Am J Cancer Res 2019;9(5):1017-1026
www.ajcr.us /ISSN:2156-6976/ajcr0094968

Original Article

Metformin reduces radiation-induced cardiac toxicity risk in patients having breast cancer

Jung-Min Yu[1,2*], Mao-Chih Hsieh[3*], Lei Qin[4], Jiaqiang Zhang[5], Szu-Yuan Wu[6,7,8]

[1]Department of Cardiovascular Surgery, Taichung Tzu Chi Hospital, Taiwan; [2]Department of Surgery, School of Medicine, Tzu Chi University, Taiwan; [3]Department of General Surgery, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [4]School of Statistics, University of International Business and Economics, Beijing, China; [5]Department of Anesthesiology, Henan provincial People's Hospital, People's hospital of Zhengzhou University, Zhengzhou, Henan Province, China; [6]Department of Radiation Oncology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [7]Department of Radiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [8]Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan. [*]Equal contributors.

Received March 16, 2019; Accepted April 15, 2019; Epub May 1, 2019; Published May 15, 2019

Abstract: To analyze the effects of metformin in reducing radiation-induced cardiac toxicity (RICT) risk during adjuvant radiotherapy (RT) after surgery for early-stage breast cancer women. We compare the consecutive occurrence of major heart events (heart failure and coronary artery disease) in women with early-stage breast cancer receiving adjuvant breast RT with metformin and in those receiving RT without metformin. A retrospective national cohort study was conducted using the Taiwan Cancer Registry of 2004-2014. This study included 6,993 women with early-stage breast cancer who received adjuvant breast RT. Metformin users were defined as patients prescribed metformin for >28 days during adjuvant breast RT. An inverse probability of treatment weighting (IPTW) Cox hazards model was used to estimate metformin effects on the occurrence of major heart events. Among women with breast cancer status post-surgery under adjuvant breast RT, 2,062 were prescribed metformin and 4,931 were not prescribed metformin. Cox proportional hazard regression analysis, with adjustment using IPTW, indicated that metformin use during adjuvant breast RT significantly reduces the risk of major heart events (adjusted hazard ratio [aHR], 0.789; 95% confidence interval [CI], 0.645-0.965; $P = 0.021$). In another negative control exposure, thiazolidinedione use during adjuvant breast RT did not statistically reduce consecutive RICT risk (aHR, 1.106; 95% CI, 0.768-1.594; $P = 0.589$). Our results suggest that metformin use during adjuvant breast RT was associated with reduced RICT risk in women with early-stage breast cancer.

Keywords: Radiation-induced cardiac toxicity, breast cancer, adjuvant breast radiotherapy, metformin

Introduction

Adjuvant breast radiotherapy (RT) improved locoregional control and disease-specific survival among patients with early-stage breast cancer [1]. Studies have reported adjuvant breast RT alone or RT in combination with other chemotherapy resulting in large cohorts of breast cancer survivors who are subject to late complications from breast RT [2-6]. These studies have argued that therapeutic benefits of adjuvant breast RT might be neutralized to some extent through delayed effects on the heart, thus decreasing the benefits of adjuvant breast RT [2-6]. Irradiation of a significant volume of the heart with a sufficiently high dose can damage virtually any component of the heart, including the myocardium, pericardium, coronary arteries, capillaries, heart valves, and heart conducting system [7]. Pericarditis is the typical acute manifestation of radiation-induced cardiac toxicity (RICT), whereas chronic RICT, including pericardial disease, coronary artery disease (CAD), cardiomyopathy, valvular disease, and conduction abnormalities, eventually leading to heart failure (HF) can manifest years or decades after adjuvant breast RT [8-10]. These complications can cause significant cardiac morbidity or mortality [11]. The data on the late RICT come primarily from survivors of breast cancer, where adjuvant breast RT is a frequent component of the initial management and survival is often prolonged, especially in early-stage breast cancer [12-14]. An aware-

ness of the potential for RICT led to the development of radiation protection drugs that might minimize irradiation injury to the heart or coronary artery.

These contemporary studies have indicated that metformin substantially decreases anthracycline-induced cardiotoxicity [15-19], although whether metformin could reduce RICT risk remains uncertain. Randomized controlled trials (RCTs) in patients with diabetes and metabolic syndrome have suggested that metformin improves peripheral endothelial function [20, 21]. Many preclinical studies have shown the protective effects of metformin on anthracycline-induced cardiotoxicity [15-19]. Furthermore, some preclinical data have shown that metformin has some radioprotective, antioxidant, and anti-fibrotic effects [22, 23]. However, no clinical data are available to prove the potential effect of metformin in decreasing RICT risk in patients with breast cancer receiving adjuvant breast RT with metformin use.

