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Original Article

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Associations of Changes in Metabolic Syndrome Status and Risk Factor Count With Incident Cardiovascular Events Among Cancer Survivors

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ABSTRACT

Objective: This study investigated the associations of changes in metabolic syndrome status and the number of metabolic syndrome risk factors after cancer diagnosis with the incidence of cardiovascular disease (CVD) events among cancer survivors.
Methods: Using nationwide health screening data, we identified 344,681 individuals diagnosed with cancer at age ≥19 years from 2012 to 2017, who survived for at least 3 years without CVD events. Participants were classified according to their metabolic syndrome status and risk factor count both before and after cancer diagnosis. A CVD event was defined as a composite of myocardial infarction, stroke, or cardiovascular death.
Results: During a median follow-up period of 5.0 years after surviving cancer for 3 years, 7,529 CVD events occurred. The cumulative incidence of CVD was highest among participants with persistent metabolic syndrome. Compared to participants consistently free of metabolic syndrome, the multivariable-adjusted hazard ratios (HRs) for CVD were 1.21 (95% confidence interval [CI], 1.13–1.30) for newly developed metabolic syndrome, 1.19 (95% CI, 1.10–1.27) for recovered metabolic syndrome, and 1.37 (95% CI, 1.30–1.45) for persistent metabolic syndrome. Participants who recovered from metabolic syndrome exhibited a lower risk compared to those with persistent metabolic syndrome (HR, 0.86; 95% CI, 0.80–0.93). Each +1 increase in risk factor count after cancer diagnosis was associated with increased CVD risk (HR, 1.09; 95% CI, 1.07–1.11).
Conclusion: Changes in metabolic syndrome status and metabolic syndrome risk factor count after cancer diagnosis were significantly associated with CVD risk among cancer survivors.

Keywords: Cancer survivors; Metabolic syndrome; Cardiovascular diseases

INTRODUCTION

The number of cancer survivors is rapidly increasing, with an estimated 53.5 million survivors worldwide in 2022.[1,2] Although improvements in cancer care have significantly reduced cancer-related mortality, they have concurrently extended survival periods, exposing cancer

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Conflict of Interest
The authors have no conflicts of interest to declare.

Data Availability Statement
The datasets analyzed during the current study are not publicly available due to the sensitive nature of the database. Requests from qualified researchers to access the data may be sent to the National Health Insurance Service at https://nhiss.nhis.or.kr.

Author Contributions
Conceptualization: Lee HH, Lee H; Data curation: Lee J, Lee HH, Kim EJ, Kim HC, Lee H; Formal analysis: Lee J; Writing – original draft: Lee J; Writing – review & editing: Lee HH, Kim EJ, Kim HC, Lee H.

survivors to a growing burden of non-cancer comorbidities.[3,4] Among these comorbidities, cardiovascular disease (CVD) is the leading cause of non-cancer mortality.[4] Furthermore, cancer survivors are at a higher risk of developing CVD due to shared risk factors and adverse effects associated with cancer treatments.[5-7] Thus, managing CVD among cancer survivors has emerged as a critical public health priority.

Cancer diagnosis can induce substantial alterations in cardiovascular risk factors through various mechanisms. Inflammatory responses triggered by cancer can adversely impact lipid profiles and promote atherosclerosis.[7,8] Additionally, elevated stress hormones, such as cortisol, may worsen insulin resistance.[9,10] These post-cancer changes in cardiovascular risk factors may subsequently influence CVD risk.[11] Metabolic syndrome, defined as a cluster of cardiovascular risk factors, serves as a comprehensive indicator for predicting CVD risk.[12] Despite its well-established role as a predictor of CVD risk in the general population, little is known about how changes in this holistic measure affect CVD risk specifically among cancer survivors.

Utilizing a nationwide health claims database in Korea, we evaluated the association between changes in metabolic syndrome status after cancer diagnosis and the risk of CVD events among cancer survivors.

MATERIALS AND METHODS

1. Data source

We utilized a Korean nationwide database provided by the National Health Insurance Service (NHIS). The NHIS operates as a universal, single-payer health insurance system that covers approximately 97% of the Korean population. The NHIS database contains detailed sociodemographic data, insurance claims with diagnosis codes classified according to the International Classification of Disease, 10th revision (ICD-10), and death records.[13] Additionally, the NHIS provides biennial health examinations for all Korean adults, collecting clinical, biochemical, and lifestyle-related data.[14] Health examination centers undergo monitoring to ensure quality control, in accordance with relevant laws and regulations. Further details on the NHIS database have been documented in previous studies.[13-15]

The study protocol was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (4-2024-0498). Due to the anonymized nature of the database, the requirement for informed consent was waived.

