J Breast Cancer. 2020 Jun;23(3):291-302
https://doi.org/10.4048/jbc.2020.23.e30
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Original Article

Coronary Event Analysis in Breast Cancer Patients Who Received Breast-Conserving Surgery and Post-Operative Radiotherapy: a Korean Nationwide Cohort Study

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Received: Jan 21, 2020
Accepted: Apr 9, 2020

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ABSTRACT

Purpose: Adjuvant breast radiotherapy (RT) following breast-conserving surgery (BCS) has been reported to induce cardiac toxicity in breast cancer patients. We investigated the incidence and risk factors of major coronary events after breast RT using Korean nationwide Health Insurance Review and Assessment data.
Methods: Using data from a nationwide quality assessment of breast cancer treatment, we identified 3,251 patients who received breast RT after BCS in 2013. Data about major coronary events were additionally collected from national claims data. We defined major coronary events according to the International Classification of Diseases, 10th revision (ICD-10) codes I20-25.
Results: A total of 172 major coronary events (5.3%) occurred among 3,251 breast cancer patients. The 1-year, 2-year, and 3-year coronary event-free survival rates were 98.1%, 96.4% and 95.2%, respectively. Patients with underlying diabetes mellitus (88.6% vs. 95.7%, $p < 0.001$), high blood pressure (HBP) (89.4% vs. 96.3%, $p < 0.001$), and cerebrovascular accident (CVA) (84.0% vs. 95.4%, $p < 0.001$) showed significantly worse 3-year coronary event-free survival rates than those without comorbidities. Multivariate analysis revealed that patient age ($p < 0.001$), HBP ($p < 0.001$), CVA ($p = 0.025$), adjuvant hormonal therapy ($p = 0.034$), and Herceptin therapy ($p < 0.001$) were significantly associated with major coronary events in breast cancer patients.
Conclusion: The incidence of major coronary events after breast RT may be higher in breast-cancer patients with risk factors such as underlying HBP or CVA, or who were in receipt of adjuvant Herceptin therapy. Heart-sparing RT techniques or intensity-modulated RT should be considered for breast-cancer patients with risk factors for heart toxicity.

Keywords: Breast neoplasms; Coronary artery disease; Radiotherapy; Risk factors

Funding

The authors wish to acknowledge the financial support of the St. Vincent's Hospital, The Catholic University of Korea, research institute of medical science foundation (SVHR-2020-13). This study is supported by a joint project using quality assessment research data between Catholic University of Korea and Korean Health Insurance Review & Assessment Service.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Lee JH, Kang MY; Data curation: Sung SY, Lee JH, Yang KH, Seo YY, Kang MY; Formal analysis: Lee JH, Yang KH, Seo YY, Kang MY; Investigation: Lee JH, Yang KH; Methodology: Lee JH, Yang KH, Seo YY, Kang MY; Project administration: Lee JH; Resources: Sung SY, Lee JH; Software: Sung SY, Lee JH; Supervision: Lee JH, Yang KH; Validation: Seo YY; Visualization: Sung SY, Lee JH; Writing - original draft: Sung SY, Lee JH; Writing - review & editing: Sung SY, Lee JH.

INTRODUCTION

The incidence of cancer has increased continuously, such that cancer is now the most common cause of mortality, accounting for 29.1% of total deaths in South Korea. Breast cancer was the most common cancer in Korean women in 2016 [1]. The incidence of breast cancer has increased an average of 4.5% per year since 2005, and the reported incidence rate had reached 85 patients per 100,000.

Breast-conserving surgery (BCS) followed by adjuvant breast radiotherapy (RT) is the current standard treatment for early-stage breast cancer patients. Addition of adjuvant breast RT after lumpectomy significantly decreased the local recurrence rate and resulted in survival outcomes equivalent to those obtained from radical mastectomy [2-5]. However, studies with long-term follow-up suggested that breast RT also increased the risk of cardiovascular morbidity [6-11]. Irradiation to the heart may damage the cardiac muscle and coronary artery, and lead to ischemic heart disease. A study conducted by Darby et al. [6] reported a significant dose-response relationship between the mean irradiation dose to the heart and the risk of ischemic heart disease.

