a 600 MET-min/week cut-off, equivalent to the 2022 American Cancer Society guideline's minimum PA recommendation,[6] we categorized pre- and post-diagnosis PAs into 0 (inactive), 1–599 (active but not meeting guideline recommendation), and ≥600 MET-min/week (active and meeting guideline recommendation). We determined post-diagnosis PA change by comparing pre- and post-diagnosis PAs, both categorically and continuously, with the continuous comparison being performed for exploratory purposes.

The primary outcome was a CVD event, defined as a composite of first hospitalization for myocardial infarction (ICD-10: I21–I23), first hospitalization for stroke (ICD-10: I60–I64), or cardiovascular death (ICD-10: I00–I99) by 31 December 2019. The positive predictive values for myocardial infarction and stroke in the database were 92.0% and 90.5%, respectively.[7] Hazard ratios (HRs) for the CVD event were calculated using cause-specific Cox models, censoring participants at non-cardiovascular death.[8] SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.3 (R Foundation, Vienna, Austria) were used for analyses.

Results

The median age of the 150 433 participants was 59 years, and 54.9% were women. The most frequent type of cancer was endocrine

* Corresponding author. Tel: +82 2 2228 1873, Fax: +82 2 392 8133, Email: hckim@yuhs.ac
† The first two authors contributed equally as co-first authors.