2. Study population

Individuals diagnosed with cancer were identified using ICD-10 codes (**Supplementary Table 1**) and the rare incurable disease code for cancer (V193).[16] A total of 1,208,036 adults aged 19 years or older were newly diagnosed with cancer from January 1, 2012, to December 31, 2017; among these, 892,782 (73.9%) survived for at least 3 years. Individuals who experienced myocardial infarction (MI) or stroke before the 3-year survival date (index date), those who did not undergo health examinations within 3 years before or after cancer diagnosis, and those with missing data for health examination variables were excluded. Consequently, the final study population comprised 344,681 participants (**Supplementary Fig. 1**).

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3. Change in metabolic syndrome status after cancer diagnosis

Metabolic syndrome was defined according to the modified criteria of the National Cholesterol Education Program's Adult Treatment Panel III, as having at least 3 of the following 5 cardiovascular risk factors: 1) waist circumference ≥90 cm (for males) or ≥85 cm (for females); 2) triglycerides ≥150 mg/dL or receiving specific treatment; 3) high-density lipoprotein cholesterol <40 mg/dL (for males) or <50 mg/dL (for females) or receiving specific treatment; 4) blood pressure ≥130/85 mmHg or receiving specific treatment; and 5) fasting glucose ≥100 mg/dL or receiving specific treatment.[17] Waist circumference criteria were modified according to cutoffs recommended by the Korean Society for the Study of Obesity for Korean adults.[18]

Metabolic syndrome status was assessed using physical measurements and laboratory results from the last health examination conducted within 3 years before (exam 1) and after (exam 2) cancer diagnosis. Prescription records from claims data within the respective 3-year periods were also considered (**Supplementary Fig. 2**). Participants were classified into 4 distinct groups based on their metabolic syndrome status before and after cancer diagnosis (presence vs. absence).

4. Covariables

Lifestyle information, including tobacco smoking, alcohol consumption, and physical activity, was collected in exam 2. For alcohol consumption and physical activity, both frequency and amount were measured. Alcohol consumption amount was calculated by multiplying drinking frequency by the amount consumed per occasion. The amount per drinking occasion was estimated assuming that 1 drink contains 7 g of ethanol[19] for health examinations conducted between 2012 and 2017, and using beverage-specific alcohol content and volume between 2018 and 2020. According to WHO guidelines, cut points of 40 g/day for male and 20 g/day for female were applied.[20] Physical activity amount was assessed using a modified International Physical Activity Questionnaire.[21] Weekly energy expenditure was estimated by multiplying activity frequency by session duration (30 minutes for moderate intensity, 20 minutes for vigorous intensity), weighted by standardized metabolic equivalent task (MET) values of 4.0 and 7.0, respectively.[22,23] A cut point of 600 MET-min/week, consistent with the 2022 American Cancer Society guideline, was applied.[24]

The Charlson Comorbidity Index (CCI)[25] was calculated using claims data from the 3-year period prior to the index date. Cancer-related information—including cancer type, presence of distant metastasis at initial diagnosis, and the use of chemotherapy and external beam radiotherapy—was also obtained from claims data.[16]

5. Outcomes

The primary outcome was a CVD event, defined as a composite of the first hospitalization for MI (ICD-10 codes: I21–I23), first hospitalization for stroke (ICD-10 codes: I60–I64), or cardiovascular death (ICD-10 codes: I00–I99). The accuracy of ICD-10 codes for MI and stroke has been validated previously.[26] Secondary outcomes were predefined as individual components of the primary composite outcome. Participants were followed up from the index date until the occurrence of an outcome event, death, or December 31, 2022, whichever came first (**Supplementary Fig. 2**).

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6. Statistical analysis

Baseline characteristics are presented as median (interquartile range) or number (%). Cumulative incidence of CVD events was estimated using the subdistribution cumulative incidence function, accounting for competing risks from non-cardiovascular death.[27,28] Incidence rates were calculated as the number of events per 1,000 person-years of follow-up. Hazard ratios (HRs) and 95% confidence intervals (CIs) for primary and secondary outcomes were estimated using cause-specific Cox proportional hazards models, censoring participants at the time of competing death.[28,29] The models were adjusted for age, sex, household income quartile, residential area, tobacco smoking, alcohol consumption frequency, physical activity frequency, CCI, cancer type, distant metastasis at initial diagnosis, use of chemotherapy and external beam radiotherapy, and year of cancer diagnosis.[16] The proportional hazards assumption was confirmed visually using log-minus-log plots and Schoenfeld residuals.

In a secondary analysis, we examined the associations between changes in metabolic syndrome risk factor count after cancer diagnosis and CVD events. Participants were categorized based on their metabolic syndrome risk factor counts (0–1, 2, 3, 4–5) in exam 1 and exam 2. Additionally, trends were estimated by analyzing metabolic syndrome risk factor counts as continuous variables.