There have been recent advances in the treatment of breast cancer, including chemotherapy, target agent, and RT techniques. Anthracycline- and taxane-based regimens are now the most commonly used for adjuvant chemotherapy [12,13]. A human epidermal growth factor 2 (HER2)-targeted agent, such as Herceptin, is used in patients with a HER2-positive tumor [14-16]. New RT techniques, including a heart-sparing technique and intensity-modulated RT (IMRT), have also been adopted to reduce radiation toxicity [17,18]. However, a heart-sparing technique such as deep inspiration breath-hold or gating, is time-consuming and IMRT is more costly than conventional RT. Thus, only patients at high-risk for major coronary events should receive these specialized RT techniques to reduce cardiac toxicity.

Since 2011, the Korean Health Insurance Review & Assessment Service (HIRA), which is a government agency, has carried out an annual nationwide quality assessment program to evaluate the treatment of breast cancer. Using these nation-wide data, we investigated the incidence and risk factors of major coronary events in patients with early-stage breast cancer who had received BCS followed by breast irradiation.

METHODS

Data source: quality assessment program

We included breast cancer patients who were newly diagnosed in 2013 using the annual data of the quality assessment program, a cross-sectional study conducted by the HIRA to monitor the quality of medical practice. The quality assessment program was conducted using national claims data and mandatory survey reports recorded by health care providers [19]. The database contained patient demographics encompassing age, type of medical insurance, stage of cancer according to the American Joint Committee on Cancer (AJCC) guidelines, and treatment(s) received, including surgery, pathologic report, endocrine therapy, chemotherapy, and RT. If the data was insufficient to assess quality of practice, a separate survey sheet was used to collect data directly from health care providers. A reliability check was carried out by means of a direct visit to the health care provider or by requesting medical records. Death data were extracted from computerized resident registration data of

the Ministry of Security and Public Administration with the review of the Ministry of Health and Welfare. Approval for this study was obtained from the Institutional Review Board (approval No. VIRB-OE222-002). The requirement for informed consent was waived because of the non-identifiable nature of the study.

We identified female patients who had received breast-cancer surgery between January 2013 and December 2013 by using International Classification of Diseases, 10th revision (ICD-10) code C50, which indicates breast cancer. Patients who had stage I–III disease according to the AJCC 8th edition and were older than 18 years were eligible for the quality assessment program. Exclusion criteria were as follows: 1) history of sarcoma or lymphoma; 2) inflammatory breast cancer or occult breast cancer, defined as disease with no primary breast lesion and positive axillary lymph nodes; 3) synchronous or metachronous bilateral breast-cancer; 4) patients who had a history of another malignancy within the past 5 years; 5) patients who had a distant metastatic lesion; and 6) patients who were pregnant.

We identified a total of 17,076 patients who had received surgical resection of breast cancer in 196 institutions and were eligible for the quality assessment program. There were 165 institutions (84.2%) that had carried out less than 150 operations a year. All patients treated in those institutions were included in the assessment. Another 31 institutions (15.8%) had carried out more than 150 operations a year. For those 31 institutions, 150 patients per institution were selected by means of random sampling according to the patient's age, stage of cancer, and institutional volume (secondary vs. tertiary) for inclusion in the study. After excluding 11 institutions due to sampling problems and exclusion criteria, a total of 7,710 patients treated in 185 institutions were included in the quality assessment.

Study population

Of the 7,710 patients who were included in the quality assessment program, only patients who had received BCS and adjuvant RT between January 1, 2013, and December 31, 2013, were included in this study. Exclusion criteria were as follows: 1) patients who had received radical mastectomy; 2) patients who did not complete post-operative RT; and 3) patients diagnosed with a major coronary event before completion of post-operative RT.

We defined the clearance period as being from January 1, 2012, to the last date of post-operative RT to clarify the diagnosis of diabetes mellitus (DM), HBP, CVA, and chronic obstructive pulmonary disease (COPD) irrelevant to breast cancer treatment. A total of 3,251 patients were identified for inclusion in this study. This study was supported by the HIRA, and approval of an Institutional Review Board was waived by the database provider. Informed consent was also waived because the patient data were collected from administrative data without identifiable personal information.