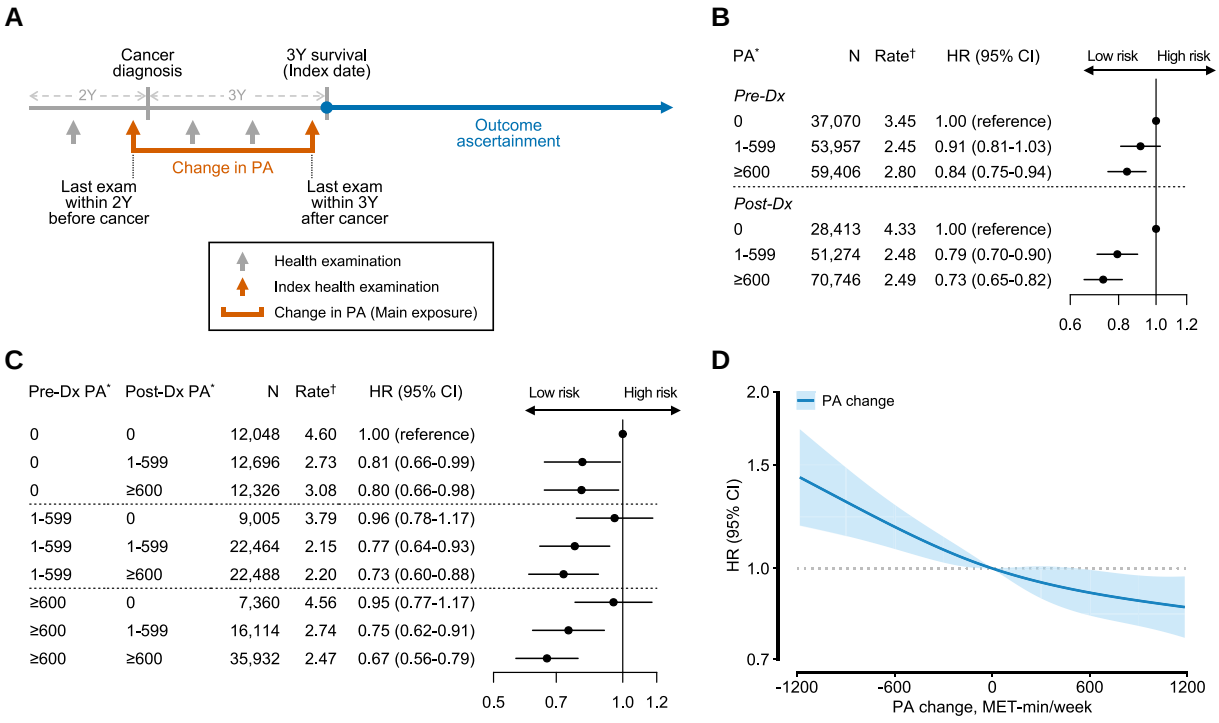

Figure 1 Post-diagnosis change in physical activity and incident cardiovascular disease among cancer survivors. (*A*) Timeline for physical activity assessment and outcome ascertainment. (*B*) Cardiovascular disease risk according to pre- and post-diagnosis physical activity categories. (*C*) Cardiovascular disease risk according to changes in physical activity categories. (*D*) Cardiovascular disease risk according to continuous changes in physical activity. In *B* and *C*, hazard ratios were adjusted for age, sex, household income quartile, residential area, tobacco smoking, alcohol consumption, body mass index (<18.5, 18.5–22.9, 23–24.9, and ≥25 kg/m^2), systolic blood pressure, fasting glucose, total cholesterol, blood pressure–lowering drug use, glucose-lowering drug use, lipid-lowering drug use, Charlson comorbidity index (0, 1, 2, and ≥3), cancer type, presence of distant metastasis at the initial diagnosis, year of cancer diagnosis, and time-varying chemotherapy regimen and external beam radiotherapy use. In *D*, the solid line and shade denote hazard ratio and 95% confidence interval, respectively; hazard ratios were adjusted for all the aforementioned covariables as well as pre-diagnosis physical activity. *Measured in MET-min/week. †Incidence rate per 1000 person-years. CI, confidence interval; CVD, cardiovascular disease; Dx, diagnosis; HR, hazard ratio; MET, metabolic equivalent of task; N, number; PA, physical activity; Y, year.

(32.5%), followed by upper gastrointestinal (15.0%), lower gastrointestinal (13.9%), and breast (9.9%).

Over a median follow-up of 4.4 years from the index date, 1874 new CVD events occurred (incidence rate, 2.84 per 1000 person-years). Both pre- and post-diagnosis PAs were inversely associated with CVD risk, with the association being stronger for post-diagnosis PA (*Figure 1B*). Each increasing category of post-diagnosis PA was associated with a lower CVD risk in every pre-diagnosis PA category (*Figure 1C*). Specifically, participants who increased their PA from 0 MET-min/week (inactive) to 1–599 MET-min/week (not meeting guideline) or ≥600 MET-min/week (meeting guideline) showed a significantly lower CVD risk than those who remained physically inactive [HR (95% confidence interval, CI): 0.81 (0.66–0.99) and 0.80 (0.66–0.98), respectively]. In contrast, participants who decreased their PA from 1–599 or ≥600 to 0 MET-min/week showed a significantly higher CVD risk than those who maintained their PA levels [HR (95% CI): 1.24 (1.00–1.53) and 1.43 (1.18–1.73), respectively]. In an exploratory continuous analysis, an inverse dose–response relationship was observed between PA change and CVD risk (*Figure 1D*).

The findings were generally consistent for all individual components of the primary outcome and across subgroups defined by age (<65 vs. ≥65 years), sex, overweight/obesity, hypertension, diabetes, and comorbidity (Charlson comorbidity index 0–1 vs. ≥2). When the study participants were stratified according to their first primary cancers,[2,9] the results were largely similar among lung, breast, male genital, endocrine, haematologic, urinary tract, and upper gastrointestinal cancer survivors.

In sensitivity analyses, the findings were in broad agreement when we: (i) excluded participants who had heart failure or atrial fibrillation before the index date; (ii) restricted the study participants to those with non-metastatic disease at the initial diagnosis; (iii) repeated the analyses using tertiles to define pre- and post-diagnosis PA groups; (iv) assigned 3.0, 4.5, and 7.5 METs to light-, moderate-, and vigorous-intensity PAs, respectively; and (v) used changes in weekly frequency of either moderate- or vigorous-intensity PA as the main exposure.

Discussion

Our study expands upon findings from the general population and demonstrates that breaking away from physical inactivity after a cancer diagnosis is associated with a reduced CVD risk, whether or not post-diagnosis PA levels meet guideline recommendations.[10] Because high-volume exercise may be limited or even unsafe for many survivors

due to cancer-related physical/psychological impairments, integrated approaches, including personalized exercise goals and management of disabling symptoms, are needed to promote exercise participation and ultimately deliver the greatest health benefits to cancer survivors.

This study offers three distinctive contributions to the area. First, our exploration of post-diagnosis PA change and CVD risk informs targeted policies and interventions for cancer survivors. Second, our study raises concerns regarding post-diagnosis physical inactivity in relation to CVD risk. Last, our finding that moving away from physical inactivity is associated with a lower CVD risk, regardless of meeting PA guideline post-diagnosis, justifies the individualization of exercise goals for cancer survivors.

The study limitations include: (i) the inability to establish causality between PA change and CVD; (ii) use of a self-reported questionnaire for PA assessment; (iii) exclusion of heart failure from the primary outcome; and (iv) limited generalizability, particularly to shorter term survivors or those who did not undergo health examinations and were consequently excluded from the study.

Conclusions

An increase in PA after a cancer diagnosis is associated with a reduced CVD risk, whereas a decrease in PA is associated with a higher CVD risk.

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Declarations

Disclosure of Interest

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Data Availability

Because of the sensitive nature of the database, requests to access the data from qualified researchers may be sent to the National Health Insurance Service at https://nhiss.nhis.or.kr.

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Ethical Approval

This study complied with the Declaration of Helsinki; the study protocol was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (Y-2021-0052).

Pre-registered Clinical Trial Number

Not applicable (this study is not a clinical trial).

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