Cancer-specific analyses were conducted to investigate the association between changes in metabolic syndrome status and incident CVD among 8 major cancer types prevalent in Korea: upper gastrointestinal (GI), lower GI, hepatobiliary/pancreatic/other GI, lung, breast/female genital organs, male genital organs, urinary tract, and endocrine cancers. Subgroup analyses stratified by age, sex, body mass index (BMI), CCI, and year of cancer diagnosis were also performed. Sensitivity analyses involved excluding the first 2 years of follow-up to address potential reverse causality, and repeating the primary analysis in a cohort of 5-year cancer survivors to evaluate the robustness of findings among long-term survivors. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.) and R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

1. Baseline characteristics

Among the 344,681 cancer survivors included (median age, 59 years; 55.0% women), 212,891 (61.8%) participants were consistently free of metabolic syndrome, 38,089 (11.1%) participants newly developed metabolic syndrome, 34,950 (10.1%) recovered from metabolic syndrome, and 58,751 (17.0%) had persistent metabolic syndrome. Participants who had metabolic syndrome after cancer diagnosis were older, more likely to be male, more frequently resided in rural areas, were less physically active, and had higher CCI scores than those without metabolic syndrome after cancer diagnosis (**Table 1**). The most common cancer type was endocrine (26.5%), followed by upper GI (12.8%), lower GI (12.4%), and breast cancer (12.3%).

2. Primary analyses

During a median follow-up of 5.0 years, 7,529 incident CVD events were recorded. The cumulative incidence of CVD was highest among participants with persistent metabolic syndrome and lowest among participants who were consistently free of metabolic syndrome

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(**Fig. 1**). Compared to participants consistently free of metabolic syndrome, the multivariable-adjusted HRs (95% CIs) for CVD events were 1.21 (1.13–1.30) among participants who newly developed metabolic syndrome, 1.19 (1.10–1.27) among those who recovered from metabolic