Data about major coronary events

Besides data from the quality assessment program, we collected additional data from the national claims data of HIRA from 2012 to 2017. The additional extracted data included the diagnosis of major coronary events, admission history, diagnostic examination, treatment procedure, and surgery. Major coronary events were defined as a diagnosis of myocardial infarction (ICD-10 codes I21-24), coronary revascularization, or death from ischemic heart disease (ICD-10 codes I20-25) [6]. The past history of underlying disease related to a major coronary event was also collected, as were past histories of DM, HBP, CVA, and COPD.

https://doi.org/10.4048/jbc.2020.23.e30

Statistical analyses

We used descriptive statistics to characterize patient demographics, institution, and patterns of treatment, including identification of surgical exploration of axillary lymph nodes, adjuvant endocrine therapy, adjuvant chemotherapy, and therapy targeted on human epidermal growth factor receptor 2 (HER2). Overall survival (OS) was defined as the time interval between the last date of post-operative RT and death by any cause or the last follow-up date. Coronary event-free survival was defined as the time interval between the last date of post-operative RT and a major coronary event, death, or the last follow-up. The Kaplan-Meier method was used to generate survival curves. The univariate and multivariate analyses used Cox proportional hazard regression. A $p < 0.05$ was regarded as statistically significant. All statistical analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, USA).

RESULTS

Baseline characteristics

The median age of all 3,251 patients was 50 years (range, 19–88). There were 2,745 patients (84.4%) < 60 years of age and 506 (15.6%) ≥ 60 years. Most patients were in the early stage of breast cancer: 1,870 patients with stage I (57.5%) and 1,114 patients with stage II (34.3%) disease. There were 229 (7.0%) patients with underlying DM, 533 (16.4%) with underlying HBP, and 69 (2.1%) with underlying CVA. Patient characteristics are described in detail in **Table 1**.

Pattern of breast-cancer treatments

Nearly all of the patients (99.7%) received axillary lymph node sampling or dissection during breast surgery. Of 3,251 patients, 2,299 (70.7%) received adjuvant hormonal therapy. Adjuvant

Table 1. Patient characteristics (n=3,251)

Factors	Values
Age (yr)	
< 60	2,745 (84.4)
≥ 60	506 (15.6)
Institution	
Tertiary	2,155 (66.3)
Secondary	1,096 (33.7)
Stage	
I	1,870 (57.5)
II	1,114 (34.3)
III	214 (6.6)
Unknown	53 (1.6)
History of DM	
No	3,022 (93.0)
Yes	229 (7.0)
History of HBP	
No	2,178 (83.6)
Yes	533 (16.4)
History of COPD	
No	3,237 (99.6)
Yes	14 (0.4)
History of CVA	
No	3,182 (97.9)
Yes	69 (2.1)

Values are presented as number (%).
COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DM = diabetes mellitus; HBP = high blood pressure.

https://doi.org/10.4048/jbc.2020.23.e30

Table 2. Patterns of breast-cancer treatment

Treatment	Values
Axillary node sampling/dissection	
No	10 (0.3)
Yes	3,241 (99.7)
Adjuvant hormone therapy	
No	952 (29.3)
Yes	2,299 (70.7)
Adjuvant HER2-targeted therapy	
No	2,770 (85.2)
Yes	481 (14.8)
Adjuvant chemotherapy	
No	996 (30.6)
Yes	2,255 (69.4)
Anthracycline-based chemotherapy	
No	1,733 (53.3)
Yes	1,518 (46.7)
Taxane-based chemotherapy	
No	2,685 (82.6)
Yes	566 (17.4)

Values are presented as number (%).
HER2 = human epidermal growth factor receptor 2.

HER2-targeted therapy was administered to 481 patients (14.8%), and 2,255 (69.4%) received adjuvant chemotherapy. Anthracycline-based chemotherapy was used in 1,518 patients (46.7%), and a taxane-based regimen was used in 566 (17.4%) patients (**Table 2**).

