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Original article

Risk of cardiac disease after adjuvant radiation therapy among breast cancer survivors

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ABSTRACT

Purpose: Adjuvant radiation therapy (RT) for breast cancer is associated with heart disease, although the impact of patient-specific factors on the interaction between cardiac risk and RT is not well-studied in cancer patients. The objective of this study is to compare acute coronary events (ACE) among the general population and women with breast cancer after adjuvant RT. Secondary analysis evaluated whether a healthy lifestyle could protect against RT-related cardiac toxicity.
Methods: The National Health Insurance Service-Health Screening Cohort (2002–2013) was used to compare ACE risks among 1015 women with breast cancer and among 8120 women without cancer who were matched according to age, comorbidities, and smoking history. The risk of developing ACE over time while accounting for competing risks from other causes of death was analyzed.
Results: During 6.1 ± 3.0 years of follow-up, the 5- and 10-year cumulative incidences of ACE were 5.5% and 11.3%, respectively. The breast cancer survivors who underwent breast radiotherapy and population-based matched sample had similar risks of ACE (hazard ratio: 0.94, 95% confidence interval: 0.69–1.28). However, in the sensitivity analysis, breast cancer survivors had increased risks of ACE if they did not exercise (hazard ratio 2.74, confidence interval: 1.27–5.91) or had a disability (hazard ratio 21.9, confidence interval: 2.50–191.6).
Conclusions: In this matched cohort study, the cardiac risk after adjuvant RT increased with decreasing physical activity. The long-term effect of physical activity on ACE is uncertain, but these results can increase physicians' awareness of the approaches to increase exercise participation level among women undergoing RT for breast cancer. Confirmatory studies with individual doses of cardiac radiation and quantification of physical activity and sedentary time are required for validating our results.

1. Introduction

Adjuvant radiation therapy (RT) is the standard treatment for women with breast cancer who are undergoing breast-conservation surgery or mastectomy with high-risk pathological features. These cases account for >80% of newly diagnosed breast cancers [1,2]. However, a large body of evidence has established that adjuvant therapies, including RT, increase the lifelong risk of heart disease [3]. Thus, breast cancer survivors have an increased burden of heart disease, relative to the general population [4]. Furthermore, a linear dose-response relationship, without a threshold, has been proposed between RT and heart disease, based on a case-control study and later validation in an institutional cohort study [5,6]. Using the same risk factors and endpoint, both studies revealed that hazard ratios increased by approximately 7.4% per Gy.

However, many questions remain regarding this relationship, as there is a growing body of literature regarding RT-induced heart disease [7,8]. We have previously reported RT-related cardiac morbidity rates using two large registries at the institution and population levels, and evaluated whether Asian women exhibited the same dose-response relationship that was detected in the Caucasian population, which is more likely to be obese, smoke more heavily, and have more heart disease-related risk factors [9].

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In that study, we failed to detect significant differences in heart-related morbidity or mortality among women with left-side and right-side disease, and we also failed to detect a dose-response relationship between the heart's RT dose and heart-related morbidity. Furthermore, it appeared that there were fewer non-tumor-related deaths, relative to the proportions that have been reported in Western countries. Therefore, we hypothesized that Asian breast cancer survivors might not have a higher risk of heart-related morbidity than women from the general population who were matched for age, comorbidities, and smoking history. A secondary analysis was also planned to examine the interaction between adjuvant breast RT and lifestyle factors, to determine whether a healthy lifestyle could help protect against cardiac toxicity.

