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Original Article

Radiation-Associated Heart Disease in Korean Women after Radiotherapy for Breast Cancer: Insights from the National Health Insurance Service Database

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Purpose This study investigated the risk of radiation-associated heart disease (RAHD) in Korean women treated with radiotherapy (RT) for breast cancer (BC) using data from the National Health Insurance Service database.

Materials and Methods A retrospective cohort analysis was conducted on 65,188 patients with BC treated with RT between 2009 and 2014 and 325,940 controls without BC or prior coronary artery disease (CAD), with 1:5 exact matching by age, type 2 diabetes mellitus, hypertension, and dyslipidemia status. CAD encompassed both incident events and fatal events. Competing risk analysis was conducted to estimate subdistribution hazard ratio (HR) with 95% confidence interval (CI) for CAD, setting mortality from non-CAD causes as a competing risk.

Results During the mean 9.9 years of follow-up period, 3,852 (1.0%) CAD and 20,999 (5.4%) death from non-CAD causes were reported. Compared to controls, participants with BC who received RT had a significantly lower risk of CAD incidence. HR (95% CI) for CAD in the BC with RT group was 0.66 (0.60-0.73, $p < 0.001$). On the other hand, HR (95% CI) for mortality from non-CAD causes was 3.57 (3.48-3.67, $p < 0.001$).

Conclusion In this large population-based cohort study, BC patients who received RT did not show an increased incidence of CAD compared with the general population without BC. Individual-level dosimetric data and longer follow-up are needed to clarify the independent risk.

Key words Breast neoplasms, Late toxicity, Radiotherapy, Cardiac mortality, Korean women

Introduction

Postoperative radiation therapy (RT) is the standard treatment for women with breast cancer (BC) undergoing breast-conserving surgery or mastectomy with high-risk pathological features. Radiation exposure to the heart during RT increases heart disease risk [1,2], with a dose-response relationship between RT dose and acute coronary events [3,4]. Since Darby et al.'s study, extensive research has examined heart toxicity in radiation oncology, with efforts to reduce cardiac radiation.

The BC incidence rate per 100,000 women in Korea has increased from 11.0 in 1999 to 30.4 in 2019, with 5-year survival rates improving from 79.3% in 1993-1995 to 93.6% in 2015-2019, partly due to earlier detection and multimodal therapy [5,6]. Few large-scale studies have assessed the association between heart radiation dose and cardiac toxicities in Korean BC survivors. Previous reports have suggested that, unlike Western populations, Korean patients may not exhibit a clear dose-response relationship between heart exposure and subsequent cardiac morbidity [7,8]. This difference may stem from genetic predisposition, baseline cardiovascular health, lifestyle, treatment variations, or shorter follow-up in prior studies. Additionally, heart-sparing techniques introduced in Korean institutions may have further masked dose-dependent effects. A population-based approach is needed to determine whether these findings reflect a genuinely lower risk or simply a methodological limitation in smaller-scale studies.

Therefore, this study examined cardiac risk after RT for BC using the National Health Insurance Service (NHIS) database. A secondary analysis explored whether a healthy lifestyle mitigates cardiac toxicity.

Materials and Methods

1. Study design

This retrospective cohort study used NHIS data, which covers over 97% of the Korean population [9]. The NHIS

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supports 40%-70% of medical expenses based on its criteria and assigns V codes to reduce costs for severe diseases to 5%. Mortality data are linked to Statistics Korea for NHIS-registered patients. Additionally, the NHIS offers biennial national health screenings for adults aged 20 years or older, with participation rates of approximately 60%-70% [10].

2. Study population

Fig. 1 presents the study population selection flowchart. Between 2009 and 2014, patients with BC who received RT and had no prior coronary artery disease (CAD) were identified. Then, we excluded participants who developed CAD or died during the 1-year lag period. Patients with BC were matched 1:5 to females without BC or prior CAD, using exact matching on age (in the corresponding year) and on type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia status. For example, in 2009, 8,996 patients with BC were matched with 44,980 controls, with analogous matching in subsequent years. In total, 65,188 patients with BC and 325,940 matched controls were included, yielding a study population of 391,128.

3. Identification of BC with RT

BC was defined using the International Classification of Diseases, 10th revision (ICD-10) code C50, along with Korea's cancer-specific insurance claim code V193. RT data were obtained by utilizing a unique specification code for RT embedded within the NHIS database. RT was categorized as 3D conformal RT (3D-CRT), intensity-modulated radiotherapy (IMRT), both, or unknown. Surgical procedures were classified as breast-conserving surgery or total mastectomy.