Studies examining the clinical utility of metformin among women with early-stage breast cancer receiving adjuvant breast RT are scarce because current studies are mostly limited by the number of cases, few events of RICT, or a lack of treatment information. To undertake this task, we used a cohort of patients having both an early-stage breast cancer identified from the Taiwan Cancer Registry Database (TCRD), which consisted of a non-screened detected population. In 2015, >63.39% of the patients diagnosed with early-stage breast cancer were at pathologic stages I-II [24]. This population provides a relatively homogenous patient group to examine RICT following adjuvant breast RT. In this study, we examined the consecutive RICT associated with metformin use among women with early-stage breast cancer who received metformin during adjuvant RT.

Patients and methods

Data source and study cohort

From the TCRD, we identified patients who had received a diagnosis of breast cancer between January 1, 2004 and December 31, 2015. The follow-up duration was from the index date to December 31, 2013. Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB 201712019). The cancer registry database of the Collaboration Center of Health Information Application contains detailed cancer-related information regarding clinical or pathological stages, pathological types, RT doses, and chemotherapy regimens used [25-32]. In this study, the diagnoses of the selected patients with left side breast cancer were confirmed according to their pathological data, and patients who had received a diagnosis of left side breast invasive ductal carcinoma (IDC) were confirmed to have no other cancer or distant metastasis.

Selection of cases and controls

Inclusion criteria were a diagnosis of left side breast IDC, age >20 years, received adjuvant breast RT, and American Joint Committee on Cancer (AJCC) pathologic stage I-II cancer without metastasis. The AJCC 7th edition was used for staging the breast IDC in all patients. Exclusion criteria were a history of cancer, HF, and CAD before breast IDC diagnosis, distant metastasis, male sex, in situ carcinoma, cigarette smoking habit, non-IDC pathology, end-stage renal disease, and use of anthracyclines or trastuzumab. The index date was the date on which patients finished adjuvant breast RT. Moreover, patients having left side breast IDC who did not receive sufficient adjuvant RT dose (≥50 Gy) to left side breast, dead before major heart events, adjuvant breast RT >2 months, or who did not receive breast surgery were excluded. Women with breast IDC who were prescribed metformin of ≥28 Gy defined daily dose (DDD) during adjuvant breast RT comprised the case group and those who were prescribed metformin of <28 Gy DDD during adjuvant breast RT comprised the control group. Among women who received and did not receive metformin during adjuvant breast RT, 2.43% and 1.98%, respectively, did not complete the adjuvant breast RT course (≥50 Gy) within 2 months; these patients were excluded. No statistical difference was observed in the completion rate of the adjuvant breast RT course between the metformin and non-metformin use groups. Patients who had undergone hypofraction breast irradiation, modern techniques such as Intensity Modulation Radiation Therapy, Volumetric Arc Therapy, or respiratory gating were not included in the current study. We only included women with left side breast IDC who were prescribed metformin (≥28 DDD) or not

prescribed metformin (<28 DDD) during adjuvant breast RT, but regardless of metformin use before or after the adjuvant breast RT. The enrolled patients were categorized into the following groups on the basis of their treatment modality to compare their consecutive major heart events (RICT) as the endpoint of interest (i.e., HF and CAD): group 1, metformin use during adjuvant breast RT; and group 2, non-metformin use during adjuvant breast RT. The endpoints of RICT were defined based on previous studies about risk of ischemic heart disease (i.e., HF and CAD) in women after RT for breast cancer [5, 33].

Study covariates

Comorbidities were determined according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes in the main diagnosis of inpatient records or if the number of outpatient visits was ≥2 within 1 year. Comorbidities with onset 6 months before the index date were recorded. Continuous variables are presented as mean ± standard deviation or median (1st quartile, 3rd quartile), where appropriate. The significant independent predictors, such as chronic obstructive pulmonary disease (COPD), diabetes complications severity index (DCSI), hypertension (HTN), transient ischemic attack (TIA), and ischemic heart disease, were determined using multivariate Cox proportional hazards regression analysis models, adjusted by using the inverse probability of treatment weighting (IPTW) to determine the hazard ratios (HRs). Generalized boosted models were used for estimating the necessary propensity score weights based on Daniel's study [34, 35]. Independent predictors were adjusted in the analysis, and major heart events among both groups were considered as end points, with group 2 (non-metformin use) as the control. For negative control exposure, we used Cox proportional hazard regression analysis using IPTW adjustment for the risk of major heart events in patients with left side early breast cancer who were prescribed thiazolidinedione or not during adjuvant breast RT. Patients taking thiazolidinedione in combination with metformin during adjuvant RT were excluded from the study. The duration and total dose of adjuvant RT were noted for each patient from the claims data.