Coronary event-free survival analyses

A total of 172 major coronary events (5.3%) occurred after adjuvant RT following BCS. During the first, second, and third year after RT, the number of events were 63, 55, and 37, respectively. The median follow-up time was 38.6 months. The 1-year, 2-year, and 3-year coronary event-free survival rates were 98.1%, 96.4%, and 95.2%, respectively (**Figure 1**). The median value was not reached.

Coronary event-free survival was analyzed in patients with an underlying disease, including DM, HBP, and CVA (**Figure 2**). The patients with underlying HBP showed a significant difference in 3-year coronary event-free survival compared to those without HBP (89.4% vs.

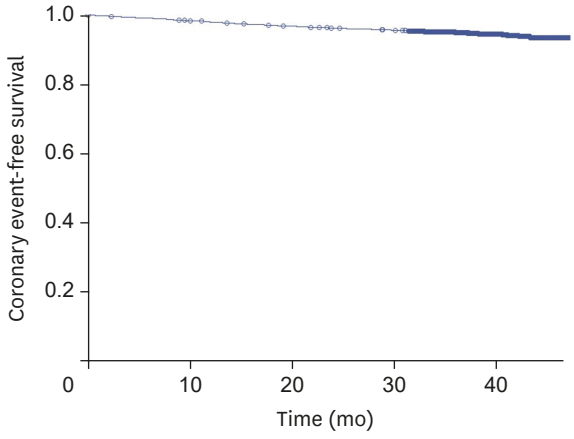

Figure 1. Coronary event-free survival curve for all patients.

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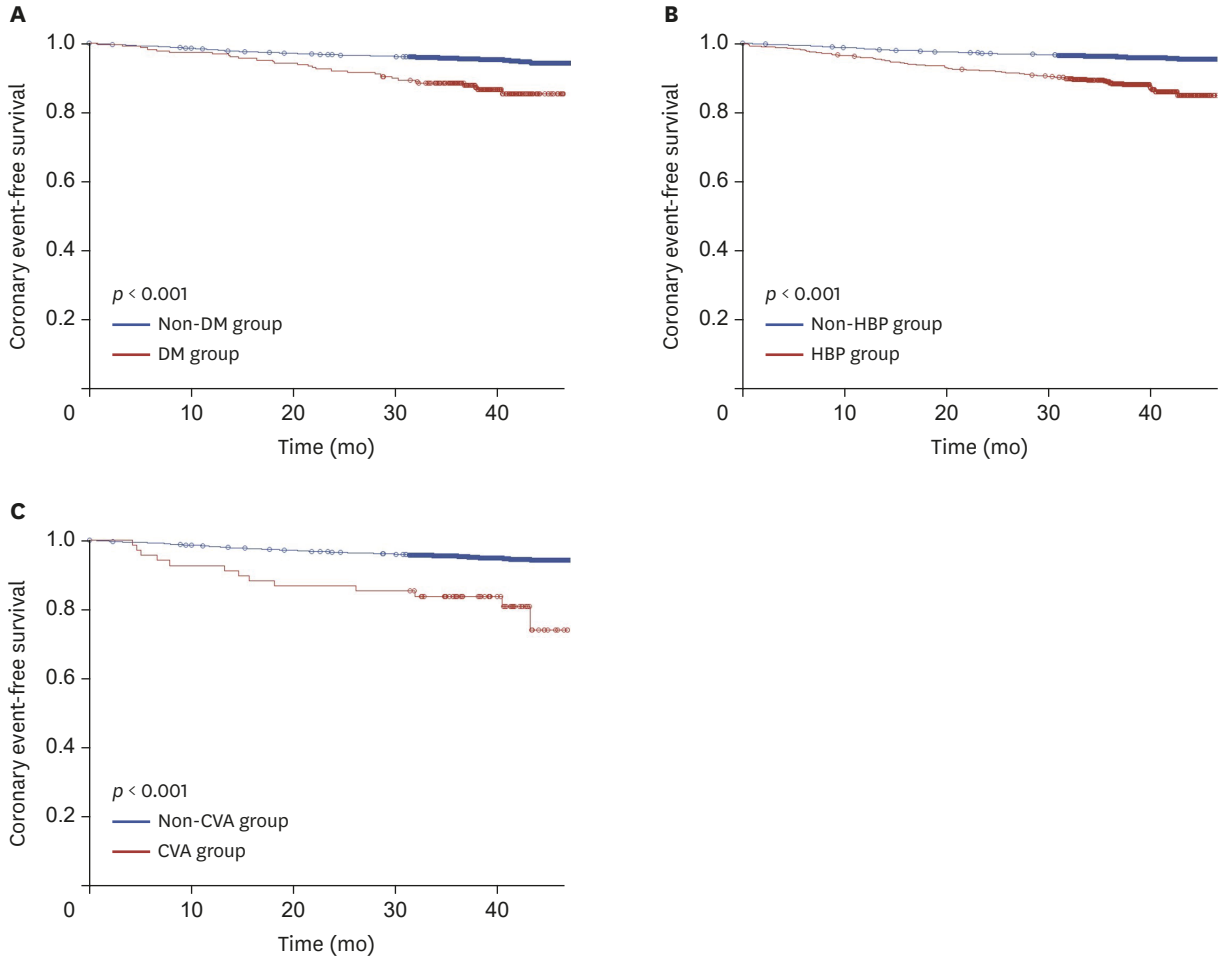