2. Materials and methods

2.1. Study population

The present study examined data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS), which includes ≥40-year-old Korean adults who complete health screenings that are administered biannually by the NHIS [10]. This cohort is maintained to provide relevant and useful data for policy makers and health researchers, especially in the fields of non-communicable diseases and health risk factors. The NHIS-HEALS database was launched in 2002 using data from a sample of 40–79-year-old participants who were followed-up through 2013. This cohort includes 514,866 participants who were randomly selected to account for 10% of all health screenings that were performed during 2002–2003. We retrospectively identified 235,741 women, including 1015 women who underwent adjuvant RT after breast surgery (partial or total mastectomy) for newly diagnosed breast cancer between 2002 and 2013. The exclusion criteria were unknown tumor laterality, bilateral tumors, and history of other malignancies. Patients who received neoadjuvant chemotherapy before surgery were also excluded because during the study period in Korea, neoadjuvant chemotherapy was generally offered to some patients with high-risk locally advanced disease, in whom recurrence and tumor-related deaths outweighed the risk of late cardiac toxicity. The present study's protocol was approved by our institutional review board (4-2017-0266) and the NHIS review committee for research support and informed consent process was waived, as there was no direct contact with subjects.

2.2. Matched cohort study design

The cases involving women who underwent adjuvant RT were matched to a control group of women who were not diagnosed with any malignancy. For this comparison, age, smoking history, and comorbidity burden (e.g., based on the Charlson comorbidity index; CCI) were considered potential confounding factors [11]. However, all of these variables can change over time. Thus, the matching was performed based on the year in which the cases underwent surgery for breast cancer. Because of the large sample size, all controls were perfectly matched for all three variables.

2.3. Outcome and explanatory variables

The study outcome was acute coronary events (ACE), which were initially identified by Darby et al. as a cardiac toxicity from RT for breast cancer, and this finding has recently been validated [5,6]. The definition of ACE includes newly diagnosed ischemic heart disease that requires anti-coagulant therapy or coronary revascularization, as well as cardiac-related death. A single-center medical chart review has validated the occurrence of ACE based on the disease codes from the International Classification of Disease and the medical procedure codes from the Electronic Data Interchange [9].

The NHIS-HEALS contains data that were obtained using a self-administered questionnaire, a physical examination, and laboratory testing. The questionnaire contains questions regarding smoking history, alcohol consumption, physical activity, recognition scale results, depressive scale results, and family histories of malignancy, cardiovascular diseases, and stroke. The physical examination provides data regarding height, weight, body mass index, waist circumference, and blood pressure. The laboratory tests examine blood parameters (lipid profile, renal function, aspartate aminotransferase, alanine aminotransferase, hemoglobin A1c, and fasting glucose) and urinary parameters (pH, protein, blood, and glucose).

Smoking history was evaluated using the following question: "Have you smoked more than 5 cigarettes per day (or 100 cigarettes total) during your life?" The responses were categorized as (1) never, (2) yes but quit smoking, or (3) yes and currently smoking. Physical activity was evaluated using the following question: "During the past week, on how many days did you perform moderate intensity physical activities that made you breathe heavier than normal?" "Moderate intensity" implied "require some effort but still talk while doing them." The responses were categorized as (1) none or (2) at least one day. Height and weight were measured using standard automatic devices, and waist circumference was measured by trained medical assistants. Height and weight were used to calculate BMI.

Data were also obtained from the participants' health claims. Based on the main diagnosis for the claims data from each year, we calculated the CCI values for each participant. In addition, the records were searched for demographic and socioeconomic factors, which included age (as a continuous variable), residential area (urban or rural), income level decile, and disabled status.

2.4. Statistical analyses

The baseline characteristics of the breast cancer survivors and the matched controls were compared using the chi-square test. A competing risk analysis was used with a time-to-ACE analysis, based on various causes of death, and the results were compared using Gray's test [12]. The end date for breast RT was used as the starting time for all competing risk analyses. Multivariate Fine and Gray regression models were used to adjust for confounding variables and evaluate the effects on ACE development [13].

Significant interactions between RT exposure, the occurrence of ACE, and other confounding factors were evaluated using sensitivity analyses for sub-groups that were divided according to age, smoking history, CCI, hypertension, BMI, cholesterol level, exercise, residential area, income level, and disabled status. In addition, we performed subgroup analyses to examine the interaction between risk factors and undergoing RT among women with breast cancer. As in our previous study, cases with left-side or right-side breast cancer were compared using Gray's test. Two-sided P-values of <0.05 were considered statistically significant. All statistical analyses that involved matching were performed using SAS software (version 9.4; Cary, NC) and all other analyses were performed using R software (version 3.4.0; R Development Core Team, Vienna, Austria).

