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Correlation of the tamoxifen use with the increased risk of deep vein thrombosis and pulmonary embolism in elderly women with breast cancer

A case–control study

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Abstract

The association between tamoxifen use and risk of deep vein thrombosis or pulmonary embolism in women with breast cancer has been reported in the Western population. The study aimed to evaluate the association between tamoxifen use and deep vein thrombosis or pulmonary embolism in older women with breast cancer in Taiwan.

We conducted a retrospective case–control study using the database of the Taiwan National Health Insurance Program. A total of 281 women subjects with breast cancer aged ≥65 years with newly diagnosed deep vein thrombosis/or pulmonary embolism from 2000 to 2011 were identified as the cases. Additionally, 907 women subjects with breast cancer aged ≥65 years without deep vein thrombosis or pulmonary embolism were randomly selected as the controls. The cases and the controls were matched with age and comorbidities. Ever use of tamoxifen was defined as subjects who had at least a prescription for tamoxifen before index date. Never use of tamoxifen was defined as subjects who never had a prescription for tamoxifen before index date. We used the multivariable logistic regression model to calculate the odds ratio (OR) and the 95% confidence interval (CI) of deep vein thrombosis or pulmonary embolism associated with tamoxifen use.

After adjustment for confounding variables, the adjusted OR of deep vein thrombosis or pulmonary embolism was 1.95 for subjects with ever use of tamoxifen (95% CI 1.45, 2.62), as compared with never use of tamoxifen. In addition, atrial fibrillation (adjusted OR 3.73, 95% CI 1.89, 7.35) and chronic kidney disease (adjusted OR 1.72, 95% CI 1.06, 2.80) were also associated with deep vein thrombosis or pulmonary embolism.

Tamoxifen use is associated with 1.95-fold increased odds of deep vein thrombosis or pulmonary embolism among older women with breast cancer in Taiwan.

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

Keywords: deep vein thrombosis, National Health Insurance Program, older people, pulmonary embolism, Taiwan, tamoxifen

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

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1. Introduction

Venous thromboembolism is a primary and leading preventable cause of death worldwide that comprises both deep vein thrombosis and pulmonary embolism.[1] A venous thrombus predominately comprises erythrocytes, platelets, and leukocytes bound together by fibrin and is formed in sites of vessel damage and areas of stagnant blood flow, such as the valve pockets of the deep veins of the calf, or extends proximally.[2] The invasion of a thrombus into the pulmonary arteries that obstructs the vessels might lead to pulmonary embolism. Per Rudolph Virchow, 3 conditions that predispose to thrombus are endothelial vessel injury, stasis or turbulence of the blood flow, and enhanced activation of clotting factors.[3] In addition, the traditional risk factors for venous thromboembolism include major trauma, major surgery, increasing age, cancer and its treatment, prior venous thromboembolism, prolonged immobility, oral contraceptives, and pregnancy.[4–6] The correlation between cancer and venous thrombosis has been established for nearly 150 years,[7] and, reportedly, breast cancer has the lowest rate of developing venous thromboembolism.[8]

Tamoxifen is an anti-estrogen drug, belonging to the class of selective estrogen receptor modulators, which can act on estrogen receptors to prevent estrogen binding. Owing to its anti-estrogenic properties, such as well-tolerated in chronic use, ready availability, relatively low cost, and well-demonstrated efficacy, tamoxifen has rapidly gained prominence in the treatment of breast cancer.[9,10] Studies have proven that tamoxifen decreases mortality and recurrence rates in patients with breast cancer and is recommended as a prophylactic agent in pre-menopausal women at the risk of breast cancer.[11,12] However, despite being a well-tolerated drug, some studies have revealed increased adverse effects, such as venous thromboembolism, related to tamoxifen.[13–15] In addition, the prophylaxis with tamoxifen in patients without breast cancer is also correlated with an increased risk of venous thromboembolism.[16] Although the risk of thromboembolic disease in Asians has been reported as lower than that in the Western population,[17,18] little data are available on the relationship between the tamoxifen use and the risk of deep vein thrombosis or pulmonary embolism in Asian women with breast cancer. Chen et al[19] reported that the risks of developing deep vein thrombosis and pulmonary embolism are not elevated in Asian patients with early breast cancer receiving adjuvant tamoxifen and that ethnic differences should be considered when planning optimal endocrine treatments for patients with early breast cancer. To the best of our knowledge, the report of Chen et al[19] is the first study to investigate the absolute and relative risk of deep vein thrombosis and pulmonary embolism in patients with early breast cancer receiving the adjuvant tamoxifen treatment by using an East Asian population database; however, the study of Chen et al[19] reached a different conclusion than studies conducted in the Western countries.