Table 1. Baseline characteristics of the participants

Variables	Total (n=344,681)	No MetS before cancer		MetS before cancer	
		No MetsS after cancer (n=212,891)	MetS after cancer (n=38,089)	No MetsS after cancer (n=34,950)	MetS after cancer (n=58,751)
Age (yr)	59 (51–68)	57 (48–65)	61 (54–69)	63 (55–70)	64 (57–72)
Sex					
Male	155,267 (45.0)	85,085 (40.0)	18,508 (48.6)	19,933 (57.0)	31,741 (54.0)
Female	189,414 (55.0)	127,806 (60.0)	19,581 (51.4)	15,017 (43.0)	27,010 (46.0)
Household income*					
Q4, highest	132,977 (38.6)	82,066 (38.5)	14,426 (37.9)	13,671 (39.1)	22,814 (38.8)
Q3	84,164 (24.4)	51,789 (24.3)	9,429 (24.8)	8,479 (24.3)	14,467 (24.6)
Q2	60,654 (17.6)	38,118 (17.9)	6,640 (17.4)	5,937 (17.0)	9,959 (17.0)
Q1, lowest	66,886 (19.4)	40,918 (19.2)	7,594 (19.9)	6,863 (19.6)	11,511 (19.6)
Residential area					
Metropolitan	153,737 (44.6)	97,449 (45.8)	16,461 (43.2)	14,770 (42.3)	25,057 (42.6)
Urban	157,911 (45.8)	97,089 (45.6)	17,492 (45.9)	16,255 (46.5)	27,075 (46.1)
Rural	33,033 (9.6)	18,353 (8.6)	4,136 (10.9)	3,925 (11.2)	6,619 (11.3)
Tobacco smoking					
Never	234,938 (68.2)	153,140 (71.9)	24,703 (64.9)	21,138 (60.5)	35,957 (61.2)
Past	79,889 (23.2)	43,925 (20.6)	9,572 (25.1)	10,252 (29.3)	16,140 (27.5)
Current	29,854 (8.7)	15,826 (7.4)	3,814 (10.0)	3,560 (10.2)	6,654 (11.3)
Alcohol consumption, frequency					
None	250,248 (72.6)	155,584 (73.1)	27,258 (71.6)	25,691 (73.5)	41,715 (71.0)
1–2 times/wk	70,151 (20.4)	44,615 (21.0)	7,593 (19.9)	6,485 (18.6)	11,458 (19.5)
≥3 times/wk	24,282 (7.0)	12,692 (6.0)	3,238 (8.5)	2,774 (7.9)	5,578 (9.5)
Alcohol consumption, amount					
None	250,248 (72.6)	155,584 (73.1)	27,258 (71.6)	25,691 (73.5)	41,715 (71.0)
<40 g/day (male), <20 g/day (female)	88,291 (25.6)	54,275 (25.5)	9,953 (26.1)	8,612 (24.6)	15,451 (26.3)
≥40 g/day (male), ≥20 g/day (female)	6,025 (1.7)	2,956 (1.4)	863 (2.3)	639 (1.8)	1,567 (2.7)
Unknown	117 (0.0)	76 (0.0)	15 (0.0)	8 (0.0)	18 (0.0)
Physical activity, frequency					
None	140,449 (40.7)	81,476 (38.3)	16,912 (44.4)	14,756 (42.2)	27,305 (46.5)
1–2 times/wk	78,755 (22.8)	51,172 (24.0)	8,373 (22.0)	7,177 (20.5)	12,033 (20.5)
3–4 times/wk	68,055 (19.7)	44,321 (20.8)	6,951 (18.2)	6,573 (18.8)	10,210 (17.4)
≥5 times/wk	57,422 (16.7)	35,922 (16.9)	5,853 (15.4)	6,444 (18.4)	9,203 (15.7)
Physical activity, amount					
None	140,449 (40.7)	81,476 (38.3)	16,912 (44.4)	14,756 (42.2)	27,305 (46.5)
<600 MET-min/week	107,921 (31.3)	69,837 (32.8)	11,435 (30.0)	9,981 (28.6)	16,668 (28.4)
≥600 MET-min/week	95,612 (27.7)	61,127 (28.7)	9,661 (25.4)	10,136 (29.0)	14,688 (25.0)
Unknown	699 (0.2)	451 (0.2)	81 (0.2)	77 (0.2)	90 (0.2)
Body mass index					
<18.5 kg/m^2	11,463 (3.3)	10,434 (4.9)	277 (0.7)	555 (1.6)	197 (0.3)
18.5–22.9 kg/m^2	129,863 (37.7)	105,231 (49.4)	7,381 (19.4)	10,286 (29.4)	6,965 (11.9)
23–24.9 kg/m^2	85,977 (24.9)	54,796 (25.7)	9,730 (25.5)	9,987 (28.6)	11,464 (19.5)
≥25 kg/m^2	117,378 (34.1)	42,430 (19.9)	20,701 (54.3)	14,122 (40.4)	40,125 (68.3)
Systolic BP (mmHg)	121 (112–132)	119 (110–129)	130 (120–137)	124 (116–133)	130 (120–139)
Diastolic BP (mmHg)	75 (70–80)	73 (68–80)	80 (72–85)	77 (70–81)	80 (72–85)
Fasting glucose (mg/dL)	97 (89–107)	93 (87–100)	104 (97–113)	98 (91–110)	110 (100–126)
Total cholesterol (mg/dL)	188 (164–214)	189 (166–214)	193 (167–220)	184 (158–211)	183 (156–211)
BP-lowering drug use	119,824 (34.8)	43,600 (20.5)	18,354 (48.2)	16,123 (46.1)	41,747 (71.1)
Glucose-lowering drug use	47,920 (13.9)	11,314 (5.3)	6,260 (16.4)	6,751 (19.3)	23,595 (40.2)
Lipid-lowering drug use	109,284 (31.7)	45,319 (21.3)	15,861 (41.6)	13,746 (39.3)	34,358 (58.5)
CCI†					
0	82,454 (23.9)	58,277 (27.4)	7,557 (19.8)	7,340 (21.0)	9,280 (15.8)
1	81,497 (23.6)	54,476 (25.6)	8,236 (21.6)	7,717 (22.1)	11,068 (18.8)
2	64,174 (18.6)	37,964 (17.8)	7,255 (19.0)	6,858 (19.6)	12,097 (20.6)
≥3	116,556 (33.8)	62,174 (29.2)	15,041 (39.5)	13,035 (37.3)	26,306 (44.8)

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Table 1. (Continued) Baseline characteristics of the participants