Statistical analysis

The cumulative incidence of major heart events was estimated using the IPTW-adjusted Kaplan-Meier method, and differences between both groups were determined using the Cox model test. After adjustment for confounders, the Cox proportional hazards method was used to model the time from the index date to major heart events among both groups. In the multivariate analysis, HRs were adjusted for age, COPD, DCSI, HTN, TIA, ischemic heart disease, and metformin use. All analyses were performed using R Core Team (2018; version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value of <0.05 was considered statistically significant.

Results

In total, 6,993 women with early pathologic stage (stage I-II) left side breast IDC who underwent breast surgery and completed adjuvant breast RT were enrolled (**Table 1**). Of these, 2,062 and 4,931 women belonged to the metformin use and non-metformin use groups, respectively. The mean follow-up duration after the index date was 5.14 years (standard deviation, 1.44 years). No significant differences were observed between the prevalence of COPD, TIA, and DCSI ≥1 in the two groups. In addition, the median ages were similar between the two groups (59.89 versus 59.35 years old in groups 1 and 2, respectively). However, in group 1, the percentage of old (age ≥60 years) patients was significantly higher than that in the group 2, 54.42% versus 44.62%, respectively. The proportion of women with HTN in group 1 (73.86%) was higher than that in group 2 (58.99%). Furthermore, significantly more patients had ischemic heart disease in group 1 (27.55%) than in group 2 (22.49%; **Table 1**). Subsequent HF were identified in 241 (4.98%) and 74 (3.59%) patients in group 2 and group 1, respectively (**Table 2**). Moreover, consecutive CAD were identified in 236 (4.79%) and 72 (3.49%) patients in group 2 and group 1, respectively. All consecutive major heart events were identified in 419 (8.50%) and 129 (6.26%) patients in group 2 and group 1, respectively. The median adjuvant breast RT dose and duration were 50.4 (50-59.4) Gy and 6.9 (5.8-8.0) weeks, respectively.

Table 1. Characteristics of women with early stages breast cancer who were and were not given metformin during adjuvant breast radiotherapy interval

	Metformin dose <28 DDD during RT (n = 4,931)		Metformin dose ≥28 DDD during RT (n = 2,062)		*P*-value
	N	(%)	N	(%)	
Age					<0.001
<60	2,731	55.38	981	47.58	
≥60	2,200	44.62	1,081	52.42	
COPD					0.363
No	4,806	97.47	2,018	97.87	
Yes	125	2.53	44	2.13	
HTN					<0.001
No	2,022	41.01	539	26.14	
Yes	2,909	58.99	1,523	73.86	
TIA					0.100
No	4,788	97.10	1,986	96.31	
Yes	143	2.90	76	3.69	
Ischemic heart disease					<0.001
No	3,822	77.51	1,494	72.45	
Yes	1,109	22.49	568	27.55	
DCSI ≥1					0.750
No	4,776	96.86	2,000	97.00	
Yes	155	3.14	62	0.30	

RT, radiotherapy; DDD, defined daily dose; COPD, chronic obstructive pulmonary disease; DCSI, Diabetes Complications Severity Index; HTN, hypertension; TIA, transient ischemic attack.

Table 2. Major heart events of women with early stage breast cancer who were and were not given metformin during adjuvant breast radiotherapy interval

	Metformin dose <28 DDD during RT (n = 4,931)		Metformin dose ≥28 DDD during RT (n = 2,062)		*P*-value
	N	(%)	N	(%)	
Heart failure					0.020
No	4,690	95.11	1,988	96.41	
Yes	241	4.89	74	3.59	
CAD					0.019
No	4,695	95.21	1,990	96.51	
Yes	236	4.79	72	3.49	
All heart events					0.002
No	4,512	91.50	1,933	93.74	
Yes	419	8.50	129	6.26	

RT, radiotherapy; DDD, defined daily dose; CAD, coronary artery disease.

Cox proportional hazard regression analysis was conducted to investigate the risk of major heart events among the patients, with adjustment using IPTW; the results indicated that age ≥60 years, HTN, TIA, ischemic heart disease, and metformin use during adjuvant breast RT were significant independent prognostic factors (**Table 3**). Age ≥60 years (adjusted HR [aHR], 1.355; 95% confidence interval [CI], 1.132-1.621; *P*<0.001), HTN (aHR, 1.412; 95% CI, 1.161-1.716; *P*<0.001), TIA (aHR, 1.400; 95% CI, 1.009-1.941; *P* = 0.044), and ischemic heart disease (aHR, 1.500; 95% CI, 1.123-1.954; *P*< 0.001) were significant independent prognostic factors for major heart events (**Table 3**). Metformin use ≥28 DDD during adjuvant breast RT could significantly reduce the risk of major heart events (aHR, 0.789; 95% CI, 0.645-0.965; *P* = 0.021).