Owing to limited research on the correlation between the tamoxifen use and the risk of deep vein thrombosis or pulmonary embolism in Asian women with breast cancer, this study aims to investigate a possible association between the tamoxifen use and deep vein thrombosis or pulmonary embolism in elderly women with breast cancer in Taiwan.

2. Methods

2.1. Study design and data source

We conducted a retrospective nationwide case–control study in Taiwan to analyze the database of the Taiwan National Health Insurance Program, which began in March 1995 and had covered 99.6% of the entire population (23 million people) of Taiwan at the end of 2015.[20–30] The details of the program are described previously.[31–34]

2.2. Sampled subjects

In this study, we considered cases of female patients with breast cancer, aged ≥65 years, who were newly diagnosed with deep vein thrombosis or pulmonary embolism (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9] codes 453.8 and 415.1) from 2000 to 2011. We defined the date of diagnosing deep vein thrombosis or pulmonary embolism as the index date. In addition, for every 1 patient with deep vein thrombosis or pulmonary embolism, nearly 3 female patients with breast cancer, aged ≥65 years, who had never been diagnosed with deep vein thrombosis or pulmonary embolism were identified from the same database as controls. We matched cases and controls with age (5-year interval), comorbidities, and the index year of diagnosing deep vein thrombosis or pulmonary embolism.

2.3. Comorbidities

We included the following comorbidities that could be potentially associated with deep vein thrombosis or pulmonary embolism before the index date: alcohol-related disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, heart failure, hyperlipidemia, hypertension, and fracture of lower limbs with/without operation. Based on the ICD-9 codes, the diagnostic precision of comorbidities has been illustrated previously.[35–39]

2.4. Assessment of tamoxifen and aromatase inhibitors use

We included the prescription histories of tamoxifen and aromatase inhibitors in this study. Ever use of medications was defined as subjects who, at least, had a prescription for medications before the index date. In contrast, never use of medications was defined as subjects who never had a prescription for medications before the index date. We adapted these definitions from previous studies.[32,33,40–43]

2.5. Statistical analysis

In this study, we compared the distribution of the demographic status, tamoxifen use, aromatase inhibitors use, and comorbidities between cases and controls using the χ^2 test for categorized variables and the *t*-test for continuous variables. In addition, the univariate and multivariate logistic regression analyses were used to calculate the odds ratio (OR) and the 95% confidence interval (CI) of deep vein thrombosis or pulmonary embolism related to the tamoxifen use. Variables that significantly correlated with deep vein thrombosis or pulmonary embolism in the univariate logistic regression model were further assessed by the multivariate logistic regression model. Furthermore, we analyzed the dose-dependent effect of the tamoxifen use on the risk of deep vein thrombosis or pulmonary embolism. The average daily dose of tamoxifen was evaluated by using the total quantity of tamoxifen divided by the total number of days supplied. We divided the average daily dose into 2 levels based on the median dose, <20 mg and ≥20 mg. All analyses were performed using the SAS statistical software (version 9.2; SAS Institute, Inc., Cary, NC). Finally, we considered the results as statistically significant when two-tailed *P* values were <.05.

Table 1

Characteristics between cases with deep vein thrombosis or pulmonary embolism and controls.