4. Outcome

The primary outcome was incident CAD. CAD encompassed both nonfatal events and fatal events. Nonfatal CAD was identified by ICD-10 codes I20-I25 or the CAD-specific claim code V192, whereas fatal CAD was defined as deaths registered by the National Statistical Office with an ICD-10 code I20-I25 as the underlying cause. The time interval for each event was calculated from the date of BC diagnosis to the date of CAD. Five matched controls were selected for each case, with the control index date set as the date of BC diagnosis for the corresponding case. Each individual's follow-up period was defined as the time from the index date to the date of CAD or, if no CAD event occurred, to the date of non-CAD death, or until December 31, 2023, which was designated as the last follow-up date. Prior NHIS database validations showed that the positive predictive value for cardiovascular diseases exceeded 90% [11,12].

5. Measurements

Data on age, sex, and health insurance premiums were available for the entire cohort in the NHIS database. T2DM was defined as the presence of ICD-10 codes E11-E14 [13]. HTN was defined as the presence of ICD-10 codes I10-I13 or I15 [14]. Dyslipidemia was defined as the presence of ICD-10

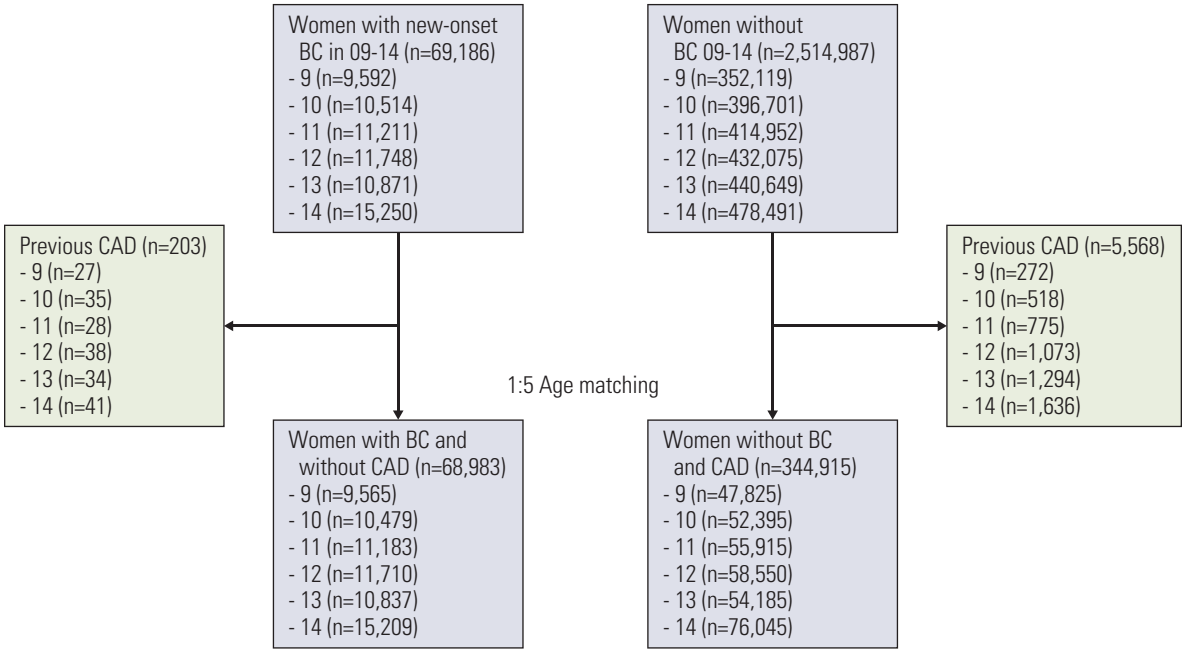

Fig. 1. Study population selection flowchart. BC, breast cancer; CAD, coronary artery disease.

code E78.5 [15]. Participants were classified as low income if they received medical aid or were in the lowest income quintile per NHIS premium data. Participants living in Seoul, Gyeonggi Province, or other metropolitan cities were classified as urban residents, whereas all others were considered rural residents.

A portion of the participants completed national health screenings, providing data on anthropometric variables (body mass index [BMI], waist circumference [WC]), and blood pressure (systolic [SBP] and diastolic [DBP]), questionnaires on lifestyle factors (smoking, alcohol consumption, and physical activity), and laboratory tests (fasting blood glucose [FBG], liver function, and cholesterol profiles). Smoking was categorized as current or non-smoker, and alcohol consumption as current drinker or non-drinker. Regular exercise was defined as vigorous activity at least three days per week or moderate activity at least five days per week.