To avoid analytic flaws, we used analogous negative control to identify and resolve confounding as well as other sources of errors [36]. In **Table 4**, we chose analogous oral hypoglycemic drugs (thiazolidinediones) as negative control exposure. After Cox proportional hazard regression analysis using IPTW adjustment, similar results indicated that age ≥60 years, HTN, TIA, and ischemic heart disease were significant independent prognostic factors (**Table 4**), but thiazolidinedione use ≥28 DDD during adjuvant breast RT could not significantly reduce the risk of subsequent major heart events (aHR, 1.106; 95% CI, 0.768-1.594; *P* = 0.589).

The estimates of the cumulative incidence of major heart events in women with left side breast IDC, obtained using the IPTW-adjusted Cox model method, were used to analyze the risk of major heart events associated with metformin use or not during adjuvant breast RT (**Figure 1**). To investigate the risk of major heart events after metformin use during adjuvant breast RT, the non-metformin group was used as the control. After IPTW adjustment for age, COPD, HTN, DCSI, ischemic

Table 3. Cox proportional hazard regression analysis using inverse probability of treatment weighting adjustment for the risk of major heart events in women with early stages breast cancer who were and were not given metformin during adjuvant breast radiotherapy interval

	Crude HR (95% CI)	Adjusted HR (95% CI)	*P*-value
Age ≥60	1.560 (1.318-1.846)	1.355 (1.132-1.621)	<0.001
COPD	1.704 (1.078-2.694)	1.451 (0.916-2.301)	0.113
HTN	1.595 (1.332-1.910)	1.412 (1.161-1.716)	<0.001
TIA	1.775 (1.295-2.434)	1.400 (1.009-1.941)	0.044
Ischemic heart disease	1.884 (1.306-2.543)	1.500 (1.123-1.954)	<0.001
DCSI (ref. = 0)			
DCSI ≥1	1.353 (1.140-1.605)	1.121 (0.930-1.352)	0.231
Metformin DDD (ref. <28 DDD)			
DDD ≥28	0.885 (0.726-1.078)	0.789 (0.645-0.965)	0.021

DDD, defined daily dose; COPD, chronic obstructive pulmonary disease; DCSI, Diabetes Complications Severity Index; HTN, hypertension; TIA, transient ischemic attack; HR, hazard ratio; CI, confidence interval.

Table 4. Cox proportional hazard regression analysis using inverse probability of treatment weighting adjustment for the risk of major heart events in women with early stages breast cancer who were and were not given thiazolidinediones during adjuvant breast radiotherapy interval

	Crude HR (95% CI)	Adjusted HR (95% CI)	*P*-value
Age ≥60	1.450 (1.229-1.757)	1.350 (1.129-1.616)	<0.001
COPD	1.693 (1.167-2.585)	1.481 (0.935-2.347)	0.094
HTN	1.584 (1.441-1.821)	1.376 (1.132-1.672)	<0.001
TIA	1.864 (1.286-2.223)	1.406 (1.014-1.951)	0.041
Ischemic heart disease	1.795 (1.328-2.461)	1.501 (1.125-1.998)	<0.001
DCSI (ref. = 0)			
DCSI ≥1	1.342 (1.211-1.598)	1.086 (0.901-1.309)	0.386
Thiazolidinedione DDD (ref. <28 DDD)			
DDD ≥28	1.213 (0.844-1.743)	1.106 (0.768-1.594)	0.589

DDD, defined daily dose; COPD, chronic obstructive pulmonary disease; DCSI, Diabetes Complications Severity Index; HTN, hypertension; TIA, transient ischemic attack; HR, hazard ratio; CI, confidence interval.

heart disease, and TIA, the Cox model *p* value of the cumulative incidence of major heart events was <0.021 (**Figure 1**). The higher cumulative incidence of major heart events was observed in the non-metformin use group. Irrespective of thiazolidinedione use during adjuvant breast RT, the Cox model *p* value after IPTW adjustment was 0.589 (**Figure 2**).