Variables	Total (n=344,681)	No MetS before cancer		MetS before cancer	
		No MetsS after cancer (n=212,891)	MetS after cancer (n=38,089)	No MetsS after cancer (n=34,950)	MetS after cancer (n=58,751)
Cancer type‡					
Head/neck	4,136 (1.2)	2,498 (1.2)	423 (1.1)	542 (1.6)	673 (1.1)
Upper GI	44,225 (12.8)	26,931 (12.7)	3,244 (8.5)	7,446 (21.3)	6,604 (11.2)
Lower GI	42,888 (12.4)	23,408 (11.0)	5,194 (13.6)	5,103 (14.6)	9,183 (15.6)
HBP/other GI	22,549 (6.5)	12,544 (5.9)	2,758 (7.2)	2,681 (7.7)	4,566 (7.8)
Lung	15,091 (4.4)	8,527 (4.0)	1,985 (5.2)	1,604 (4.6)	2,975 (5.1)
Other resp./intrathoracic	3,398 (1.0)	1,952 (0.9)	416 (1.1)	379 (1.1)	651 (1.1)
Bone/cartilage	956 (0.3)	595 (0.3)	115 (0.3)	86 (0.2)	160 (0.3)
Skin	9,337 (2.7)	5,144 (2.4)	1,215 (3.2)	953 (2.7)	2,025 (3.4)
Mesothelium/soft tissue	2,517 (0.7)	1,546 (0.7)	301 (0.8)	229 (0.7)	441 (0.8)
Breast	42,436 (12.3)	30,382 (14.3)	4,257 (11.2)	2,769 (7.9)	5,028 (8.6)
Female genital organs	17,230 (5.0)	11,695 (5.5)	1,934 (5.1)	1,196 (3.4)	2,405 (4.1)
Male genital organs	25,225 (7.3)	13,290 (6.2)	3,456 (9.1)	2,848 (8.1)	5,631 (9.6)
Urinary tract	17,643 (5.1)	8,888 (4.2)	2,411 (6.3)	1,909 (5.5)	4,435 (7.5)
Central nervous system	3,264 (0.9)	2,001 (0.9)	410 (1.1)	305 (0.9)	548 (0.9)
Endocrine	91,185 (26.5)	61,771 (29.0)	9,641 (25.3)	6,752 (19.3)	13,021 (22.2)
Hodgkin lymphoma	323 (0.1)	185 (0.1)	53 (0.1)	23 (0.1)	62 (0.1)
Non-Hodgkin lymphoma	5,212 (1.5)	3,172 (1.5)	620 (1.6)	494 (1.4)	926 (1.6)
Leukemia	2,186 (0.6)	1,214 (0.6)	291 (0.8)	272 (0.8)	409 (0.7)
Other hematologic	3,354 (1.0)	2,046 (1.0)	388 (1.0)	322 (0.9)	598 (1.0)
Unspecified	15,653 (4.5)	9,943 (4.7)	1,753 (4.6)	1,505 (4.3)	2,452 (4.2)
Chemotherapy					
Alkylating agents	29,992 (8.7)	20,325 (9.5)	3,397 (8.9)	2,275 (6.5)	3,995 (6.8)
Antimetabolites	37,809 (11.0)	22,573 (10.6)	4,070 (10.7)	4,873 (13.9)	6,293 (10.7)
Antitumor antibiotics	33,021 (9.6)	21,586 (10.1)	3,883 (10.2)	2,782 (8.0)	4,770 (8.1)
Biologic agents	17,675 (5.1)	10,476 (4.9)	2,331 (6.1)	1,663 (4.8)	3,205 (5.5)
Hormonal agents	65,890 (19.1)	44,311 (20.8)	7,353 (19.3)	5,064 (14.5)	9,162 (15.6)
Molecular targeted agents	5,237 (1.5)	2,962 (1.4)	662 (1.7)	651 (1.9)	962 (1.6)
Microtubule inhibitors	24,395 (7.1)	15,774 (7.4)	3,011 (7.9)	2,028 (5.8)	3,582 (6.1)
Platinum-based agents	26,265 (7.6)	15,462 (7.3)	3,058 (8.0)	3,124 (8.9)	4,621 (7.9)
Topoisomerase inhibitors	4,391 (1.3)	2,513 (1.2)	595 (1.6)	482 (1.4)	801 (1.4)
Other chemotherapeutics	1,370 (0.4)	781 (0.4)	194 (0.5)	124 (0.4)	271 (0.5)
External beam radiotherapy	42,634 (12.4)	28,182 (13.2)	4,632 (12.2)	3,607 (10.3)	6,213 (10.6)
Distant metastasis	6,630 (1.9)	3,922 (1.8)	842 (2.2)	711 (2.0)	1,155 (2.0)
Year of cancer diagnosis	2014 (2013–2016)	2014 (2013–2016)	2014 (2013–2016)	2014 (2013–2016)	2014 (2013–2016)

Values as median (interquartile range) or number (%).
MetS, metabolic syndrome; Q, quartile; MET, metabolic equivalent of task; BP, blood pressure; CCI, Charlson Comorbidity Index; GI, gastrointestinal.
*Categorized based on quartiles among the entire Korean population.
†Excluding diabetes and cancer.
‡The sum exceeds 100% due to patients with multiple cancer diagnoses.

syndrome, and 1.37 (1.30–1.45) among those with persistent metabolic syndrome (**Fig. 2** and **Supplementary Table 2**). Participants who recovered from metabolic syndrome exhibited a significantly lower risk of CVD compared to those with persistent metabolic syndrome (HR, 0.86; 95% CI, 0.80–0.93) (**Supplementary Table 2**). Similar trends were observed for secondary outcomes, including MI, stroke, and cardiovascular death (**Supplementary Table 3**).