Figure 2. Coronary event-free survival curves between (A) DM group vs. non-DM group, (B) HBP group vs. non-HBP group, and (C) CVA group vs. non-CVA group.
DM = diabetes mellitus; HBP = high blood pressure; CVA = cerebrovascular accident.

96.3%, $p < 0.001$). The patients with underlying DM also had significantly lower 3-year coronary event-free survival rates than did those without DM (88.6% vs. 95.7%, $p < 0.001$), as did those with underlying CVA compared to those without CVA (84.0% vs. 95.4%, $p < 0.001$). Univariate analysis revealed that patient age ($p < 0.001$), underlying DM ($p < 0.001$), HBP ($p < 0.001$), CVA ($p < 0.001$), and receipt of adjuvant HER2-targeted therapy ($p = 0.005$) were significant risk factors for occurrence of a major coronary event (**Table 3**). On multivariate analysis, patient age ($p < 0.001$), underlying HBP ($p < 0.001$), underlying CVA ($p = 0.025$), receipt of adjuvant hormonal therapy ($p = 0.034$), and adjuvant HER2-targeted therapy ($p < 0.001$) were significantly associated with occurrence of a major coronary event (**Table 4**). Adjuvant HER2-targeted therapy significantly increased the risk (hazard ratio [HR], 1.971; 95% confidence interval [CI], 1.351–2.875, $p < 0.001$), but adjuvant hormonal therapy significantly decreased the risk of a major coronary event (HR, 0.700; 95% CI, 0.502–0.975, $p = 0.034$).

Overall survival analyses

The 1-year, 2-year, and 3-year OS rates were 99.8%, 99.2%, and 98.4%, respectively (**Figure 3**). Patients with underlying HBP showed a significantly lower 3-year OS than did those without HBP (97.2% vs. 98.6%, $p < 0.001$). The 3-year OS did not show a significant difference according to the presence of DM (97.3% vs. 98.5%, $p = 0.150$) or CVA (98.4% vs. 100%, $p = 0.640$)

https://doi.org/10.4048/jbc.2020.23.e30

Table 3. Univariate analysis for coronary event-free survival

Factors	Hazard ratio	95% CI	*p*-value
Age (yr)			< 0.001
< 60	1		
≥ 60	3.458	2.543–4.702	
Institution			0.064
Tertiary	1		
Secondary	1.333	0.983–1.809	
Stage			0.710
I	1		
II	1.167	0.853–1.598	
III	0.846	0.427–1.675	
History of DM			< 0.001
No	1		
Yes	2.835	1.912–4.203	
History of HBP			< 0.001
No	1		
Yes	3.184	2.339–4.334	
History of COPD			0.179
No	1		
Yes	2.601	0.645–10.493	
History of CVA			< 0.001
No	1		
Yes	3.979	2.260–7.004	
Adjuvant hormone therapy			0.077
No	1		
Yes	0.753	0.549–1.032	
Adjuvant HER2-targeted therapy			0.004
No	1		
Yes	1.698	1.185–2.435	
Adjuvant chemotherapy			0.233
No	1		
Yes	0.827	0.605–1.130	
Anthracycline based chemotherapy			0.501
No	1		
Yes	0.901	0.665–1.221	
Taxane based chemotherapy			0.638
No	1		
Yes	0.904	0.595–1.374	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DM = diabetes mellitus; HBP = high blood pressure; HER2 = human epidermal growth factor receptor 2.