Discussion

Breast cancer has been the most commonly diagnosed cancer worldwide [37, 38]. Breast cancer incidence has decreased in North America but not in Asia, where it continues to show an increasing trend [38]. A notable manifestation of the bimodal age distribution of breast cancer is observed in women [39]. The occurrence of early-onset breast cancer in the Asian population is earlier than that in the Western population, resulting in a higher incidence of breast cancer in young Asian women [40-42]. Moreover, the occurrence of late-onset breast cancer in Asian women is earlier (40-50 years) than in the Western countries (60-70 years), peaking at the age of 45-50 years in most women [40-42]. In our previous study, adjuvant breast RT was found to increase RICT risk in patients with breast cancer, particularly in younger patients [35]. Therefore, it should be offered with optimal heart-sparing techniques or radioprotection drugs, particularly in younger patients with early-stage breast cancer with good prognosis and long life expectancy [35]. In this study, we evaluated the radioprotective effect of metformin on RICT. Furthermore, this is the first study to estimate the effect of metformin use in reducing RICT

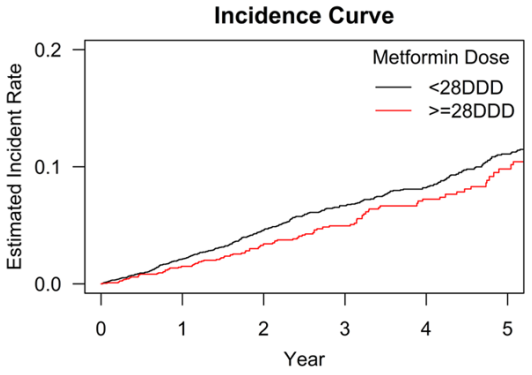

Figure 1. Estimates of the cumulative incidence of major heart events in women with early stages breast cancer who were and were not given metformin during adjuvant breast radiotherapy interval, as obtained using the inverse probability of treatment weighting-adjusted Kaplan-Meier method. Note: *P* value of Cox model test for cumulative incidence of major heart events of the two groups was 0.021.

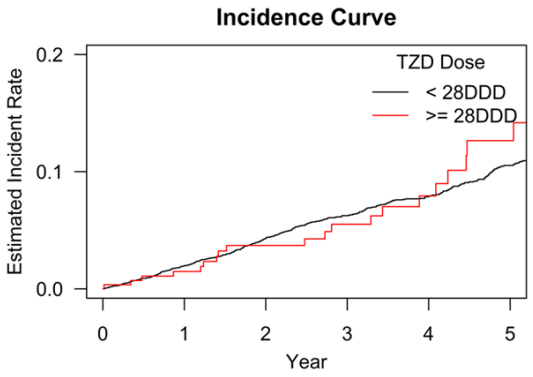

Figure 2. Estimates of the cumulative incidence of major heart events in women with early stages breast cancer who were and were not given thiazolidinediones during adjuvant breast radiotherapy interval, as obtained using the inverse probability of treatment weighting-adjusted Kaplan-Meier method. Note: *P* value of Cox model test for cumulative incidence of major heart events of the two groups was 0.589.

risk in patients with breast cancer receiving adjuvant breast RT.

The proportion of people in old age and with HTN and ischemic heart diseases in group 1 was greater than that in group 2, and the differences between the two groups in terms of COPD, TIA, and DCSI were nonsignificant (**Table 1**). Age, HTN, and ischemic heart diseases are major risk factors for CAD or HF [43-51]. HTN increases the risk of CAD or HF at all ages [46, 47]. The prevalence of CAD or HF has been increasing due to an increase in the aging population [43-45]. Ischemic heart diseases are a dominant cause of CAD or HF [49-51], adjuvant breast RT with scatter irradiation to coronary artery or heart might aggravate and speed up the process of CAD or HF [5, 35]. Patients with ischemic heart disease may have CAD or HF because of prior myocardial infarction followed by left ventricular dysfunction and remodeling, or hibernating myocardium due to chronic but potentially reversible ischemic dysfunction [50, 51]. In addition, CAD may be present in patients with HF from other causes and may sometimes be overlooked as a contributing factor [49]. Therefore, in our study, the endpoints of major heart events include CAD and HF (**Table 2**). In the metformin use group, the number of patients with comorbidities such as old age, HTN, and ischemic heart diseases is greater but that with major heart events is lower than that of the non-metformin use group (**Table 2**). For the competing event, metformin users had a relatively high risk of major heart events compared with non-metformin users. Despite the competition of unclear bias to the endpoint, the Cox model would be biased toward null with regard to the effect of metformin users having greater than expected proportions of underlying diseases and old age; hence, the conclusions of the current study should remain valid.