3. Results

3.1. Population characteristics

Table 1 shows the two groups' baseline demographic

Table 1
Demographic characteristics of the cases and matched controls (N = 9135).

	Women without cancer (n = 8120)		Women with breast cancer[a] (n = 1015)		Total	P
	N	%	N	%		
Age, years						
<49	1808	22.3%	226	22.3%	2034	1.000
50-59	3992	49.2%	499	49.2%	4491	
60-69	1856	22.9%	232	22.9%	2088	
≥70	464	5.7%	58	5.7%	522	
Smoking						
Never	7880	97.0%	985	97.0%	8865	1.000
Former	88	1.1%	11	1.1%	99	
Current	152	1.9%	19	1.9%	171	
Charlson comorbidity index						
Mean (SD)	2.45	(1.7)	2.45	(1.8)	2.5 (1.8)	1.000
History of hypertension						
No	5286	65.1%	646	63.6%	5932	0.360
Yes	2834	34.9%	369	36.4%	3203	
History of cardiac disease						
No	7500	92.4%	930	91.6%	8430	0.406
Yes	620	7.6%	85	8.4%	705	
BMI before reference date[b]						
<25.0 kg/m^2	5492	67.6%	668	65.8%	6160	0.105
25.0–29.9 kg/m^2	2353	29.0%	300	29.6%	2653	
≥30.0 kg/m^2	275	3.4%	47	4.6%	322	
Cholesterol						
Normal	3958	48.7%	554	54.6%	4512	0.002
Borderline	2878	35.4%	318	31.3%	3196	
High	1284	15.8%	143	14.1%	1427	
Weekly physical exercise						
No	1329	16.4%	132	13.0%	1461	0.014
Yes	6710	82.6%	869	85.6%	7579	
No response	81	1.0%	14	1.4%	95	
Residential area						
Capital	1512	18.6%	226	22.3%	1738	0.002
Metropolitans	2260	27.8%	302	29.8%	2562	
Rural	4348	53.5%	487	48.0%	4835	
Income (quartiles)						
Q1 (lowest)	1460	18.0%	153	15.1%	1613	<.0001
Q2	1897	23.4%	199	19.6%	2096	
Q3	2298	28.3%	279	27.5%	2577	
Q4 (highest)	2465	30.4%	384	37.8%	2849	
Disabled status						
No	8092	99.7%	1014	99.9%	9106	0.188
Yes	28	0.3%	1	0.1%	29	
Follow-up duration, years						
Mean (SD)	6.1	(3.0)	6.1	(3.0)	6.1 (3.0)	1.000

SD: standard deviation, BMI: body mass index.
[a] Women with newly diagnosed breast cancer who underwent breast surgery and adjuvant radiation therapy with or without systemic therapy.
[b] The reference date refers to the date of the first radiation treatment.

characteristics. The two groups were successfully matched without any significant differences in terms of age, smoking status, CCI, history of hypertension, history of cardiac disease, BMI, disability, and follow-up duration. Both groups had large proportions of individuals who never smoked (cancer survivors: 97% vs. controls: 97%) and had a normal weight based on a BMI of <25.0 kg/m^2 (cancer survivors: 65.8% vs. 67.6%). The breast cancer survivors were slightly more likely to report performing regular exercise and maintained cholesterol levels within the normal range. Furthermore, the breast cancer survivors were more likely to live in urban areas and have an income in the highest quartile.

3.2. Cardiac events

The mean follow-up time for all participants was 6.1 years (standard deviation: 3.0 years). The 5-year and 10-year cumulative incidences of ACE were 5.5% and 11.3%, respectively. Both groups had similar cumulative incidences of ACE (Fig. 1A). According to the competing risk estimates, similar results were observed for the 5-year incidence of ACE (breast cancer survivors: 4.5% vs. controls: 5.6%) and the 10-year incidence (breast cancer survivors: 9.2% vs. controls: 11.5%) (Gray's $P = .645$).