All measurements were taken after fasting for at least eight hours. BMI was calculated as weight (kg) divided by height (m^2). SBP and DBP were measured after a five-minute seated rest. Laboratory tests included FBG, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C).

6. Statistical analysis

Data are presented as number (%) for categorical variables and mean±standard deviation for continuous variables. Group differences for categorical and continuous variables were compared using the chi-square and independent t tests, respectively.

Cumulative incidence rates of CAD and mortality from non-CAD causes were illustrated using survival curves. Subdistribution hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Fine and Gray's modified Cox proportional hazards models, considering mortality from non-CAD causes as a competing risk. The model was adjusted for low income and residential areas. Subgroup analyses stratified by age (< 50, 50-60, and > 60 years), T2DM, HTN, and dyslipidemia were displayed in a forest plot based on the fully adjusted model. For sensitivity analyses, we evaluated CAD risk within the BC with RT group according to surgical type. CAD was further stratified into angina pectoris (ICD-10 I20), myocardial infarction (I21-I23), and other CAD (I24-I25), and the risk for each subset was calculated separately. The risk of nonfatal and fatal CAD was also evaluated. Major adverse cardiovascular events (MACE) were defined as a composite of CAD, heart failure, stroke, and cardiovascular mortality, and the associated risk was likewise analyzed.

All analyses were performed using SAS ver. 7.1 (SAS Institute Inc.) and R ver. 4.0.3 (R Foundation for Statistical Computing). Two-sided p-values < 0.05 were considered statistically significant.

Results

1. Baseline characteristics of the study population

Table 1 shows a comparison of the baseline characteristics between the control and BC with RT groups.

Before matching, BC with RT participants were younger (51.0±10.2 vs. 50.8±10.1 years; p=0.016) and had higher proportions of T2DM, HTN, dyslipidemia, and urban residence, with fewer individuals of low income than controls (p < 0.001 for all). After matching, age and the proportions of T2DM, HTN, and dyslipidemia were identical (p > 0.99 for all), but the BC with RT group still had a lower proportion of low income and a higher proportion of urban residence (p < 0.001 for all).

Among participants who underwent national health screenings, both before and after matching the BC with RT group had greater mean age and WC and lower mean SBP and DBP than controls. Low income remained less prevalent, whereas urban residence remained more prevalent in the BC with RT group (p < 0.001 for all). Lifestyle profiles showed lower proportions of current smokers, current drinkers, and regular exercisers (p < 0.001 for all). Laboratory tests revealed higher AST, ALT, and TG and lower total cholesterol and HDL-C levels compared with controls (p < 0.001 for all). Before matching, mean FBG level and the proportions of HTN, T2DM, and dyslipidemia were higher in the BC with RT group (p < 0.001 for all), however, after matching, only HTN remained significantly more prevalent (p=0.011).

S1 Table summarizes treatment characteristics in the BC with RT group. RT was predominantly delivered as 3D-CRT (63,013 patients, 96.7%); 71 (0.1%) received IMRT, 198 (0.3%) received both modalities, and RT type was unspecified in 1,906 cases (2.9%). Surgical management comprised 58,476 (89.7%) breast-conserving surgeries and 916 (1.4%) total mastectomies; the remaining 5,796 (8.9%) patients did not undergo surgery.

2. Risk of incident CAD

During a mean 9.9 years of follow-up period, 3,852 (1.0%) CAD and 20,999 (5.4%) death from non-CAD causes were reported. Group-wise, as shown in Table 2, the CAD cases were lower in the BC with RT group (444 cases; 0.7%) than in controls (3,408 cases; 1.0%). Conversely, mortality from non-CAD causes was markedly higher in the BC with RT group (8,286 deaths; 12.7%) than in controls (12,713 deaths; 3.9%). Fig. 2 shows cumulative CAD (A) and mortality from