HTN, TIA, old age, and ischemic heart disease were independent risk factors after Cox proportional hazard regression analysis using IPTW adjustment for the risk of major heart events in patients with left side breast cancer irrespective of whether they were prescribed metformin during adjuvant breast RT (**Tables 3** and **4**). The findings were compatible with previous studies about risk factors for CAD or HF [43-51]. To avoid analytic flaws, we used analogous negative control to identify and resolve confounding as well as other sources of error [36]. In **Table 4**, we choose analogous oral hypoglycemic drugs (thiazolidinediones) as negative control exposure because metformin and thiazolidinediones have similar efficacy as monotherapy and similar indications for patients with diabetes [52]. After Cox proportional hazard regression analysis using IPTW adjustment, the similar results indicated that age, HTN, TIA, and ischemic heart disease were significantly independent prognostic factors (**Table 4**), but thiazolidinedione use ≥28 DDD during adjuvant breast RT could not significantly reduce the risk of subsequent major heart events (**Table 4**

and **Figure 2**). If our results were highly affected by user bias, we would have found reduced RICT risk in all patients who received thiazolidinediones or metformin. Although we cannot totally remove the potential user bias from our study because of the nature of an observational study, all our analogous negative control analyses support the robustness of our results.

The strengths of this study were its large sample size, homogenous population, and the novelty of the treatment for reducing RICT risk. This large-scale cohort study with a relatively long follow-up period evaluated the long-term RICT risk in patients with breast cancer patients. This is the first study to reveal that metformin use during adjuvant breast RT could lower RICT risk in patients with early-stage breast cancer. In clinical practice, metformin may be prescribed for patients with left side breast cancer patients receiving adjuvant breast RT. Metformin use specifically during adjuvant breast RT can be considered for clinical practice or further selection of thoracic RT with scatter irradiation dose to heart or coronary artery in future clinical trials.

This study had some limitations. First, because all patients in this study were Asian, the corresponding ethnic susceptibility is unclear; hence, our results should be cautiously extrapolated to non-Asian populations. Second, comorbidities were diagnosed solely according to ICD-9-CM codes. However, the Bureau of National Health Institute randomly reviews charts and interviews patients to verify the diagnosis accuracy. Thus, hospitals with outlier chargers or practices may be audited and subsequently charged with heavy penalties if instances of malpractice or discrepancies are identified. Finally, the TCRD does not contain information on dietary habits, socioeconomic status, or body mass index, which may be risk factors for major heart events. Therefore, a large-scale randomized trial of carefully selected patients receiving suitable treatments is essential to obtain crucial information on population specificity and disease occurrence. Considering the magnitude and statistical significance of the observed outcomes in this study, these limitations probably did not affect the conclusions.

Conclusions

Metformin use significantly reduces RICT in patients with left side breast cancer receiving adjuvant breast RT.

Acknowledgements

Taipei Medical University and Wan Fang Hospital (108-wf-swf-09) & Lei Qin's work is supported by National Natural Science Foundation of China (61603092), National Statistical Science Research Key Project (2016LZ35), University of International Business and Economics Huiyuan outstanding young scholars research funding (17YQ15), "the Fundamental Research Funds for the central Universities" in UIBE (CXTD10-10) & China National Natural Science Foundation (No: 81771149).

Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB No. 201712019).

Disclosure of conflict of interest

None.

Abbreviations

RT, radiotherapy; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; aHR, adjusted hazard ratio; IPTW, inverse probability of treatment weighting; TCRD, Taiwan Cancer Registry Database; HF, heart failure; CAD, coronary artery disease; HTN, hypertension; DDD, defined daily dose; COPD, chronic obstructive pulmonary disease; DCSI, Diabetes Complications Severity Index; RICT, radiation-induced cardiac toxicity; IDC, invasive ductal carcinoma.

Address correspondence to: Dr. Szu-Yuan Wu, Department of Radiation Oncology, Wan Fang Medical Center, Taipei Medical University, No. 111, Section 3, Hsing-Long Road, Taipei 116, Taiwan. E-mail: szuyuanwu5399@gmail.com; Jiaqiang Zhang, Department of Anesthesiology, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Zhengzhou, Henan Province, China. E-mail: jqzhang@henu.edu.cn

References

[1] Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L, Whelan T, Wang Y and Peto R. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in