3. Secondary analyses

A consistent, gradual increase in CVD risk was observed with increasing numbers of metabolic syndrome risk factors, both before and after cancer diagnosis. Specifically, multivariable-adjusted HRs (95% CIs) for CVD were 1.06 (1.04–1.09) per +1 metabolic syndrome risk factor count before cancer diagnosis, and 1.09 (1.07–1.11) per +1 metabolic syndrome risk factor count after cancer diagnosis (**Fig. 3**).

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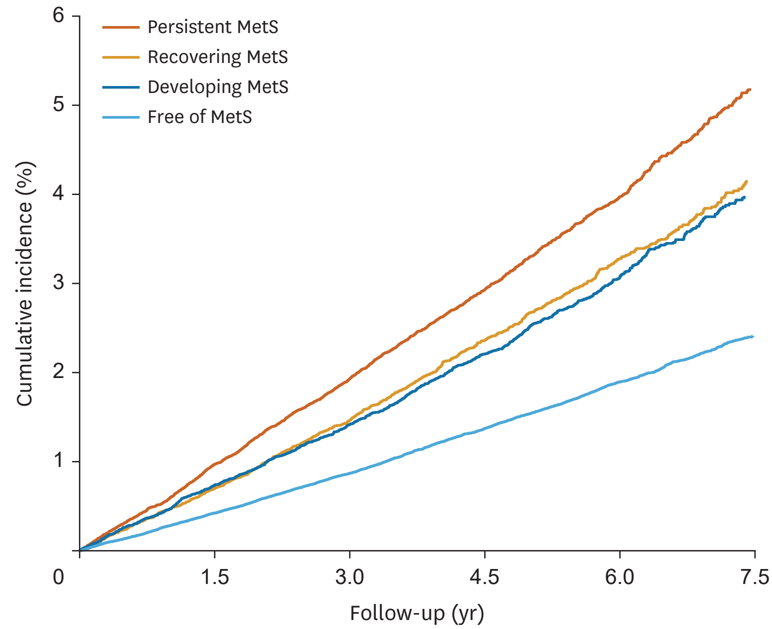

No. at risk						
Persistent MetS	58,751	56,484	47,371	32,656	17,955	4,620
Recovering MetS	34,950	33,657	28,728	20,168	11,394	3,275
Developing MetS	38,089	36,727	31,106	21,939	12,326	3,621
Free of MetS	212,891	207,607	179,558	128,515	75,585	18,488

Fig. 1. Cumulative incidence of cardiovascular disease according to changes in MetS after cancer diagnosis.
MetS, metabolic syndrome.

MetS status				
Before cancer	After cancer	No.	Rate*	HR (95% CI)
No	No	212,891	3.28	1.00 (reference)
No	Yes	38,089	5.46	1.21 (1.13–1.30)
Yes	No	34,950	5.75	1.19 (1.10–1.27)
Yes	Yes	58,751	7.22	1.37 (1.30–1.45)

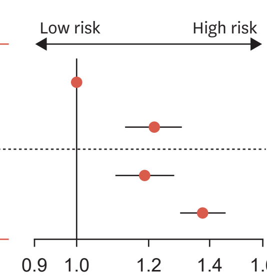

Fig. 2. Risk of cardiovascular disease according to changes in MetS after cancer diagnosis.
HRs were adjusted for age, sex, household income, residential area, tobacco smoking, alcohol consumption frequency, physical activity frequency, Charlson Comorbidity Index, cancer type, presence of distant metastasis, year of cancer diagnosis, and chemotherapy and external beam radiotherapy use.
MetS, metabolic syndrome; HR, hazard ratio; CI, confidence interval.
*Incidence rate per 1,000 person-years.

4. Cancer-specific analyses

Participants who newly developed metabolic syndrome after cancer diagnosis had higher CVD risk compared to those consistently free of metabolic syndrome among survivors of upper GI (HR, 1.24; 95% CI, 1.02–1.50), lower GI (HR, 1.52; 95% CI, 1.30–1.79), and endocrine cancers (HR, 1.30; 95% CI, 1.05–1.61) (**Supplementary Table 4**). Additionally, participants who recovered from metabolic syndrome had lower CVD risk compared to those with persistent metabolic syndrome among survivors of upper GI (HR, 0.80; 95% CI, 0.67–0.95), lower GI (HR, 0.82; 95% CI, 0.68–0.98), and lung cancers (HR, 0.71; 95% CI, 0.52–0.97).