Table 1. Baseline characteristics of the study population

Variable	Before matching				After matching			
	Control	BC with RT	Total	p-value	Control	BC with RT	Total	p-value
No.	2,494,462	65,424	2,559,886		325,940	65,188	391,128	
Matched variables								
Age (yr)	51.0±10.2	50.8±10.1	51.0±10.2	0.016	50.9±10.1	50.9±10.1	50.9±10.1	> 0.99
HTN	558,620 (22.4)	15,968 (24.4)	574,588 (22.4)	< 0.001	79,715 (24.5)	15,943 (24.5)	95,658 (24.5)	> 0.99
T2DM	264,412 (10.6)	8,894 (13.6)	273,306 (10.7)	< 0.001	44,325 (13.6)	8,865 (13.6)	53,190 (13.6)	> 0.99
DLD	269,639 (10.8)	10,720 (16.4)	280,359 (11.0)	< 0.001	52,520 (16.1)	10,504 (16.1)	63,024 (16.1)	> 0.99
Unmatched variables								
Low income	468,490 (18.8)	10,999 (16.8)	479,489 (18.7)	< 0.001	64,035 (19.6)	10,690 (16.4)	74,725 (19.1)	< 0.001
Residential area								
Rural	757,510 (30.4)	16,412 (25.1)	773,922 (30.2)	< 0.001	98,498 (30.2)	16,350 (25.1)	114,848 (29.4)	< 0.001
Urban	1,736,952 (69.6)	49,012 (74.9)	1,785,964 (69.8)		227,442 (69.8)	48,838 (74.9)	276,280 (70.6)	
National Health Screening Program participants[a]								
No.	804,349	16,636	820,985		106,870	16,605	123,475	
Age (yr)	52.0±9.4	52.7±9.4	52.0±9.4	< 0.001	51.9±9.3	52.7±9.4	52.0±9.3	< 0.001
BMI (kg/m^2)	23.6±3.2	23.6±3.3	23.6±3.2	0.077	23.6±3.3	23.6±3.3	23.6±3.3	0.266
WC (cm)	77.0±8.5	77.3±8.7	77.0±8.5	< 0.001	77.2±8.6	77.3±8.7	77.2±8.6	0.094
SBP (mmHg)	120.2±15.1	120.0±15.3	120.2±15.1	0.025	120.4±15.1	120.0±15.3	120.3±15.2	0.002
DBP (mmHg)	74.7±9.9	74.4±9.9	74.7±9.9	0.001	74.8±9.9	74.5±9.9	74.7±9.9	< 0.001
Low income	161,263 (20.0)	2,911 (17.5)	164,174 (20.0)	< 0.001	22,910 (21.4)	2,879 (17.3)	25,789 (20.9)	< 0.001
Residential area								
Rural	257,017 (32.0)	4,332 (26.0)	261,349 (31.8)	< 0.001	33,852 (31.7)	4,328 (26.1)	38,180 (30.9)	< 0.001
Urban	547,332 (68.0)	12,304 (74.0)	559,636 (68.2)		73,018 (68.3)	12,277 (73.9)	85,295 (69.1)	
Current smoker	24,341 (3.0)	414 (2.5)	24,755 (3.0)	< 0.001	3,309 (3.1)	413 (2.5)	3,722 (3.0)	< 0.001
Alcohol drinker	185,727 (23.2)	2,330 (14.1)	188,057 (23.0)	< 0.001	24,663 (23.2)	2,324 (14.1)	26,987 (22.0)	< 0.001
Regular exerciser	119,563 (14.9)	3,238 (19.5)	122,801 (15.0)	< 0.001	16,088 (15.1)	3,234 (19.5)	19,322 (15.7)	< 0.001
FBG (mg/dL)	96.5±21.1	97.5±21.1	96.6±21.1	< 0.001	97.6±23.2	97.5±21.1	97.5±22.9	0.782
AST (U/L)	21.0±19.7	22.9±24.0	21.0±19.8	< 0.001	21.3±22.1	23.0±24.0	21.5±22.4	< 0.001
ALT (U/L)	23.8±16.1	25.3±17.2	23.8±16.2	< 0.001	23.9±16.6	25.3±17.2	24.1±16.6	< 0.001
TCHOL (mg/dL)	199.8±37.1	195.4±37.8	199.7±37.1	< 0.001	200.2±37.8	195.5±37.8	199.5±37.8	< 0.001
TG (mg/dL)	96 (68-138)	101 (72-146)	96 (68-138)	< 0.001	97 (69-140)	101 (72-146)	97 (69-141)	< 0.001
HDL-C (mg/dL)	58.4±14.0	56.5±13.9	58.3±14.0	< 0.001	58.2±14.0	56.5±13.9	58.0±14.0	< 0.001
HTN	195,656 (24.3)	4,494 (27.0)	200,150 (24.4)	< 0.001	27,907 (26.1)	4,491 (27.0)	32,398 (26.2)	0.011