17 randomised trials. Lancet 2011; 378: 1707-1716.
[2] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C and Wang Y. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087-2106.
[3] Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early breast cancer trialists' collaborative group. Lancet 2000; 355: 1757-1770.
[4] Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, Dodwell D, Ewertz M, Gray R, Jagsi R, Pierce L, Pritchard KI, Swain S, Wang Z, Wang Y, Whelan T, Peto R and McGale P. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol 2017; 35: 1641-1649.
[5] Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C and Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368: 987-998.
[6] Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, Peto R, Baum M, Fisher B, Host H, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994; 12: 447-453.
[7] Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, Mabuchi K, Marks LB, Mettler FA, Pierce LJ, Trott KR, Yeh ET and Shore RE. Radiation-related heart disease: current knowledge and future prospects. Int J Radiat Oncol Biol Phys 2010; 76: 656-665.
[8] Moreira LA, Silva EN, Ribeiro ML and Martins Wde A. Cardiovascular effects of radiotherapy on the patient with cancer. Rev Assoc Med Bras (1992) 2016; 62: 192-196.
[9] Jaworski C, Mariani JA, Wheeler G and Kaye DM. Cardiac complications of thoracic irradiation. J Am Coll Cardiol 2013; 61: 2319-2328.
[10] Groarke JD, Nguyen PL, Nohria A, Ferrari R, Cheng S and Moslehi J. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. Eur Heart J 2014; 35: 612-623.
[11] Gyenes G, Rutqvist LE, Liedberg A and Fornander T. Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. Radiother Oncol 1998; 48: 185-190.
[12] Hojris I, Overgaard M, Christensen JJ and Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy committee of the Danish breast cancer cooperative group. Lancet 1999; 354: 1425-1430.
[13] Gyenes G. Late cardiac morbidity and mortality in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 2007; 25: 2489; author reply 2489-2490.
[14] Harris EE, Correa C, Hwang WT, Liao J, Litt HI, Ferrari VA and Solin LJ. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol 2006; 24: 4100-4106.
[15] Kobashigawa LC, Xu YC, Padbury JF, Tseng YT and Yano N. Metformin protects cardiomyocyte from doxorubicin induced cytotoxicity through an AMP-activated protein kinase dependent signaling pathway: an in vitro study. PLoS One 2014; 9: e104888.
[16] Argun M, Uzum K, Sonmez MF, Ozyurt A, Derya K, Cilenk KT, Unalmis S, Pamukcu O, Baykan A, Narin F, Elmali F and Narin N. Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats. Anatol J Cardiol 2016; 16: 234-241.
[17] Zilinyi R, Czompa A, Czegledi A, Gajtko A, Pituk D, Lekli I and Tosaki A. The cardioprotective effect of metformin in doxorubicin-induced cardiotoxicity: the role of autophagy. Molecules 2018; 23.
[18] Tseng YT. Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats. Anatol J Cardiol 2016; 16: 242-243.
[19] Ekstrom N, Svensson AM, Miftaraj M, Franzen S, Zethelius B, Eliasson B and Gudbjornsdottir S. Cardiovascular safety of glucose-lowering agents as add-on medication to metformin treatment in type 2 diabetes: report from the Swedish national diabetes register. Diabetes Obes Metab 2016; 18: 990-998.
[20] Mather KJ, Verma S and Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol 2001; 37: 1344-1350.
[21] Vitale C, Mercuro G, Cornoldi A, Fini M, Volterrani M and Rosano GM. Metformin improves endothelial function in patients with metabolic syndrome. J Intern Med 2005; 258: 250-256.
[22] Xu G, Wu H, Zhang J, Li D, Wang Y, Zhang H, Lu L, Li C, Huang S, Xing Y, Zhou D and Meng A. Metformin ameliorates ionizing irradiation-induced long-term hematopoietic stem cell inju-