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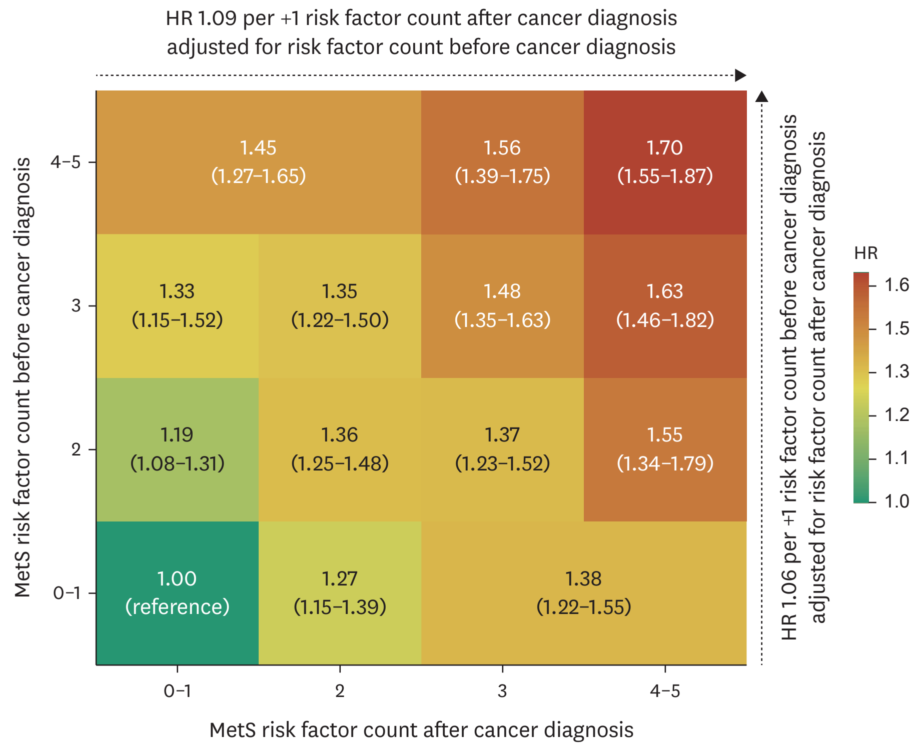

Fig. 3. Risk of cardiovascular disease according to changes in MetS risk factor count after cancer diagnosis.
HRs (95% confidence intervals) were reported. HRs were adjusted for age, sex, household income, residential area, tobacco smoking, alcohol consumption frequency, physical activity frequency, Charlson Comorbidity Index, cancer type, presence of distant metastasis, year of cancer diagnosis, and chemotherapy and external beam radiotherapy use. For groups with fewer than 1% of the study population, data were combined with the adjacent group.
HR, hazard ratio; MetS, metabolic syndrome.

5. Subgroup and sensitivity analyses

Subgroup analyses demonstrated consistent findings across various subgroups defined by age, sex, BMI, CCI, and year of cancer diagnosis (**Supplementary Table 5**). Sensitivity analyses further confirmed the robustness of results, with findings remaining consistent after excluding the first 2 years of follow-up, and upon repeating the primary analyses in a cohort of 5-year cancer survivors (**Supplementary Figs. 3** and **4**).

DISCUSSION

In this Korean nationwide study of cancer survivors, changes in metabolic syndrome status after cancer diagnosis were significantly associated with subsequent CVD risk. Individuals who newly developed metabolic syndrome after cancer diagnosis had a 21% higher risk of CVD compared to those consistently free of metabolic syndrome. Conversely, participants who recovered from metabolic syndrome exhibited a 14% lower CVD risk compared to those with persistent metabolic syndrome. Additionally, our secondary analyses showed that a higher count of metabolic syndrome risk factors, both before and after cancer diagnosis, was progressively associated with an increased risk of CVD. These associations were consistent across subgroup analyses and remained robust in sensitivity analyses.

CVD among cancer survivors is increasingly recognized as an important public health concern. However, current cardio-oncology guidelines primarily emphasize treatment-related

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cardiotoxicity, such as cardiotoxic chemotherapy agents and chest radiotherapy, with limited attention given to comprehensive preventive strategies for CVD among cancer survivors as a whole.[30] Specifically, it remains unclear whether established preventive measures for CVD in the general population can also be effectively applied to cancer survivors. Clarifying this point is crucial for systematically incorporating such strategies into cardio-oncology guidelines. Building upon prior research that demonstrated associations between changes in metabolic syndrome status and CVD risk in the general population,[31,32] our study extends these observations to cancer survivors. Thus, our findings emphasize the importance of managing metabolic health as a critical component of CVD prevention among cancer survivors.