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Table 1. Continued

Variable	Before matching				After matching			
	Control	BC with RT	Total	p-value	Control	BC with RT	Total	p-value
T2DM	89,928 (11.2)	2,486 (14.9)	92,414 (11.3)	< 0.001	15,400 (14.4)	2,482 (14.9)	17,882 (14.5)	0.069
DLD	103,990 (12.9)	3,041 (18.3)	107,031 (13.0)	< 0.001	19,989 (18.7)	3,012 (18.1)	23,001 (18.6)	0.084

Values are presented as mean±SD, number (%), or median (range). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BC, breast cancer; BMI, body mass index; DBP, diastolic blood pressure; DLD, dyslipidemia; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; RT, radiotherapy; SBP, systolic blood pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus; TCHOL, total cholesterol; TG, triglyceride; WC, waist circumference. [a]Variables collected exclusively in the subset who underwent the National Health Screening Program.

Table 2. Incidence of CAD, mortality from non-CAD causes in the study population

	Control	BC with RT
No.	325,940	65,188
Follow-up time (yr)	10.0±2.1	9.4±2.8
Incident CAD[a] cases	3,408	444
Mortality from non-CAD causes	12,713	8,286

BC, breast cancer; CAD, coronary artery disease; RT, radiotherapy. [a]Includes nonfatal and fatal CAD.

non-CAD causes (B) rates in the two groups. During the follow-up period, the BC with RT group showed consistently and significantly lower cumulative CAD rates than the control group ($p < 0.001$) (Fig. 2A). In contrast, the BC with RT group showed consistently and significantly higher cumulative rates of mortality from non-CAD causes than the control group ($p < 0.001$) (Fig. 2B). Table 3 shows modified Cox regression analysis results for CAD considering mortality from non-CAD causes as a competing risk. Consistent with the cumulative survival curves, patients with BC who received RT had a significantly lower risk of developing CAD than the control group. In the unadjusted model, the HR for CAD in the BC with RT group was 0.65 (95% CI, 0.59 to 0.72; $p < 0.001$). This reduced risk persisted in the adjusted model (HR, 0.66; 95% CI, 0.60 to 0.73; $p < 0.001$). In contrast, risk of mortality from non-CAD causes was markedly higher in the BC with RT group than in the control group. In the unadjusted model, the BC with RT group exhibited a more than threefold increase in mortality risk (HR, 3.47; 95% CI, 3.38 to 3.57; $p < 0.001$). This elevated risk persisted in the adjusted model (HR, 3.57; 95% CI, 3.48 to 3.67; $p < 0.001$).

3. Subgroup analysis

Fig. 3A displays a forest plot of CAD risk according to age, T2DM, HTN, and dyslipidemia. Across age strata, the difference was not significant (HR, 0.83; 95% CI, 0.63 to 1.09; p=0.177) in adults aged < 50 years. However, the BC with RT group exhibited a significantly lower risk of CAD than the control group, with adjusted HRs (95% CIs) of 0.60 (0.50-0.71, $p < 0.001$) in those aged 50-60 years and 0.66 (0.58-0.76, $p < 0.001$) in those aged > 60 years. A decrease in CAD risk was consistently observed irrespective of T2DM, HTN, or dyslipidemia status. The corresponding HRs (95% CIs) for CAD in the BC with RT group versus the control group were 0.62 (0.53-0.73, $p < 0.001$) in the T2DM subgroup, 0.69 (0.61-0.78, $p < 0.001$) in the non-T2DM subgroup, 0.65 (0.57-0.73, $p < 0.001$) in the HTN subgroup, 0.67 (0.57-0.79, $p < 0.001$) in the non-HTN subgroup, 0.57 (0.47-0.70, $p < 0.001$) in the dyslipidemia subgroup, and 0.70 (0.62-0.78, $p < 0.001$) in the non-dyslipidemia subgroup.