Variable	Cases N = 281		Controls N = 907		*P* value*
	n	(%)	n	(%)	
Age group, y					.06
65–74	131	(46.6)	438	(48.3)	
75–84	116	(41.3)	400	(44.1)	
≥85	34	(12.1)	69	(7.6)	
Age, y, mean ± standard deviation†	76.6 ± 6.85		75.6 ± 6.34		.02
Duration of exposure to tamoxifen, y, mean ± standard deviation†	1.85 ± 1.67		2.03 ± 1.76		.27
Ever use of tamoxifen	177	(63.0)	407	(44.9)	<.001
Ever use of aromatase inhibitors	61	(21.7)	147	(16.2)	.03
Comorbidities*					
Alcohol-related disease	1	(0.36)	4	(0.44)	.85
Atrial fibrillation	22	(7.83)	18	(1.98)	.001
Cerebrovascular disease	49	(17.4)	121	(13.3)	.09
Chronic kidney disease	30	(10.7)	54	(5.95)	.01
Chronic obstructive pulmonary disease	86	(30.6)	244	(26.9)	.23
Coronary artery disease	158	(56.2)	492	(54.2)	.56
Diabetes mellitus	73	(26.0)	217	(23.9)	.48
Heart failure	81	(28.8)	171	(18.9)	.0004
Hyperlipidemia	126	(44.8)	428	(47.2)	.49
Hypertension	222	(79.0)	702	(77.4)	.57
Fracture of lower limbs with/without operation	46	(16.4)	118	(13.0)	.15

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

* Chi-square test comparing cases and controls.

† *t*-test comparing cases and controls.

3. Results

3.1. Characteristics of the study population

Table 1 summarizes the characteristics of the study population. We recognized 281 cases of newly diagnosed deep vein thrombosis or pulmonary embolism and 907 controls in 2000 to 2011. The mean ages (standard deviation) of our study population were 76.6 (6.85) years in cases and 75.6 (6.34) years in controls, with statistical significance (*t* test, $P = .02$). In addition, the mean duration of exposure to tamoxifen (standard deviation) was 1.85 (1.67) years in cases and 2.03 (1.76) years in controls, without statistical significance (*t* test, $P = .27$). The results revealed that cases with deep vein thrombosis or pulmonary embolism were more likely to demonstrate a higher proportion of ever use of tamoxifen than controls (63% vs 44.9%; χ^2 test, $P < .001$). In addition, cases demonstrated a higher tendency to exhibit greater proportions of ever use of aromatase inhibitors, atrial fibrillation, chronic kidney disease, and heart failure than controls (χ^2 test, $P < .05$ for all).

3.2. Correlation of the risk of deep vein thrombosis or pulmonary embolism with the tamoxifen use, aromatase inhibitors use, and comorbidities

Table 2 summarizes the risk of deep vein thrombosis or pulmonary embolism associated with the tamoxifen use,

Table 2

Crude and adjusted odds ratio and 95% confidence interval of deep vein thrombosis or pulmonary embolism associated with tamoxifen use, aromatase inhibitors use, and comorbidities by logistical regression model.

Variable	Crude OR (95%CI)	Adjusted OR* (95%CI)
Age (per 1 year)	1.02 (1.00, 1.05)	1.00 (0.98,1.03)
Ever use of tamoxifen (never use as a reference)	2.09 (1.59, 2.75)	1.95 (1.45, 2.62)
Ever use of aromatase inhibitors (never use as a reference)	1.43 (1.03, 2.00)	1.27 (0.90, 1.80)
Comorbidities (yes vs no)		
Alcohol-related disease	0.81 (0.09, 7.24)	
Atrial fibrillation	4.20 (2.22, 7.94)	3.73 (1.89, 7.35)
Cerebrovascular disease	1.37 (0.96, 1.97)	
Chronic kidney disease	1.89 (1.18, 3.02)	1.72 (1.06, 2.80)
Chronic obstructive pulmonary disease	1.20 (0.89, 1.61)	
Coronary artery disease	1.08 (0.83, 1.42)	
Diabetes mellitus	1.12 (0.82, 1.52)	
Heart failure	1.75 (1.28, 2.37)	1.38 (0.99, 1.92)
Hyperlipidemia	0.91 (0.70, 1.19)	
Hypertension	1.10 (0.79, 1.52)	
Fracture of lower limbs with/without operation	1.31 (0.90, 1.90)	

CI = confidence interval; OR = odds ratio.

* Variables found to be statistically significant in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model. Mutually adjusted for age, ever use of aromatase inhibitors, atrial fibrillation, chronic kidney disease, and heart failure.

Table 3

Average daily dose of tamoxifen use and risk of deep vein thrombosis or pulmonary embolism.