Table 2 and Supplementary Fig. S1 show that various explanatory variables were significantly associated with an increased risk of ACE, including increased age, greater comorbidity (higher CCI), underlying hypertension, increased BMI, abnormal cholesterol levels, and having a disability. However, the risks of incident ACE were similar between breast cancer survivors and the control group, with an adjusted hazard ratio of 0.94 (95% confidence interval: 0.69–1.28, Fine and Gray's $P = .69$).

Consistent with the primary analysis, the ACE risks were similar in most sensitivity analyses (Fig. 2). However, breast cancer survivors had increased risks of ACE if they did not exercise (hazard ratio 2.74, confidence interval: 1.27–5.91) or had a disability (hazard ratio 21.9, confidence interval: 2.50–191.6). In addition, there was a trend towards a higher risk of incident ACE among breast cancer survivors who were obese (>30.0 kg/m^2), although this relationship had a broad confidence interval that crossed 1.0.

3.3. Subgroup analysis

We repeated the analyses among only the breast cancer survivors who underwent RT. Table 3 shows that several risk factors from Table 2 (increased age, higher CCI, underlying hypertension, and increased BMI) retained their statistical significance in the subanalyses, with similar effect sizes. However, in the subanalyses, physical exercise was associated with a lower risk of ACE (adjusted hazard ratio: 0.37) and disabled status was associated with a higher risk of ACE (adjusted hazard ratio: 21.9), even after adjusting for all explanatory variables. The risk of ACE was not associated with RT for left-side disease (Fig. 1B) or the use of anthracyclines.

4. Discussion

The present study examined data from Korean breast cancer survivors and women from the general population who were matched for age, comorbidities, and smoking history to determine whether adjuvant RT for breast cancer was associated with an increased cumulative incidence of heart disease. No difference in the two groups' risks of ACE was detected at a mean follow-up of 6.1 ± 3.0 years. To the best of our knowledge, this is the largest population-level analysis from an East Asian country, although the results have important clinical implications for the management of RT-related cardiac disease throughout the world.

In this study, breast cancer survivors had ACE rates that were similar to ACE rates among control subjects at 5 years (breast cancer survivors: 4.6% vs. control subjects: 5.7%) and at 10 years (breast cancer survivors: 9.6% vs. control subjects: 11.7%). These cumulative incidences among patients with breast cancer are slightly higher than the rates from a Dutch cohort study of 910 women with breast cancer (5 years: 1.9%, 9 years: 3.9%) [6]. The discrepancy might be related to the facts that the Dutch study excluded women who underwent mastectomy and was performed at a single high-volume institution, which could have generated a cohort with a younger age distribution than in the general population. Nevertheless, the present study demonstrated that the cumulative risks of ACE were similar among breast cancer survivors after RT and among a matched sample of women from the general population, even after adjusting for possible confounding variables. This finding is consistent with the results of our previous analyses of institutional and national registries [9]. For example, during a 7-year follow-up, the standardized mortality ratio (cardiac-related