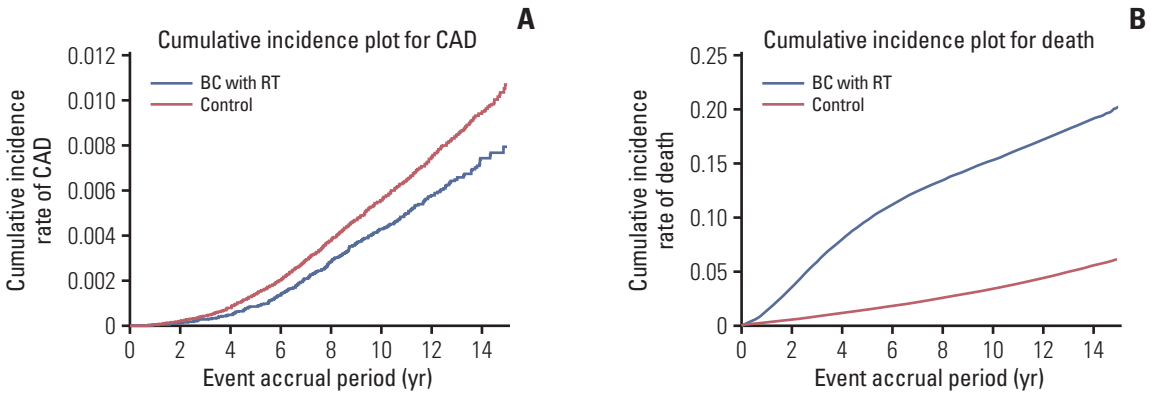


Fig. 2. Cumulative coronary artery disease (CAD) (A) and mortality from non-CAD causes (B) rates in the two groups. BC, breast cancer; RT, radiotherapy.

Table 3. Risk of CAD in patients with BC who received RT with mortality from non-CAD causes as a competing risk

	Control HR	BC with RT HR (95% CI)	p-value
Risk of CAD[a]			
Unadjusted	1 (reference)	0.65 (0.59-0.72)	< 0.001
Adjusted[b]	1 (reference)	0.66 (0.60-0.73)	< 0.001
Risk of mortality from non-CAD causes			
Unadjusted	1 (reference)	3.47 (3.38-3.57)	< 0.001
Adjusted	1 (reference)	3.57 (3.48-3.67)	< 0.001

BC, breast cancer; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; RT, radiotherapy. [a]Includes nonfatal and fatal CAD, [b]Adjusted for low income and residential area.

Fig. 3B shows the risk of non-CAD mortality by the same subgroups. Non-CAD mortality remained higher in the BC with RT group than in the control group regardless of age, T2DM, HTN, or dyslipidemia status. The corresponding HRs (95% CIs) for non-CAD mortality were 8.24 (7.80-8.71, p < 0.001) in age < 50 years, 4.62 (4.38-4.86, p < 0.001) in age 50-60 years, 1.84 (1.76-1.93, p < 0.001) in age > 60 years, 2.11 (2.00-2.24, p < 0.001) in the T2DM subgroup, 4.31 (4.17-4.45, p < 0.001) in the non-T2DM subgroup, 2.19 (2.10-2.29, p < 0.001) in the HTN subgroup, 5.20 (5.02-5.40, p < 0.001) in the non-HTN subgroup, 2.72 (2.54-2.91, p < 0.001) in the dyslipidemia subgroup, and 3.79 (3.67-3.90, p < 0.001) in the non-dyslipidemia subgroup.

4. Sensitivity analysis

S2 Table presents the sensitivity analyses by surgical type. The risk of CAD did not differ between breast-conserving surgery group and total mastectomy group (adjusted HR, 1.13; 95% CI, 0.53 to 2.38; p=0.754). However, total mastectomy group showed higher risk of mortality from non-CAD causes than breast-conserving surgery group (adjusted HR, 1.40; 95% CI, 1.18 to 1.67; p < 0.001).

S3 Table compares the risk of nonfatal CAD setting fatal CAD and mortality from non-CAD causes as competing risks between the BC with RT group and the control group. The adjusted HRs (95% CIs) for nonfatal CAD, fatal CAD, non-CAD mortality were 0.66 (0.59-0.74, p < 0.001), 0.59 (0.45-0.77, p < 0.001), and 3.50 (3.41-3.60, p < 0.001), respectively.

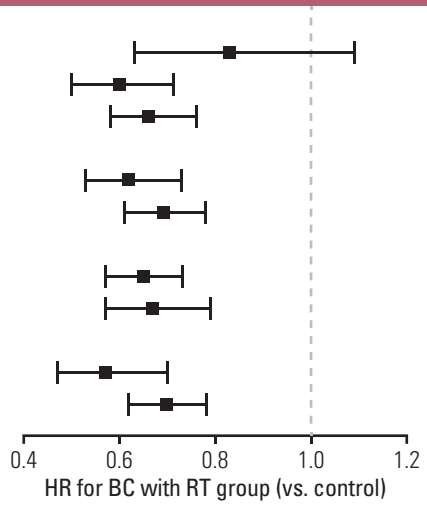
S4 Table shows risk of CAD subsets between the BC with RT group and the control group. The adjusted HRs (95% CIs) for angina pectoris, myocardial infarction, other CAD, and non-CAD mortality were 0.65 (0.57-0.74, p < 0.001), 0.60 (0.49-0.74, p < 0.001), 0.93 (0.70-1.24, p=0.624), and 3.49 (3.39-3.59, p < 0.001) respectively.