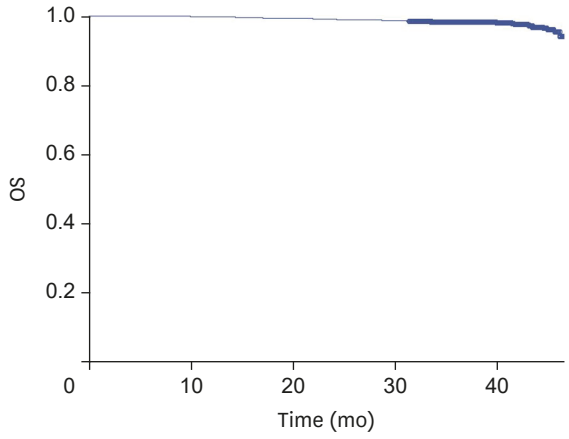

Figure 3. OS curve for all patients.
OS = overall survival.

https://doi.org/10.4048/jbc.2020.23.e30

Table 4. Multivariate analysis for coronary-event free survival

Factors	Hazard ratio	95% CI	*p*-value
Age (yr)			< 0.001
< 60	1		
≥ 60	2.312	1.614–3.312	
Institution			0.088
Tertiary	1		
Secondary	1.307	0.961–1.778	
History of DM			0.104
No	1		
Yes	1.440	0.928–2.234	
History of HBP			< 0.001
No	1		
Yes	1.887	1.312–2.716	
History of CVA			0.025
No	1		
Yes	1.969	1.089–3.560	
Adjuvant hormone therapy			0.034
No	1		
Yes	0.700	0.502–0.975	
Adjuvant HER2-targeted therapy			< 0.001
No	1		
Yes	1.971	1.351–2.875	
Adjuvant chemotherapy			0.126
No	1		
Yes	0.765	0.544–1.078	

CI = confidence interval; CVA = cerebrovascular accident; DM = diabetes mellitus; HBP = high blood pressure; HER2 = human epidermal growth factor receptor 2.

(**Supplementary Table 1**). On multivariable analysis, AJCC stage ($p < 0.001$), history of HBP ($p = 0.016$), and receipt of adjuvant hormonal therapy ($p < 0.001$) were significantly associated with OS (**Supplementary Table 2**).

DISCUSSION

Adjuvant breast RT following BCS, which is the current standard treatment in patients with early-stage breast cancer, contributes excellent local control and good cosmetic outcome [2,3,20,21]. However, breast RT is sometimes accompanied by radiation toxicity to the skin, lungs, and heart. Cardiotoxicity is a late toxicity induced by breast irradiation. As the 5-year survival outcome for breast cancer has reached over 95% and life expectancy has been prolonged, there has been increasing interest in cardiotoxicity.

A study based on 8 trials that began before 1,975 analyzed cause-specific mortality for 10-year survivors of breast cancer [7]. The authors reported an increase in coronary-related cause of death among patients who had received breast RT compared to those who did not ($p = 0.001$). Patients with left-side tumors also showed a mortality rate significantly higher than that of those with right-side tumors. We suggest that the risk of cardiac toxicity might be associated with breast RT, especially in cases with a left-side breast tumor. Another study by Darby et al. [6] included a total of 2,168 patients who had received RT between 1958 and 2001. Their findings revealed a dose-response relationship between radiation dose to the heart and increased risk of major coronary events, specifically that a 1 Gy increase in the mean radiation dose to the heart corresponded with a 7.4% increase in the rate of major coronary events [6].