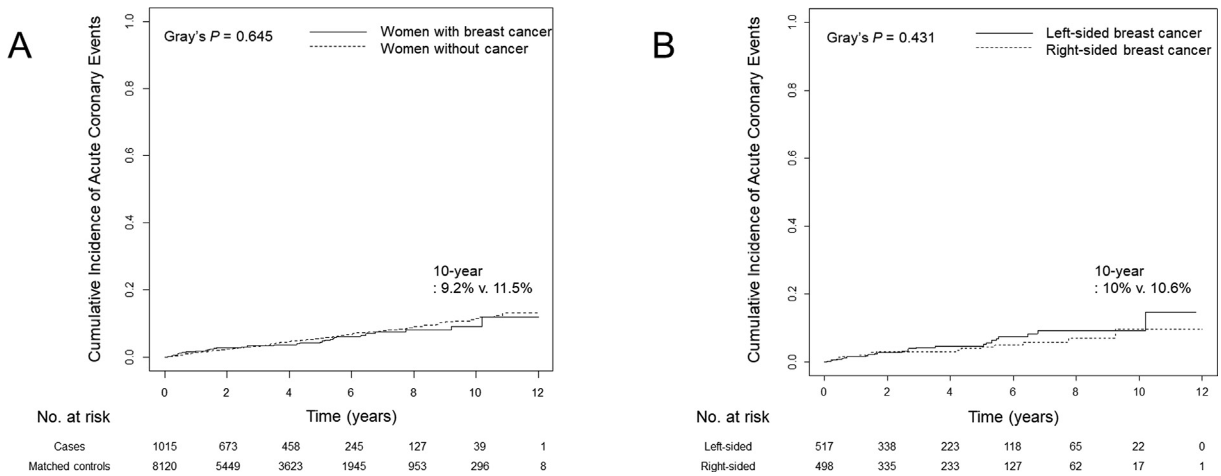

Fig. 1. Cumulative incidences of acute coronary events (a) among breast cancer survivors who underwent radiation therapy (RT) and women from the general population who were matched for age, comorbidities, and smoking history, as well as (b) among breast cancer survivors who underwent RT for left-side and right-side tumors.

Table 2
Unadjusted and adjusted hazard ratios for acute coronary events in the overall cohort (N = 9135).

Variable	Unadjusted			Adjusted		
	HR	95% CI	Gray's *P*	HR	95% CI	Gray's *P*
Age, year (Continuous)	1.05	1.04–1.06	<.001	1.02	1.01–1.04	<.001
Smoking (y v n)	1.21	0.69–2.10	0.51	1.21	0.69–2.11	0.5
Charlson comorbidity index (Continuous)	1.28	1.21–1.35	<.001	1.17	1.10–1.24	<.001
History of hypertension (y v n)	2.52	1.09–3.04	<.001	1.72	1.39–2.12	<.001
BMI, kg/m^2 (Continuous)	1.09	1.06–1.12	<.001	1.05	1.02–1.08	<.001
Cholesterol (high/borderline v normal)	1.38	1.14–1.67	<.001	1.27	1.04–1.54	0.002
Weekly physical exercise (y v n)	0.83	0.62–1.11	0.21	1.02	0.75–1.37	0.91
Residential area (metropolitans v rural)	1.13	0.93–1.36	0.22	1.04	0.86–1.26	0.69
Income (bottom 50% v upper 50%)	0.95	0.79–1.15	0.62	0.96	0.79–1.16	0.67
Disabled status (y v n)	4.41	1.79–10.9	0.001	3.08	1.30–7.31	0.011
Cases v matched controls[a]	0.93	0.69–1.27	0.65	0.94	0.69–1.28	0.69

HR: hazard ratio, CI: confidence interval.
[a] Cases refers to women with newly diagnosed breast cancer who underwent breast surgery and adjuvant radiation therapy, and matched controls refers to age-, smoking-, and comorbidity-matched women without cancer from the general population.

deaths divided by the expected cardiac death rate in the reference population) was not significantly higher among breast cancer survivors than age-matched women from the general population. However, these results are in stark contrast to the findings from Western countries [4]. For example, Bradshaw et al. compared 1413 women with breast cancer to 1411 age-matched women without breast cancer, and reported that breast cancer survivors had an increased risk of cardiovascular disease-related mortality (hazard ratio: 1.8). Thus, Asian and Western populations may exhibit different effects of cancer treatment (e.g., adjuvant RT) on heart-related morbidity, and establishing the causes of the differential effects could be useful for developing guidelines to minimize the risks of RT-related cardiac disease.

In the field of cardiology, moderate physical activity has clearly been established as providing protection against coronary heart disease and related mortality [14–16]. The INTERHEART case-control study, which included patients in 52 countries from all inhabited continents, demonstrated that a lack of physical activity accounted for 12% of the population-attributable risk of myocardial infarction [14]. In the present study, 86% of breast cancer survivors reported performing at least moderate physical activity, which contrasts with the estimates of approximately 25% in American surveys [17,18]. Another cross-sectional study of a representative group of American individuals revealed that physical activity declined dramatically with age, and that women were less physically active than men [19]. The present study first revealed a significant interaction between the cardio-toxic effect of adjuvant RT and the absence of physical activity in patients with breast cancer. Despite the importance of exercise and healthy lifestyle choices, little is known about how to effectively increase a patient's exercise participation level. In our previous randomized study, patients who received only their physician's exercise recommendation did not change their lifestyle behavior, although including an exercise motivation package increased the exercise level [20]. In this context, we reiterated that, women undergoing RT for breast cancer should be strongly encouraged to perform physical exercise with all sorts of ways including an education session, pedometers, printed materials, and a biofeedback.