Variable	Case number /control number	Crude OR	(95% CI)	Adjusted OR*	(95% CI)
Never use of tamoxifen as a reference	104/500	1.00	(reference)	1.00	(reference)
Average daily dose of tamoxifen use					
<20 mg	133/322	1.99	(1.48, 2.66)	1.85	(1.36, 2.53)
≥20 mg	44/85	2.49	(1.63, 3.79)	2.36	(1.51, 3.68)

Adjusted for age, ever use of aromatase inhibitors, atrial fibrillation, chronic kidney disease, and heart failure.

The cut-off point of average daily dose is the median dose. CI = confidence interval; OR = odds ratio.

* Variables found to be statistically significant in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model.

aromatase inhibitors use, and comorbidities. After adjusting confounding variables in this study, the multivariate unconditional logistic regression model revealed that the adjusted OR of deep vein thrombosis or pulmonary embolism was 1.95 for subjects with ever use of tamoxifen (95% CI: 1.45–2.62), compared with never use of tamoxifen. Furthermore, atrial fibrillation (adjusted OR, 3.73; 95% CI: 1.89–7.35) and chronic kidney disease (adjusted OR, 1.72; 95% CI: 1.06–2.80) correlated with deep vein thrombosis or pulmonary embolism.

3.3. Risk of deep vein thrombosis or pulmonary embolism associated with the dosage of tamoxifen

Table 3 presents a sub-analysis on the risk of deep vein thrombosis or pulmonary embolism related to the dosage of the tamoxifen use. The adjusted ORs of deep vein thrombosis or pulmonary embolism were 1.85 for patients with average daily dose of tamoxifen use <20 mg (95% CI: 1.36–2.53) and 2.36 for patients with average daily dose of tamoxifen use ≥20 mg (95% CI: 1.51–3.68), compared with never use of tamoxifen. The findings of this study suggested a dose-dependent effect of the tamoxifen use on the risk of deep vein thrombosis or pulmonary embolism.

4. Discussion

Venous thromboembolic events are the leading severe complications associated with adjuvant hormonal therapy for breast cancer. Several studies have established a correlation between the use of tamoxifen in breast cancer and an increased incidence of venous thromboembolism. However, Chen et al[19] reported that the risk of developing deep vein thrombosis and pulmonary embolism is not increased in Asian patients with early breast cancer receiving adjuvant tamoxifen. This case–control study established a correlation between the tamoxifen use and 1.95-fold increased odds of developing deep vein thrombosis or pulmonary embolism among older female patients with breast cancer in Taiwan. In a sub-analysis on the risk of deep vein thrombosis or pulmonary embolism associated with the dosage of tamoxifen use, the adjusted ORs of deep vein thrombosis or pulmonary embolism were 1.85 and 2.36 for patients with an average daily dose of tamoxifen use <20 mg and ≥20 mg, compared with never use of tamoxifen. Based on these findings, a dose-dependent effect of tamoxifen use on the risk of deep vein thrombosis or pulmonary embolism could be assumed. Of note, the findings of this study corroborate with some previous studies. A Danish population study revealed that women treated with tamoxifen were at a higher risk for developing deep vein thrombosis and pulmonary embolism during the first 2 years after the exposure (RR, 3.5; 95% CI: 2.1–6.0).[13] In addition, Onitilo et al[15] demonstrated that the tamoxifen use seemingly led to a clustering phenomenon of venous thromboembolism events at the start of therapy, and they observed a persistent effect on thromboembolism events for female patients with sustained exposure to tamoxifen over time. Likewise, Decensi et al[44] revealed a hazards ratio of 1.63 for venous thromboembolism among patients receiving tamoxifen for breast cancer prevention, compared with those not receiving tamoxifen. This study deduces that the tamoxifen use is associated with increased odds of deep vein thrombosis or pulmonary embolism, corroborate with some previous studies in the Western population.

