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Association between tamoxifen use and acute myocardial infarction in women with breast cancer

Shih-Wei Lai, MD[a,b], Cheng-Li Lin, MS[a,c], Kuan-Fu Liao, MD, PhD[d,e,*]

Abstract

The relationship between tamoxifen use and acute myocardial infarction in women with breast cancer remains uncertain. The goal of the study was to assess whether tamoxifen use could be associated with acute myocardial infarction in women with breast cancer in Taiwan.

A population-based case–control study was conducted to analyze the database of the Taiwan National Health Insurance Program. Totally, 489 women with breast cancer aged 20 to 84 years having the first episode of acute myocardial infarction from 2000 to 2011 were found as the cases. In addition, 1718 women with breast cancer aged 20 to 84 years without any type of ischemic heart disease were selected as the matched controls. Ever use of tamoxifen was classified as the studied women who had at least a prescription for tamoxifen before the index date. Never use of tamoxifen was classified as the studied women who never had a prescription for tamoxifen before the index date. We used the multivariable logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) for acute myocardial infarction associated with tamoxifen use.

In a multivariable-adjusted analysis, women with acute myocardial infarction were 1.71 times more likely to be exposed to tamoxifen than those women without acute myocardial infarction (adjusted OR 1.71, 95% CI 1.38–2.13).

The odds of tamoxifen use are 1.71 times higher in women with acute myocardial infarction versus those women without acute myocardial infarction in Taiwan.

Abbreviation: ICD-9 code = International Classification of Diseases, 9th Revision, Clinical Modification.

Keywords: acute myocardial infarction, breast cancer, Taiwan National Health Insurance Program, tamoxifen, woman

1. Introduction

Currently, tamoxifen is the most commonly used and very effective agent as adjuvant therapy for the treatment of breast cancer.[1,2] Recent epidemiological studies have shown that tamoxifen use may be associated with increased risk of ischemic cerebrovascular disease, Alzheimer disease, and Parkinson disease,[3–5] but the relationship between tamoxifen use and acute myocardial infarction still remains controversial worldwide. To date, the current evidence has shown that tamoxifen use has favorable effects on serum lipid profiles.[6–8] Thus, some studies showed that tamoxifen use was associated with a reduced risk of acute myocardial infarction.[9–11] To the contrary, some studies showed that tamoxifen use was not associated with beneficial or adverse effects on acute myocardial infarction.[12,13] Therefore, results from the above studies seem to be conflicting.

Cardiovascular disease ranked the second leading cause of total female death in Taiwan in 2016, and 8577 cases died of cardiovascular disease, accounting for 12.35% of total female death.[14] Breast cancer ranked the fourth leading cause of female cancer death in Taiwan in 2016, and 2176 cases died of breast cancer, accounting for 11.73% of total female cancer death.[14] Although conflicting data have been found in studies involving Caucasian populations, the relationship between tamoxifen use and acute myocardial infarction in Taiwan has not been fully elucidated. If the relationship actually exits, clinicians can get more information on this field. Therefore, a population-based case–control study was conducted to investigate the following questions:

(1) whether tamoxifen use could be associated with acute myocardial infarction in women with breast cancer in Taiwan?
(2) is there a duration-dependent effect of tamoxifen use?

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Insurance reimbursement claims data used in this study are available for public access. Patient identification numbers were scrambled to ensure confidentiality. Patient informed consent was not required. This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

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[a] College of Medicine, China Medical University, [b] Department of Family Medicine, and, [c] Management Office for Health Data, China Medical University Hospital, Taichung, [d] College of Medicine, Tzu Chi University, Hualien, [e] Division of Hepatogastroenterology, Department of Internal Medicine, Taichung Tzu Chi Hospital, Taichung, Taiwan.

[*] Correspondence: Kuan-Fu Liao, Division of Hepatogastroenterology, Department of Internal Medicine, Taichung Tzu Chi Hospital, No.66, Sec. 1, Fongsing Road, Tanzi District, Taichung City, 427, Taiwan (e-mail: kuanfuliaog@gmail.com).