S5 Table shows the risk of MACE in the BC with RT group versus the control group. Compared with controls, the BC with RT group had a significantly lower risk of MACE. The adjusted HRs (95% CIs) for MACE and non-CAD mortality were 0.91 (0.86-0.97, p=0.004) and 3.96 (3.85-4.08, p < 0.001), respectively.

A

Risk of CAD by subgroups

Subgroups	HR (95% CI)	p-value	Interaction p-value
Age (yr)			
< 50	0.83 (0.63-1.09)	0.177	< 0.001
50-60	0.60 (0.50-0.71)	< 0.001	
> 60	0.66 (0.58-0.76)	< 0.001	
T2DM			
Yes	0.62 (0.53-0.73)	< 0.001	< 0.001
No	0.69 (0.61-0.78)	< 0.001	
HTN			
Yes	0.65 (0.57-0.73)	< 0.001	< 0.001
No	0.67 (0.57-0.79)	< 0.001	
Dyslipidemia			
Yes	0.57 (0.47-0.70)	< 0.001	< 0.001
No	0.70 (0.62-0.78)	< 0.001	



B

Risk of non-CAD mortality by subgroups

Subgroups	HR (95% CI)	p-value	Interaction p-value
Age (yr)			
< 50	8.24 (7.80-8.71)	< 0.001	< 0.001
50-60	4.62 (4.38-4.86)	< 0.001	
> 60	1.84 (1.76-1.93)	< 0.001	
T2DM			
Yes	2.11 (2.00-2.24)	< 0.001	< 0.001
No	4.31 (4.17-4.45)	< 0.001	
HTN			
Yes	2.19 (2.10-2.29)	< 0.001	< 0.001
No	5.20 (5.02-5.40)	< 0.001	
Dyslipidemia			
Yes	2.72 (2.54-2.91)	< 0.001	< 0.001
No	3.79 (3.67-3.90)	< 0.001	

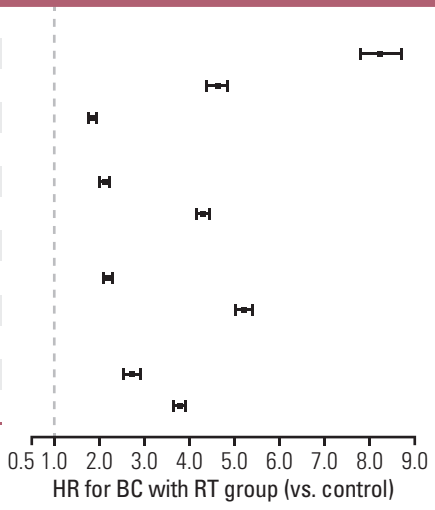


Fig. 3. Forest plot illustrating the risk of coronary artery disease (CAD) (A) and mortality from non-CAD causes (B), stratified by age, type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia. BC, breast cancer; CI, confidence interval; RT, radiotherapy.

Discussion

In this study, we examined the incidence of radiation-associated heart disease (RAHD) in Korean women who underwent RT for BC using NHIS data. Our findings showed that patients with BC who received RT had a significantly lower incidence of CAD compared with the control group. Even with a significantly higher risk of all-cause mortality, the BC with RT group's risk of CAD mortality remained lower than that of the control group.

We employed a 1:5 matched cohort design to preserve the temporal relationship between radiotherapy exposure and CAD onset and to allow direct calculation of incidence rates and HRs via time-to-event analysis. Although CAD incidence was low (1.0%), our large sample and fivefold matching on age, T2DM, HTN, and dyslipidemia ensured adequate

power and minimized selection bias. By contrast, nested case–control studies require complex risk-set sampling and can complicate adjustment for time-dependent confounders. We acknowledge that future investigations could adopt nested case–control or case–cohort methodologies to evaluate additional covariates not captured in our current dataset.