https://doi.org/10.4048/jbc.2020.23.e30

Despite these findings, the association between breast RT and cardiac toxicity has so far been controversial. The incidence of cardiac toxicity has changed with the development of RT techniques over time. A study using the Surveillance, Epidemiology, and End Results database analyzed 16,270 women who had been diagnosed with breast cancer between 1986 and 1993 and reported no significant difference in the risk of hospitalization for cardiac events between women with left- versus right-side breast cancer [22]. The authors conducted additional analyses for patients with a long-term follow up of 10 to 15 years, and again observed no significant difference in cardiac events between the 2 groups. Another recent study, which included breast-cancer patients who had been treated between 2000 and 2010, compared women who received breast RT with those who did not and found there was no significant difference in cardiac morbidity or mortality associated with breast irradiation [23].

Most of the studies that reported elevated mortality from cardiac causes included patients who had received RT before the 1970s, and primarily included patients treated with 2-dimensional RT techniques. After adoption of computed tomography (CT) scans in the 1990s, the use of planning CT increased [24]. Three-dimensional RT techniques allowed evaluation of the irradiated heart dose and adjustment of the angle of tangential beams. Use of heart-sparing RT techniques, including deep inspiration breath holding and gating techniques or IMRT, has also increased for breast-cancer patients in recent years [25-27]. A pattern-of-care study reported that heart-sparing techniques are offered in 90.2% of German radiation oncologic departments [17]. Advances in planning CT and heart-sparing techniques have undoubtedly contributed to the more favorable results of recent studies that showed no elevation of cardiac toxicity after breast RT.

This study investigated the incidence and risk factors for a major coronary event after adjuvant RT in 3,251 patients in an Asian population in 2013. The 3-year coronary event-free survival was 95.2%, and the 3-year OS rate was 98.4%. After a median 38.6 months of follow-up, a total of 172 patients (5.3%) experienced major coronary events. A study that analyzed 2,577 Korean patients with breast cancer reported that overall and breast cancer-specific survivals at 10 years were 94.9 and 96.5%, respectively [28]. They suggested that the excessive cardiac risk after breast RT may be small in healthy women who had fewer risk factors. Despite the indirect comparison, our results are consistent with recent studies that reported no elevation of cardiac toxicity after breast irradiation in breast-cancer patients who are otherwise healthy.

In contrast, patients with underlying DM, HBP, and CVA showed significantly worse 3-year coronary event-free survival than did those without DM, HBP, or CVA, which are well-known risk factors for myocardial infarction. A previous study by Darby et al. [6] concluded that the rates of major coronary events were increased in patients with cardiac-risk factors such as DM and other circulatory diseases. In our study, underlying HBP was significantly associated with the decreased 3-year OS rate. Furthermore, adjuvant HER2-targeted therapy was also significantly associated with major coronary events, increasing the risk of a major coronary event by 1.971 times. Evaluation of irradiated cardiac dose and use of heart-sparing techniques should be considered for patients with high-risk factors, including underlying comorbidities such as HBP or DM and receipt of HER2-targeted therapy [29]. In our analysis, anti-hormonal treatment significantly decreased the risk of death from a major coronary event in the multivariate analysis (HR, 0.007; 95% CI, 0.502–0.975; $p = 0.034$). It has been suggested that estrogen plus progestin may increase the risk of coronary heart disease among post-menopausal women, especially during the first year after the initiation of hormone

https://doi.org/10.4048/jbc.2020.23.e30

use in a randomized trial [30]. Thus, anti-hormonal treatment could reduce or delay the occurrence of a coronary artery event in post-menopausal breast cancer patients.

Our study has some limitations due to the retrospective cohort design. Our use of the National Health Insurance Review and Assessment data prevents us from being able to obtain information about laterality of breast cancer and individual irradiated dose to the heart. The relatively short follow-up period also suggests that the results of this study should be interpreted with caution.

In conclusion, underlying HBP and CVA and receipt of HER2-targeted therapy were risk factors for major coronary events. Thus, heart-sparing RT techniques or IMRT are recommended for breast-cancer patients with these risk factors in order to reduce cardiac toxicity.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Univariate analysis for overall survival

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Supplementary Table 2

Multivariate analysis for overall survival

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