A second noticeable difference in the characteristics of our Asian population and Western populations is the prevalence of overweight status or obesity, which are both associated with increased risks of various diseases, especially cardiac disease. For example, Asian women with breast cancer tend to have a slenderer physique and a much lower BMI than women in Western countries. Similar to in our previous report [9], women with breast cancer had an average BMI of 23.7 kg/m^2 and only 3.7% were considered obese ($\geq$30 kg/m^2). In contrast, the average BMIs in Western countries are 29.6 kg/m^2 for women who are 60–69 years old and 28 kg/m^2 for women with breast cancer, with Western obesity rates of up to 50% [21]. Moreover, some studies have implied that cancer treatment

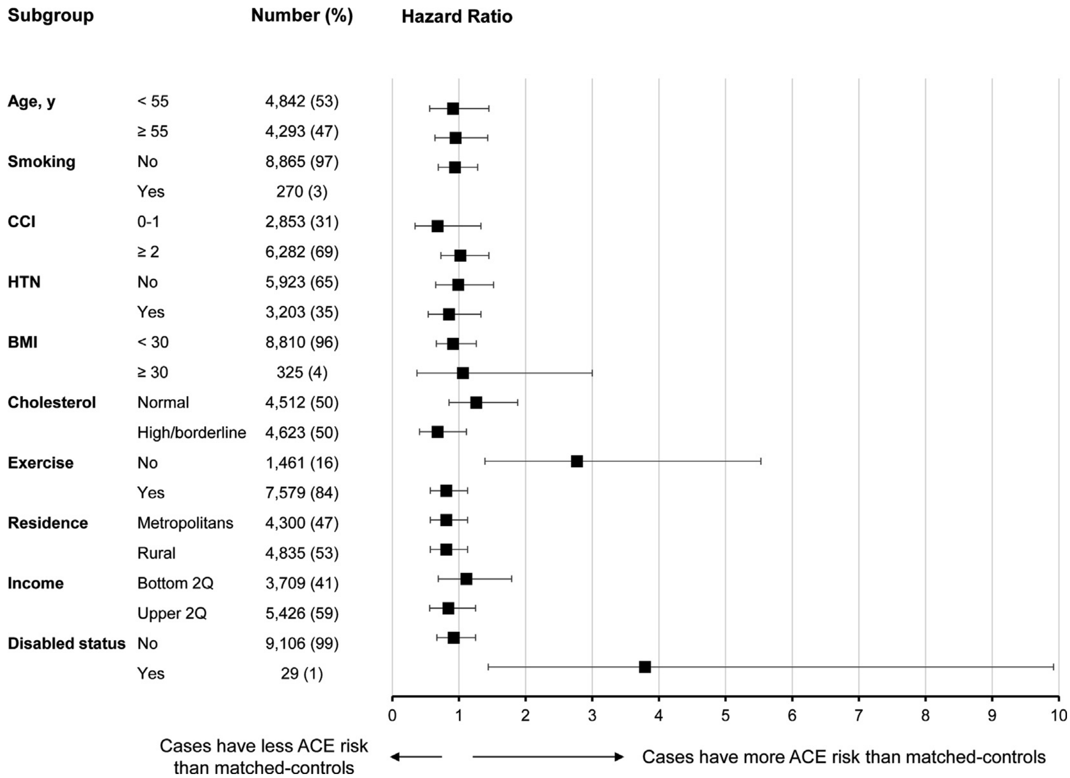

Fig. 2. Forest plot for the sensitivity analysis of acute coronary event (ACE).
CCI, Charlson comorbidity index; HTN, hypertension; BMI, body mass index.