Reportedly, estrogens enhance the risk of developing venous thromboembolism.[45,46] In some studies, women during pregnancy and while receiving estrogen have demonstrated increased levels of von Willebrand factor, factor VIII, fibrinogen, and decreased levels of anti-thrombin, protein S.[47–49] Tamoxifen is an anti-estrogen drug, belonging to the class of selective estrogen receptor modulators, which also exerts partial estrogen-agonistic effects on particular receptor subtypes. Assumedly, the estrogenic activity of tamoxifen might elevate the risk of venous thromboembolism, and its effects on anticoagulant proteins seem to be similar to the effects of postmenopausal estrogen. The pathological mechanism underlying the association of tamoxifen with venous thromboembolism is not entirely understood. Hemostatic risk factors for venous thromboembolism include defects of the anticoagulant system, namely activated protein C resistance and deficiencies of anti-thrombin, protein C, and protein S.[50–54] Cushman et al[55] established a correlation between the tamoxifen treatment and reduction in anti-thrombin and protein S levels. Some studies have reported postmenopausal estrogen reductions in anti-thrombin, which correlated with increased prothrombin fragment 1 to 2.[56,57] Prothrombin fragment 1 to 2 is a marker of thrombin action that might enhance the risk of venous thromboembolism. In addition, the reduced level of protein S by tamoxifen might reflect the reduced anticoagulant function,[58,59] and increase the risk of venous thromboembolism.

In contrast, an in vitro study demonstrated that tamoxifen increased the Ca^{2+} influx and led to an increased platelet activity by the PI^3 and NADPH oxidase pathways.[60] In addition, it revealed that thrombotic effects of tamoxifen are associated with the oxidative mechanisms in thrombocytes. In addition, an experimental study in rats revealed that the chronic tamoxifen use increased the intimal thickness in arteries.[61] Another experimental study in rats revealed that the chronic tamoxifen consumption in the presence of anastomosis led to a prominent endothelial proliferation in rat femoral veins.[62] Rudolph Virchow has described the correlation of vascular endothelial injury with thrombus, suggesting that an increased intimal thickness and prominent endothelial proliferation might also predispose to thrombus formation, partially explaining a venous thrombogenic activity of tamoxifen.

5. Limitations

This study has some limitations. First, whether patients actually used prescribed tamoxifen could not be ascertained in an observational study. Hence, the prescription history was used as a proxy for the tamoxifen usage. Besides, there was no reason to suspect a difference in the noncompliance of the tamoxifen usage between case and control groups. Second, we did not record some risk factors for venous thromboembolism, such as obesity, cigarette smoking, congenital thrombophilia, recent surgery or trauma, the stage of cancer disease, chemotherapy, and radiotherapy, in this database because of inherent limitations. Reportedly, women with the body mass index $>29\,kg/m^2$ have a 3-fold increase in the pulmonary embolism risk, which, in turn, significantly increases over the baseline among women who smoked, at least, 25 cigarettes per day.[63] In addition, chemotherapy and radiotherapy increase the risk of deep vein thrombosis or pulmonary embolism. Hence, further studies are required to illustrate the association of these potential confounding variables and tamoxifen and the risk of venous thromboembolism. However, we used chronic obstructive pulmonary disease rather than cigarette smoking. These points have been explained previously.[64,65] Third, this study is a retrospective analysis since correlation does not infer causality. Finally, we did not record the breast cancer histology or estrogen receptor status in this database because of inherent limitations. Perhaps, these parameters could be associated with both the outcome and the exposure, thereby confounding the results to some extent.

6. Strengths

Of note, this study also has some strengths. First, we used a well-organized database to provide complete information. Second, the diagnoses of deep vein thrombosis or pulmonary embolism and comorbidities were based on ICD-9 codes, the diagnostic accuracy of which has been thoroughly investigated in previous studies.[35–39,66–70] Finally, we used an appropriate statistical methodology and reviewed the literature thoroughly.

7. Conclusion

This study deduces that the tamoxifen use is associated with 1.95-fold increased odds of deep vein thrombosis or pulmonary embolism among older women with breast cancer in Taiwan, with a likely dose-dependent effect of the tamoxifen use on the risk of deep vein thrombosis or pulmonary embolism. As deep vein thrombosis and pulmonary embolism are primary and common preventable causes of death worldwide, physicians prescribing tamoxifen as either primary or adjuvant cancer therapy should investigate cases comprehensively and closely monitor thromboembolic events during tamoxifen therapy in breast cancer.

Author contributions

Specific author contributions: Hsien-Feng Lin, Kuan-Fu Liao, and Ching-Mei Chang participated in data interpretation, revised the article, and contributed equally to the article.
Cheng-Li Lin and Chung-Y. Hsu conducted data analysis.
Shih-Wei Lai contributed to the conception of the article, initiated the draft of the article, and revised the article.
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Formal analysis: Cheng-Li Lin.
Investigation: Kuan-Fu Liao.
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