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2. Methods

2.1. Study design and data source

The methodological details were documented in previous studies.[15–17] A population-based case–control study was conducted to analyze the database of the Taiwan National Health Insurance Program. The program was launched in March 1995 and has covered 99.6% of 23 million citizens living in Taiwan.[18,19]

2.2. Study subjects

Women with breast cancer aged 20 to 84 years having the first episode of acute myocardial infarction from 2000 to 2011 were found as the cases (based on International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9 code] 410). The date of a subject being diagnosed with the first episode of acute myocardial infarction was defined as the index date. In addition, for every 1 case with the first episode of acute myocardial infarction, approximately 4 women with breast cancer aged 20 to 84 years without any type of ischemic heart disease were randomly selected as the matched controls. The cases and the matched controls were matched with age (5-year interval), comorbidities, and the year of the index date.

2.3. Comorbidities

Based on the ICD-9 codes, comorbidities which could be associated with acute myocardial infarction before the index date were adapted from previous studies,[19–23] including alcohol-related disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension. Data on cigarette smoking and body mass index were not available in the database. In order to avoid subjects being mistakenly diagnosed, being mistakenly coded, or being mistakenly coded by similar clinical manifestations with unconfirmed diagnosis, only those women who had the same diagnosis for at least 3 consecutive clinical records in the ambulatory care and/or at least 1 time of hospitalization diagnosis during the study period could be included for analysis. Principal diagnosis and secondary diagnosis were applied equally. Therefore, acute myocardial infarction and comorbidities were recorded for at least 3 visits and/or at least 1 time of hospitalization. These strict inclusion criteria were adapted from previous studies.[24,25]

2.4. Definition of drug exposure

The definition of drug exposure was adapted from previous studies.[26–28] The prescription histories of tamoxifen and aromatase inhibitors were included in the study. Ever use of the drug was defined as a subject who had at least a prescription for drug studied before the index date. Never use of the drug was defined as a subject who never had a prescription for drug studied before the index date.

2.5. Statistical analysis

We investigated the distributions of the demographic status, tamoxifen use, aromatase inhibitors use, and comorbidities between the cases and the matched controls by using the Chi-square test for categorized variables and the *t* test for continuous variables. Variables found to be statistically significant in a univariable logistic regression model were further tested by a multivariable logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were used to estimate the association between acute myocardial infarction and tamoxifen use. All analyses were performed using the SAS statistical software (version 9.2; SAS Institute, Inc., Cary, NC). The results were considered statistically significant when 2-tailed *P* values were $<.05$.

3. Results

3.1. Basic information of the study population

Table 1 discloses the basic information of the study population. W found 489 cases with the first episode of acute myocardial infarction and 1718 matched controls. The mean ages (standard deviation) were 68.4 (9.9) years in cases and 68.0 (9.9) years in matched controls, without statistical significance (*t* test, $P=.33$).

Table 1

Basic information between cases with acute myocardial infarction and matched controls.

Variable	Matched controls N = 1718 n (%)	Cases with acute myocardial infarction N = 489 n (%)	*P* value*
Age group, years			.99
20–49	75 (4.4)	21 (4.3)	
50–64	519 (30.2)	147 (30.1)	
65–84	1124 (65.4)	321 (65.6)	
Age (years), mean ± standard deviation†	68.0 ± 9.9	68.4 ± 9.9	.33
Ever use of tamoxifen	856 (49.8)	320 (65.4)	<.001
Ever use of aromatase inhibitors	251 (14.6)	118 (24.1)	<.001
Comorbidities*			
Alcohol-related disease	15 (0.87)	9 (1.84)	.07
Cerebrovascular disease	305 (17.8)	116 (23.7)	.003
Chronic kidney disease	307 (17.9)	121 (24.7)	.001
Chronic obstructive pulmonary disease	313 (18.2)	106 (21.7)	.09
Diabetes mellitus	793 (46.2)	244 (49.9)	.14
Hyperlipidemia	939 (54.7)	283 (57.9)	.21
Hypertension	1426 (83.0)	413 (84.5)	.45

Data are presented as the number of subjects in each group with percentages given in parentheses.

* Chi-square test and

† *t* test comparing subjects with acute myocardial infarction and matched controls.

Table 2

Crude and adjusted odds ratio and 95% confidence interval of association between acute myocardial infarction, tamoxifen use, and comorbidities by logistical regression model.

