Association of Tamoxifen Use and Reduced Cardiovascular Events Among Asian Females With Breast Cancer

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**Background:** Tamoxifen is used for breast cancer treatment and has been reported to be beneficial for the cardiovascular system, but it is unclear whether tamoxifen exhibits a favorable cardiovascular effect in Asian patients.

**Methods and Results:** From January, 1998 to December, 2006, a breast cancer cohort study was conducted using the Taiwan National Health Insurance database. Patients were divided according to whether tamoxifen was used. Study endpoints were occurrence of acute myocardial infarction (AMI), ischemic or hemorrhagic stroke and total cardiovascular events. A total of 3,690 female subjects were enrolled (mean age 50.1±11.3), 2,056 of whom received tamoxifen and 1,634 did not. During a mean follow-up of 6.9 years, the tamoxifen group had a significantly lower incidence of AMI (0.15% vs. 0.67%, P=0.008), ischemic stroke (1.99% vs. 3.30%, P=0.008), hemorrhagic stroke (0.15% vs. 0.55%, P=0.029), and total cardiovascular events (2.24% vs. 4.16%, P<0.001) than the non-exposed group. After adjusting for comorbidities, tamoxifen was independently associated with a reduced risk of myocardial infarction (hazard ratio [HR] 0.22; 95% confidence interval [CI] 0.07–0.70), ischemic stroke (HR 0.52; 95% CI 0.35–0.78), hemorrhagic stroke (HR 0.25; 95% CI 0.07–0.92), and total cardiovascular events (HR 0.54; 95% CI 0.37–0.78).

**Conclusions:** In Asian female breast cancer patients, tamoxifen use was associated with reduced risks of AMI, ischemic, hemorrhagic stroke and total cardiovascular events. (Circ J 2014; 78: 135–140)

**Key Words:** Acute myocardial infarction; Stroke; Tamoxifen; Total cardiovascular events

Tamoxifen was first approved by the Food and Drug Administration of the USA in 1977 for the treatment of advanced breast cancer and was primarily used for estrogen receptor-positive tumors. The efficacy of tamoxifen for breast cancer treatment in reducing breast cancer-related morbidities and mortality has been confirmed by several trials. Furthermore, additional benefits beyond cancer treatment have been reported, including cardiovascular risk factor modification and favorable pre- and postmenopausal bone density. In 1988, a clinical study demonstrated that tamoxifen was associated with increased high-density lipoprotein cholesterol (HDL-C) as well as a decreased serum level of low-density lipoprotein cholesterol (LDL-C). In addition, a double-blinded, randomized clinical trial reported similar cardioprotective benefits of tamoxifen, which suggests that it can modulate cardiovascular risk factors and has additional protective benefits for the cardiovascular system. In a recent prospective study, tamoxifen appeared to be associated with reduced coronary artery disease because of effects of modulating lipid metabolism. A randomized clinical trial conducted in the early 1990s observed significantly lowered coronary artery disease mortality with prolonged tamoxifen use. However, not all clinical observations support the evidence that tamoxifen is beneficial for the cardiovascular system. Another more extensive trial demonstrated that tamoxifen remained more neutral in terms of cardioprotection. Because a divergence exists regarding the cardiovascular benefits of tamoxifen, coupled with the limited amount of data on tamoxifen...
usage among Asian populations, we aimed to elucidate this issue using a large, nationwide cohort database. The database of the National Health Insurance (NHI) of Taiwan has collected medical information from more than 99% of residents in Taiwan since 1996, with the complete data of every diagnosis and treatment of each resident. The aim of this study was to investigate the influence of tamoxifen on the future risk of developing acute myocardial infarction (AMI), ischemic or hemorrhagic stroke, and total cardiovascular events among Asian female patients with breast cancer.

**Methods**

**Database**

The NHI program in Taiwan has operated since 1996 and enrolled nearly all of the nation’s inhabitants. Currently, the National Health Research Institutes (NHRI) in Taiwan produce and manage the complete NHI Research Database, which is based on NHI claims, and has published several dozens of extracted datasets for researchers. The NHRI has released a cohort dataset composed of 1,000,000 randomly sampled people who were alive during the year 2000, and has collected all records on those individuals since 1995. These random samples have been confirmed as an accurate representation of the population of Taiwan. Each patient’s original identification number has been encrypted to protect privacy. This cohort dataset consists of de-identified secondary data released to the public for research purposes, and therefore this study was exempt from full review by the Institutional Review Board. The encrypting procedure of the data is consistent, so NHI claims belonging to the same patient can be linked.

**Breast Cancer Patient and Outcome Identification**

Female patients who were newly diagnosed with breast cancer (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 174.xx–175.xx) were identified from the database, and patients were classified into the tamoxifen exposure group (if tamoxifen was administered for breast cancer treatment) or the non-exposure group. In order to elucidate the relationship between tamoxifen use and further cardiovascular risk, patients with preexisting cardiovascular disease, such as coronary artery disease (410.xx–414.xx), ischemic stroke (433.x1, 434.x1, 438.xx), hemorrhagic stroke (430.xx–432.9) or peripheral artery disease (440.xx–444.xx) were excluded from our study. The patients were examined for comorbidities, including diabetes mellitus (250.xx), cardiac arrhythmia (427.xx, 785.0, 785.1), hyperlipidemia (272.xx), congestive heart failure (428.xx), and chronic obstructive pulmonary disease (490–496.xx), 365 days before the date of diagnosis of breast cancer. The diagnosis code of any comorbidity must have appeared at least twice and lasted longer than 30 days before officially being regarded as a comorbidity. Medications before enrollment were also reviewed within the database, which included angiotensin-converting enzyme (ACE) inhibitors, β-adrenergic antagonists, calcium-channel blockers, diuretics, statins, antiplatelet agents (aspirin or clopidogrel) and thiazides. The primary study endpoints were defined by ICD-9-CM for AMI, ischemic stroke, hemorrhagic stroke and total cardiovascular events. Cardiovascular mortality and all-cause mortality were also analyzed as the secondary study endpoints.