The Organisation for Economic Co-operation and Development has reported significant variations in baseline cardiac risk across countries [16]. Korea's cardiac mortality rate is approximately one-thirtieth of that in the United States, and Korean females have among the highest projected life expectancies among developed nations [17]. Since most RAHD research originates from countries with high cardiac mortality rates, its applicability to the Korean population is uncertain. Retrospective studies in Korea have failed to establish a clear association between RT and RAHD or to demonstrate a dose-response relationship between RT dose and heart-related morbidity, possibly due to these population differences [7,8].

Efforts to minimize cardiac radiation exposure in patients with BC have continued. Heart-sparing techniques, including active breathing control [18], deep inspiration breath-hold [19,20] and continuous positive airway pressure [21] have been developed to minimize cardiac radiation exposure and reduce RAHD risk. Additionally, thoracic tumor treatments have explored ventilator-assisted RT to limit tumor motion, maintain lung volume, and increase the distance between the heart and chest wall have also been explored in BC [22]. Historically, RT in BC has been delivered using 2D RT or 3D-CRT over approximately 6 weeks with daily fraction doses of 1.8-2 Gy. However, advancements have shifted toward IMRT, incorporating moderate hypo-fractionated RT with doses ≥ 2.5 Gy [23], reducing treatment to 3-4 weeks. Recently, the FAST-Forward trial investigated an accelerated RT regimen delivering 26 Gy in five fractions over 1 week, showing equivalent efficacy to moderate hypo-fractionated RT with greater patient convenience [24]. This approach has become the standard of care. Consequently, as per-fraction doses increase, protecting normal organs, particularly the heart and lungs, has become even more critical.

Although our findings indicate a lower CAD incidence in the RT-treated BC group, these results require careful interpretation. Several factors could explain this unexpected outcome. Increased medical surveillance and lifestyle modifications among BC survivors may contribute to improved cardiovascular health. The higher prevalence of regular exercise and lower smoking and alcohol consumption rates in the BC with RT group support this hypothesis. Moderate physical activity is well-established as a protective factor against CAD and related mortality [25,26]. Additionally, population differences may play a role. For instance, Asian females generally have lower BMI than Western females [27]. However, whether these lifestyle factors fully account for the observed cardioprotective effects remains unclear.

Despite these findings, this study has limitations. First, residual confounding is possible due to the lack of data on cardiotoxic agents such as doxorubicin and trastuzumab that could affect cardiac outcomes. Second, information on BC laterality and staging was unavailable, making it difficult to determine whether left-sided BC, which is more prone to direct cardiac radiation exposure, influenced our findings. The absence of staging data also prevents differentiation between RT limited to the breast and RT including regional lymph node irradiation. In cases involving internal mammary node irradiation (IMNI), the mean heart dose is significantly higher. According to the Korean Radiation Oncology Group 08-06 study [28], a phase III trial investigating IMNI effects, patients who received IMNI had higher mean heart doses than those who did not [29]. Moreover, the lack of individual dosimetric data is a major limitation. A recent study has demonstrated considerable inter-patient variability in dose exposure, which impacts the risk of acute coronary events [30]. An observational study with patients with BC who did not receive RT is necessary to isolate the effect of RT. Third, although Fine and Gray competing risk models were used to adjust for mortality, early overall mortality was markedly higher in the BC-RT group. This may have led to an underestimation of RAHD events, as patients needed to survive long enough to develop them. Future studies should therefore employ even longer follow-up—ideally exceeding 20 years—and consider analytic strategies such as landmark analyses or dynamic risk modeling to more accurately disentangle RAHD from competing cancer mortality. Finally, because NHIS coverage for IMRT in Korea began in 2015, most patients in this study likely received 3D-CRT. A follow-up study is underway to assess IMRT's association with RAHD in patients treated after 2015.

In conclusion, in this large population-based cohort study, BC patients who received RT did not show an increased incidence of CAD compared with the general population without breast cancer. While the findings may offer some reassurance, individual-level dosimetric data and longer follow-up are needed to clarify the independent risk.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The study adhered to the ethical guidelines of the 1964 Declaration of Helsinki and subsequent amendments and was approved by the Institutional Review Board (IRB) of Eulji University (IRB num-

ber: 2024-09-007). Informed consent was waived due to the use of anonymized data from the NHIS database, in accordance with the Personal Data Protection Act.

Author Contributions

Conceived and designed the analysis: Lee JH, Kim TH.
Collected the data: Lee JH, Kim TH.
Contributed data or analysis tools: Lee JH, Kim TH.
Performed the analysis: Lee JH, Park J, Kim TH.
Wrote the paper: Lee JH, Kim TH.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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