Variable	Crude OR (95%CI)	Adjusted* OR (95%CI)
Age (every 1 year)	1.01 (1.00, 1.02)	
Ever use of tamoxifen (never use as a reference)	1.91 (1.55, 2.35)	1.71 (1.38, 2.13)
Ever use of aromatase inhibitors (never use as a reference)	1.86 (1.45, 2.38)	1.55 (1.20, 2.01)
Comorbidities (yes vs no)		
Alcohol-related disease	2.13 (0.93, 4.90)	
Cerebrovascular disease	1.44 (1.13, 1.84)	1.41 (1.10, 1.80)
Chronic kidney disease	1.51 (1.19, 1.92)	1.49 (1.17, 1.90)
Chronic obstructive pulmonary disease	1.24 (0.97, 1.59)	
Diabetes mellitus	1.16 (0.95, 1.42)	
Hyperlipidemia	1.14 (0.93, 1.40)	
Hypertension	1.11 (0.95, 1.47)	

CI = confidence interval, OR = odds ratio.

* Variables found to be statistically significant in a univariable logistic regression model were further tested by a multivariable logistic regression model. Adjustment for aromatase inhibitors use, cerebrovascular disease, and chronic kidney disease.

The cases had significantly higher proportions of ever use of tamoxifen and ever use of aromatase inhibitors than the matched controls (Chi-square test, 65.4% vs 49.8%, and 24.1% vs 14.6%, $P < .001$). The cases had significantly higher proportions of cerebrovascular disease and chronic kidney disease than the matched controls (Chi-square test, 23.7% vs 17.8%, $P = .003$, and 24.7% vs 17.9%, $P = .001$, respectively).

3.2. Association between acute myocardial infarction, tamoxifen use, and comorbidities

In a multivariable-adjusted analysis, women with acute myocardial infarction were 1.71 times more likely to be exposed to tamoxifen than those women without acute myocardial infarction (adjusted OR 1.71, 95% CI 1.38–2.13, Table 2). In addition, ever use of aromatase inhibitors (adjusted OR 1.55, 95% CI 1.20–2.01), cerebrovascular disease (adjusted OR 1.41, 95% CI 1.10–1.80), and chronic kidney disease (adjusted OR 1.49, 95% CI 1.17–1.90) were also related to acute myocardial infarction.

3.3. Association between acute myocardial infarction and cumulative duration of tamoxifen use

In a multivariable-adjusted analysis, the odds of tamoxifen use for every 1 month increase in use duration were 1.01 times higher in women with acute myocardial infarction versus those women without acute myocardial infarction (adjusted OR 1.01, 95% CI 1.001–1.01, Table 3). The sub-analysis disclosed that the odds of the cumulative duration of tamoxifen use ≤ 5 years were 1.71 times higher in women with acute myocardial infarction versus those women without acute myocardial infarction (adjusted OR 1.71, 95% CI 1.37–2.14). The odds of the cumulative duration of tamoxifen use >5 years were 1.95 times higher in women with acute myocardial infarction versus those women without acute myocardial infarction (adjusted OR 1.95, 95% CI 1.19–3.17).

4. Discussion

In the present study, we observed that women with acute myocardial infarction were 1.71 times more likely to be exposed to tamoxifen than those women without acute myocardial infarction (Table 2). We observed that there was a duration-dependent effect of tamoxifen use associated with the risk of acute myocardial infarction (Table 3). That is the longer duration of tamoxifen use, the greater risk of acute myocardial infarction. In addition, women with cumulative duration of tamoxifen use >5 years were associated with a higher risk of acute myocardial infarction than those women with cumulative duration of tamoxifen use ≤ 5 years (adjusted OR 1.95 vs 1.71). One recent study showed that women receiving 10 years of tamoxifen use could have a better prognosis than those women receiving 5 years of tamoxifen use, such as reducing recurrence and mortality,[29] but our study showed that women with acute myocardial infarction were 1.95 times more likely to be exposed to tamoxifen use >5 years than those women without acute myocardial infarction. Therefore, we suggest that the benefit and the risk of long-time tamoxifen use should be balanced in clinical practice.

Based on the above discussions, our findings are contrary to previous studies showing that tamoxifen use was associated with reduced risk of acute myocardial infarction.[9–11], and also contrary to other studies showing that tamoxifen use was not associated beneficial or adverse effects on acute myocardial infarction.[12,13] Similarly, 1 meta-analysis showed that tamoxifen use was associated with improved prognosis, but no statistical difference was detected in cardiovascular deaths.[30] We cannot over explain acute myocardial infarction was significantly associated with increased odds of tamoxifen use by our case–control study. One study has shown that HER2 codon 655 G-allele might correlate with a significant reduction of high-density lipoprotein–cholesterol levels in women with breast cancer on tamoxifen therapy, which could be associated with a higher risk of cardiovascular disease.[31] In addition, tamoxifen is derived from diethylstilbestrol.[32] Diethylstilbestrol therapy is associated with an increased risk of cerebral venous thrombosis.[33] This

Table 3

Association between acute myocardial infarction and cumulative duration of tamoxifen use.