Table 3
Unadjusted and adjusted hazard ratios for ACE among breast cancer survivors who underwent radiation therapy.

Variable	Unadjusted			Adjusted		
	HR	95% CI	Gray's *P*	HR	95% CI	Gray's *P*
Age, year (Continuous)	1.05	1.05–1.09	0.005	1.04	1.00–1.08	0.071
Smoking (y v n)	1.22	0.17–8.89	0.842	NI		
Charlson comorbidity index (Continuous)	1.32	1.14–1.54	<.001	1.17	0.99–1.38	0.068
History of hypertension (y v n)	2.14	1.19–3.85	0.011	NI		
BMI, kg/m^2 (Continuous)	1.08	0.99–1.17	0.071	NI		
Cholesterol (high/borderline v normal)	1.26	0.69–2.30	0.443	NI		
Weekly physical exercise (y v n)	0.27	0.13–0.57	0.001	0.37	0.17–0.79	0.010
Residential area (metropolitans v rural)	1.53	0.84–2.78	0.167	NI		
Income (bottom 50% v upper 50%)	1.35	0.75–2.43	0.316	NI		
Disabled status (y v n)	22.1	3.02–162.1	0.002	21.9	2.50–191.6	0.005
Laterality (left-sided v right-sided)	1.28	0.71–2.29	0.413	NI		
Anthracycline chemotherapy (y v n)	1.21	0.68–2.16	0.515	NI		

HR: hazard ratio, CI: confidence interval, NI: not included in the final step of the multivariate analysis.
[a)] Cases refers to women with newly diagnosed breast cancer who underwent breast surgery and adjuvant radiation therapy, and matched controls refers to age-, smoking-, and comorbidity-matched women without cancer from the general population.

may interact with BMI. For example, a 2015 study revealed that weight gain increased the non-cancer mortality rate among breast cancer survivors, and Guenancia et al. reported that chemotherapy-induced cardiotoxicity risk was highest at a BMI of ≥30 kg/m^2 and lowest at a BMI of <25 kg/m^2 [22,23].

A regression model clearly demonstrated that exposure to RT for breast cancer was associated with the long-term risk of ACE, and that model incorporated various factors, such as age, mean heart radiation dose, BMI of ≥30 kg/m^2, current smoking status, and histories of circulatory disease, chronic obstructive pulmonary disease, and diabetes [5,6]. Although the proportional risks of ACE were similar regardless of the specific risk factors, the absolute risk became smaller among patients with risk factors. Thus, given the potential effects of BMI and its disparities in different cohorts, it is possible that the absolute risk may further decrease when the BMI cut-off value is lower than 30 kg/m^2. Unfortunately, the present study only included a small proportion of patients who were obese or overweight, and we were unable to perform a complete statistical analysis to examine the risk of ACE in this subgroup. Thus, further studies of populations with broader BMI distributions are needed to determine whether the absolute risk from adjuvant RT is exacerbated among women with low BMI values.

In the present study, patients with adjuvant RT for breast cancer mostly received adjuvant hormone therapy, chemotherapy, and/or target agent at the same time, obscuring the possible correlation between RT and ACE risk. Compared with tamoxifen that was not associated with adverse cardiovascular effects in the most recent overview review of randomized trials [24,25], aromatase inhibitors were associated with a higher risk of cardiovascular disease [26]. Furthermore, hormone therapy causes fatigue and musculoskeletal syndromes, resulting in patients having a more sedentary lifestyle, which could also have detrimental effects on ACE. Anthracycline therapy and trastuzumab are also associated with increased risks of heart failure [27], and studies have revealed that exercise prevents anthracycline-related heart failure [28]. With respect to no association with anthracycline use and ACE risk in the present study, exercise might have prevented anthracycline-related heart failure risk. However, considering that these adverse effects mostly occurred during adjuvant treatment but not thereafter, we inferred that adjuvant RT may have been the main cause of persistent risk observed during the follow-up [29].