Our results are consistent with previous studies and further expand upon their implications. Earlier studies found that cancer survivors with metabolic syndrome had a higher risk of CVD than those without metabolic syndrome. However, these studies typically assessed metabolic syndrome status at a single time point post-cancer diagnosis, without capturing temporal changes.[33] Additionally, prior research showed that changes in individual cardiovascular risk factors—including smoking,[34] physical activity,[23] and BMI[11]—after cancer diagnosis influenced CVD risk among survivors. While these studies addressed isolated risk factors, they did not evaluate the combined impact of multiple risk factors on CVD risk. By examining associations between changes in overall metabolic syndrome status after cancer diagnosis and subsequent CVD risk among cancer survivors, our study addresses these gaps, offering a more comprehensive understanding of metabolic health's impact on CVD in cancer survivors.

Furthermore, changes in the count of metabolic syndrome risk factors after cancer diagnosis were significantly linked to subsequent CVD risk. Previous studies have indicated that risk factor count and continuous severity score of metabolic syndrome are related to increased CVD risk, underscoring the importance of assessing metabolic syndrome beyond a simple binary classification.[35,36] Additionally, earlier research has demonstrated cumulative effects of metabolic syndrome risk factor counts on CVD outcomes.[36] Extending these findings, our study highlights the importance of closely monitoring metabolic syndrome severity and its longitudinal trajectory among cancer survivors. Regular health screening programs could be critical for tracking these trajectories, thus enabling timely interventions and mitigating long-term cardiovascular risks in this population.

Our findings suggest that interpreting the impact of metabolic syndrome changes on CVD risk among cancer survivors is complex, given that cancer type and treatment intensity might differentially influence metabolic risk factors. For example, recovery from metabolic syndrome might not always represent true metabolic improvement, as cancer-related weight loss and cachexia, which are factors independently associated with increased CVD risk,[11,37] could lead to a misclassification of individuals as "recovered." This issue is particularly relevant for upper GI, lower GI, and lung cancers, where weight loss is more common.[38] Despite this potential bias, our results still demonstrated a significantly reduced CVD risk among participants classified as metabolically recovered, suggesting that the actual protective effect may be even more pronounced. Similarly, the absence of significant findings in other cancer types may reflect an underestimation of true effects due to such misclassification. Therefore, further research is necessary to better delineate how cancer type and treatment intensity influence metabolic syndrome recovery and its implications for CVD risk.

This study has several strengths. First, to our knowledge, this is the first study evaluating associations between changes in metabolic syndrome status after cancer diagnosis and

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subsequent CVD risk in cancer survivors. Second, utilizing a nationwide claims database from a single-payer health insurance system allowed us to identify nearly all cancer survivors in Korea comprehensively. Third, the large sample size facilitated detailed subgroup analyses, enhancing the robustness and generalizability of the findings within this population.

Nevertheless, several limitations should be acknowledged. First, the observational nature of the study restricts causal inference. Although extensive covariate adjustment was performed, residual confounding cannot be entirely excluded. Second, detailed cancer-related clinical information, such as cancer stage and pathological subtype, was unavailable in our database. However, including data on distant metastasis at initial diagnosis, chemotherapy, and external beam radiotherapy in our models likely partially captures cancer severity. Third, the generalizability of findings might be limited by the exclusion of individuals who did not participate in health examinations or who had missing data on health examination variables. Nevertheless, baseline characteristics of participants included in the analysis were generally similar to those excluded due to non-participation or missing data in health examinations (**Supplementary Table 6**). Finally, as the data were derived exclusively from the Korean population, caution is necessary when generalizing the findings to other ethnicities.

In conclusion, our study demonstrated that changes in metabolic syndrome status and the number of metabolic syndrome risk factors following cancer diagnosis are significantly associated with CVD risk among cancer survivors. Regular monitoring and proactive management of metabolic syndrome could help mitigate the burden of subsequent CVD in this growing population.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Classification of cancer types and corresponding ICD-10 codes

Supplementary Table 2
Crude, age-/sex-adjusted, and multivariable-adjusted risk of cardiovascular disease according to changes in MetS after cancer diagnosis

Supplementary Table 3
Risk of secondary outcomes according to changes in MetS after cancer diagnosis

Supplementary Table 4
Cancer-specific risk of cardiovascular disease according to changes in MetS after cancer diagnosis

Supplementary Table 5
Risk of cardiovascular disease according to changes in MetS after cancer diagnosis in subgroups

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Supplementary Table 6

Baseline characteristics of the participants and individuals excluded due to non-participation or missing data in health examinations

Supplementary Fig. 1

Study flowchart.

Supplementary Fig. 2

Timeline for MetS assessment and outcome ascertainment. Change in MetS between the last exam within 3 years before the cancer diagnosis and the last exam within 3 years after the cancer diagnosis was used as the exposure. Follow-up started 3 years after cancer diagnosis.

Supplementary Fig. 3

Risk of cardiovascular disease according to changes in MetS after cancer diagnosis after excluding the first 2 years of follow-up.

Supplementary Fig. 4

Risk of cardiovascular disease according to changes in MetS after cancer diagnosis in 5-year cancer survivors.

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