Variable	Case number/control number	Crude OR (95% CI)	Adjusted OR* (95% CI)
Never use of tamoxifen as a reference	169/862	1.00 (reference)	1.00 (reference)
Cumulative duration of tamoxifen use (for every 1 month increase in use duration)	320/856	1.01 (1.003, 1.01)	1.01 (1.001, 1.01)
Cumulative duration of tamoxifen use			
≤ 5 years	293/792	1.89 (1.53, 2.33)	1.71 (1.37, 2.14)
>5 years	27/64	2.15 (1.33, 3.47)	1.95 (1.19, 3.17)

CI = confidence interval, OR = odds ratio.

* Variables found to be statistically significant in a univariable logistic regression model were further tested by a multivariable logistic regression model. Adjustment for aromatase inhibitors use, cerebrovascular disease, and chronic kidney disease.

effect also partially explains why tamoxifen therapy could be associated with a higher risk of cardiovascular disease. Furthermore, due to results from the above studies being still conflicting, more real-world data are needed to clarify this issue.

5. Limitation

This study had several limitations. First, although we demonstrated that acute myocardial infarction was significantly associated with increased odds of tamoxifen use, a causal effect cannot be elucidated by our case–control study. Second, due to the inherent limitation of the database used, data of serum lipid profiles were not recorded. We could not investigate the relationship between tamoxifen use and serum lipid profiles. It indicates a future research direction. Third, due to the same limitation, cigarette smoking and body mass index were not documented in the database. Chronic obstructive pulmonary disease was used instead of cigarette smoking. This point has been mentioned in previous studies.[34,35] Similarly, we included diabetes mellitus, hyperlipidemia, and hypertension as a surrogate for obesity. Fourth, although radiation therapy for breast cancer was associated with increased risk of myocardial infarction (adjusted OR 2.0, 95% CI 1.1–3.5),[13] due to the same limitation, cardiotoxic treatments such as left-sided radiation therapy for breast cancer was not documented. Fifth, due to the same limitation, the type of breast cancer such as in situ or invasive was not documented. Sixth, the underlying mechanisms of the relationship between tamoxifen use and acute myocardial infarction cannot be completely elucidated by our case–control study. It indicates a future research direction. Seventh, in view of the event number of acute myocardial infarction on tamoxifen therapy being likely low, that was why a case–control study, rather than a cohort study, was conducted. Moreover, the possibility of time-window bias in the case–control study cannot be completely excluded. Eighth, due to the high lethality of acute myocardial infarction, it is possible that cases of acute myocardial infarction have died without any contact with the clinics/hospitals and, therefore, the case number of acute myocardial infarction could be underestimated. Ninth, due to lack of genetic correlations and lack of comparison with other ethnic groups, interpretation of our results should consider these limitations.

6. Strength

Although the relationship between Tamoxifen use and acute myocardial infarction remains uncertain, this is the first preliminary observation to prove a positive association between acute myocardial infarction and tamoxifen use in women with breast cancer in Taiwan. Breast cancer really preceded the onset of acute myocardial infarction in our study. Acute myocardial infarction and comorbidities were included by strict inclusion criteria mentioned in the method section. In spite of not novelty, we highlighted that there was a duration-dependent effect of tamoxifen use associated with the risk of acute myocardial infarction, particularly for women with cumulative duration of tamoxifen use >5 years.

7. Conclusion

Although conflicting conclusions exist on the currently available studies, we observe that the odds of tamoxifen use are 1.71 times higher in women with acute myocardial infarction versus those women without acute myocardial infarction in Taiwan. There is a duration-dependent effect of tamoxifen use associated with the risk of acute myocardial infarction.

Author contributions

Conceptualization: Shih-Wei Lai.
Data curation: Shih-Wei Lai.
Formal analysis: Cheng-Li Lin, Kuan-Fu Liao.
Investigation: Shih-Wei Lai.
Methodology: Shih-Wei Lai.
Supervision: Shih-Wei Lai.
Validation: Shih-Wei Lai.
Writing – original draft: Shih-Wei Lai.
Writing – review and editing: Shih-Wei Lai.

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