As expected, the risk of ACE was associated with increased age, greater BMI, higher CCI, prolonged follow-up, underlying hypertension, high cholesterol levels, and being disabled. However, the present study also has several limitations. First, although the two groups were matched according to three clinically relevant factors, the retrospective design may have obscured other inherent differences between the two groups. Several variables, including physical activity and cholesterol levels, were slightly imbalanced between cases and controls. The direction of causality was unclear, and women who experienced any abnormalities in their body probably modified their lifestyle before they were diagnosed with cancer. Second, the longer-term effects of a healthy lifestyle on RT-related heart disease remain unclear based on our relatively short follow-up. It is unknown whether physical activity produces sustained benefit in the long term, or whether it simply delays development of ACE. Third, data regarding trastuzumab use were unavailable. Fourth, evaluating individuals who participated in the national health screening might have produced a bias toward a more health-conscious sample. Fifth, we only obtained data on baseline characteristics at breast cancer diagnosis and not during follow-up; thus, investigating the temporal effect of adjuvant systemic treatment on physical activity was not possible. There was a lack of detailed information on disability. Sixth, we could not analyze the dose-response relationship by increasing physical activity levels because of missing data. Finally, the present study only evaluated East Asian women, who were predominantly slender and tended to not smoke.

Although data regarding the RT technique, cardiac dose, and use of internal mammary node irradiation could not be obtained in the present study, the data could be inferred from several reports. Unlike other Western countries, internal mammary node irradiation was used more frequently in up to 50% of patients with locally advanced breast cancer according to a nationwide survey in Korea [30,31]. In a recent report from the Korean Radiation Oncology Group 08-06 study, which was a nationwide phase III clinical trial investigating the effects of internal mammary nodes irradiation in positive breast cancer patients, individual case review of RT plans were conducted for 102 participants who were randomly selected from 747 participants in 13 hospitals based on data on internal mammary node irradiation, tumor laterality, and type of surgery [32]. The tangent technique (62.7%) was the most commonly used technique, followed by photon/electron mix technique (23.5%) and reverse hockey stick technique (13.7%). The mean heart dose was 4.05 ± 3.29 Gy overall, 5.49 Gy for patients with tumors in the left breast, and 2.67 Gy for those with tumors in the right breast. In patients without internal mammary node irradiation, the heart dose was 5.16 vs. 1.79 Gy for the left vs. right breast, respectively. These results were similar to those from Western countries [9,33]. In an analysis of 308,861 US women from the SEER database, the cardiac mortality ratio was 1.20 (95% confidence interval, 1.04–1.38), which is similar to the hazard ratio of 1.28 (95% confidence interval, 0.71–2.29) in the present study, implying that the issue may be related to the statistical power [34]. According to 2018 nationwide practice pattern survey in Korea, 81.3% of respondents from 54 hospitals routinely underwent the heart-sparing technique for left breast tumors since 2012–2015 (accepted for publication elsewhere).

In conclusion, similar risks of heart disease were observed among Korean breast cancer survivors who underwent adjuvant RT and women from the general population who were matched according to age, comorbidities, and smoking history. Furthermore, most of the subjects had healthy lifestyle factors, which included no cigarette smoking, performing at least moderate physical exercise, and maintaining an appropriate weight, and these women might be underrepresented in Western studies. The present study also revealed that performing at least moderate physical activity was associated with protection against RT-related cardiac disease. The long-term effect of physical activity on ACE is uncertain, but these findings suggest that patients who undergo breast RT should be encouraged to increase their exercise participation level with all sorts of ways in order to optimize their long-term quality of life.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Authors' contributions

Conception and design: Y.B. Kim, E. Park.
Development and methodology: J.S. Chang, J. Shin, Y.B. Kim, E. Park.
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Shin, Y.B. Kim, E. Park.
Analysis and interpretation of data (e.g. statistical analysis, biostatistics, computational analysis): J.S. Chang, J. Shin, Y.B. Kim, E. Park.
Writing, review, and/or revision of the manuscript: J.S. Chang, J. Shin, Y.B. Kim, E. Park.
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y.B. Kim, E. Park.
Study supervision: J.S. Chang, J. Shin, Y.B. Kim, E. Park.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2018.11.003.

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