ry in mice. Free Radic Biol Med 2015; 87: 15-25.
[23] Birben E, Sahiner UM, Sackesen C, Erzurum S and Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J 2012; 5: 9-19.
[24] National health insurance administration, ministry of health and welfare, Taiwan, R.O.C. (2015). 2017.
[25] Yen YC, Hsu HL, Chang JH, Lin WC, Chang YC, Chang CL, Chow JM, Yuan KS, Wu ATH and Wu SY. Efficacy of thoracic radiotherapy in patients with stage IIIB-IV epidermal growth factor receptor-mutant lung adenocarcinomas who received and responded to tyrosine kinase inhibitor treatment. Radiother Oncol 2018; 129: 52-60.
[26] Lin YK, Hsieh MC, Wang WW, Lin YC, Chang WW, Chang CL, Cheng YF and Wu SY. Outcomes of adjuvant treatments for resectable intrahepatic cholangiocarcinoma: chemotherapy alone, sequential chemoradiotherapy, or concurrent chemoradiotherapy. Radiother Oncol 2018; 128: 575-583.
[27] Lin YK, Hsieh MC, Chang CL, Chow JM, Yuan KS, Wu ATH and Wu SY. Intensity-modulated radiotherapy with systemic chemotherapy improves survival in patients with nonmetastatic unresectable pancreatic adenocarcinoma: a propensity score-matched, nationwide, population-based cohort study. Radiother Oncol 2018; 129: 326-332.
[28] Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM and Wu SY. Treatment outcomes for unresectable intrahepatic cholangiocarcinoma: Nationwide, population-based, cohort study based on propensity score matching with the Mahalanobis metric. Radiother Oncol 2018; 129: 284-292.
[29] Yen YC, Chang JH, Lin WC, Chiou JF, Chang YC, Chang CL, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Effectiveness of esophagectomy in patients with thoracic esophageal squamous cell carcinoma receiving definitive radiotherapy or concurrent chemoradiotherapy through intensity-modulated radiation therapy techniques. Cancer 2017; 123: 2043-2053.
[30] Lin WC, Ding YF, Hsu HL, Chang JH, Yuan KS, Wu ATH, Chow JM, Chang CL, Chen SU and Wu SY. Value and application of trimodality therapy or definitive concurrent chemoradiotherapy in thoracic esophageal squamous cell carcinoma. Cancer 2017; 123: 3904-3915.
[31] Chen TM, Lin KC, Yuan KS, Chang CL, Chow JM and Wu SY. Treatment of advanced nasopharyngeal cancer using low- or high-dose concurrent chemoradiotherapy with intensity-modulated radiotherapy: a propensity score-matched, nationwide, population-based cohort study. Radiother Oncol 2018; 129: 23-29.
[32] Chang CL, Yuan KS and Wu SY. High-dose or low-dose cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell cancer. Head Neck 2017; 39: 1364-1370.
[33] Lee CH, Zhang JF, Yuan KS, Wu ATH and Wu SY. Risk of cardiotoxicity induced by adjuvant anthracycline-based chemotherapy and radiotherapy in young and old Asian women with breast cancer. Strahlenther Onkol 2019; Epub ahead of print].
[34] McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R and Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med 2013; 32: 3388-3414.
[35] Lee CH, Zhang JF, Chen JH and Wu SY. Cardiotoxicity induced by adjuvant anthracycline-based chemotherapy and radiotherapy in young and old asianwomen with breast cancer. Strahlenther Onkol 2019; [Epub ahead of print].
[36] Lipsitch M, Tchetgen Tchetgen E and Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010; 21: 383-388.
[37] Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, Carlson RW, Azavedo E and Harford J. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the breast health global initiative global summit 2007. Cancer 2008; 113: 2221-2243.
[38] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.
[39] Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, Bartlett JM, Gelmon K, Nahleh Z, Bergh J, Cutuli B, Pruneri G, McCaskill-Stevens W, Gralow J, Hortobagyi G and Cardoso F. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010; 28: 2114-2122.
[40] Parkin DM, Bray F, Ferlay J and Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.
[41] Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, Sandelin K, Derossis A, Cody H and Foulkes WD. Is breast cancer the same disease in Asian and Western countries? World J Surg 2010; 34: 2308-2324.
[42] Youlden DR, Cramb SM, Yip CH and Baade PD. Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer Biol Med 2014; 11: 101-115.
[43] Curtis LH, Whellan DJ, Hammill BG, Hernandez AF, Anstrom KJ, Shea AM and Schulman KA. Incidence and prevalence of heart failure in elderly persons, 1994-2003. Arch Intern Med 2008; 168: 418-424.

[44] Barker WH, Mullooly JP and Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation 2006; 113: 799-805.
[45] Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB and Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham heart study. Circulation 2001; 103: 1245-1249.
[46] Lewington S, Clarke R, Qizilbash N, Peto R and Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-1913.
[47] Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ and Levy D. Lifetime risk for developing congestive heart failure: the Framingham heart study. Circulation 2002; 106: 3068-3072.
[48] Cleland JG and McGowan J. Heart failure due to ischaemic heart disease: epidemiology, pathophysiology and progression. J Cardiovasc Pharmacol 1999; 33 Suppl 3: S17-29.
[49] Bortman G, Sellanes M, Odell DS, Ring WS and Olivari MT. Discrepancy between pre- and post-transplant diagnosis of end-stage dilated cardiomyopathy. Am J Cardiol 1994; 74: 921-924.
[50] Allman KC, Shaw LJ, Hachamovitch R and Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002; 39: 1151-1158.
[51] Marwick TH. The viable myocardium: epidemiology, detection, and clinical implications. Lancet 1998; 351: 815-819.
[52] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R and Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American diabetes association and the European association for the study of diabetes. Diabetes Care 2009; 32: 193-203.