**Statistical Analysis**

Microsoft SQL Server 2005 (Microsoft Corp, Redmond, WA, USA) was used for data management and computing, and SPSS software (v. 15.0, SPSS Inc, Chicago, IL, USA) was used for statistical analysis. All data were expressed as frequency (percentage) or mean standard deviation. The parametric continuous data between the exposed and non-exposed groups were compared by unpaired Student’s t-test. The categorical data between the 2 groups were compared with chi-square test and Yates’ correction or Fisher’s exact test, as appropriate. Survival analysis was assessed using Kaplan-Meier analysis, with the significance based on the log-rank test. The survival time was calculated from the date of enrollment to the development of AMI, ischemic stroke or hemorrhagic stroke. Multiple regression analysis was carried out using Cox proportional hazard regression analysis to evaluate the effect of tamoxifen use on determining the occurrence of AMI, stroke, or total cardiovascular events. Subsequent subgroup analysis was performed to investigate the effects of tamoxifen use among other risk factors for cardiovascular events, such as age, sex, history of diabetes mellitus, hyperlipidemia, hypertension, and coronary
Cardiovascular Effects of Tamoxifen

From January 1, 1998 to December 31, 2006, 3,690 female breast cancer patients were identified (mean age 50.1±11.3), 2,056 of whom received tamoxifen treatment and 1,634 did not. The baseline characteristics of both groups did not significantly differ in terms of age, prevalence of diabetes mellitus, arrhythmia, hyperlipidemia, heart failure, and chronic obstructive pulmonary disease (Table 1). Usage of medications that may influence heart outcomes, including ACE inhibitors, β-adrenergic blockers, calcium-channel blockers, statins, aspirin and thiazides, did not differ significantly either.

During an average follow-up of 6.9 years, 3(0.15%), 41 (1.99%) and 3 (0.15%) of the 2,056 subjects who had received tamoxifen therapy experienced AMI, ischemic stroke and hemorrhagic stroke, respectively (Table 2). By comparison, the non-exposed group had a significantly higher incidence of AMI (11/1,634 subjects, 0.67%) (P=0.008), ischemic stroke (54/1,634 subjects, 3.30%) (P=0.008) and hemorrhagic stroke (9/1,634 subjects, 0.55%) (P=0.029), implying that tamoxifen was associated with a reduced risk of cardiovascular events.

**Table 2. Association Between Tamoxifen Use and Cardiovascular Events Among Asian Patients With Breast Cancer**

<table>
<thead>
<tr>
<th>Event</th>
<th>Crude HR (95% CI)</th>
<th>*Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Tam (-)</td>
</tr>
<tr>
<td>AMI, n (%)</td>
<td>14</td>
<td>11 (0.67)</td>
</tr>
<tr>
<td>Ischemic stroke, n (%)</td>
<td>95</td>
<td>54 (3.30)</td>
</tr>
<tr>
<td>Hemorrhagic stroke, n (%)</td>
<td>12</td>
<td>9 (0.55)</td>
</tr>
<tr>
<td>Total cardiovascular events, n (%)</td>
<td>114</td>
<td>68 (4.16)</td>
</tr>
</tbody>
</table>

Data are mean±SD and n (%). *Included age, diabetes mellitus, dysrhythmia, dyslipidemia, heart failure and use of antihypertensive agents. AMI, acute myocardial infarction; CI, confidence interval; Tam, tamoxifen; ref, reference.

**Results**

From January 1, 1998 to December 31, 2006, 3,690 female breast cancer patients were identified (mean age 50.1±11.3), 2,056 of whom received tamoxifen treatment and 1,634 did not. The baseline characteristics of both groups did not significantly differ in terms of age, prevalence of diabetes mellitus, arrhythmia, hyperlipidemia, heart failure, and chronic obstructive pulmonary disease (Table 1). Usage of medications that may influence heart outcomes, including ACE inhibitors, β-adrenergic blockers, calcium-channel blockers, statins, aspirin and thiazides, did not differ significantly either.

During an average follow-up of 6.9 years, 3(0.15%), 41 (1.99%) and 3 (0.15%) of the 2,056 subjects who had received tamoxifen therapy experienced AMI, ischemic stroke and hemorrhagic stroke, respectively (Table 2). By comparison, the non-exposed group had a significantly higher incidence of AMI (11/1,634 subjects, 0.67%) (P=0.008), ischemic stroke (54/1,634 subjects, 3.30%) (P=0.008) and hemorrhagic stroke (9/1,634 subjects, 0.55%) (P=0.029), implying that tamoxifen was associated with a reduced risk of cardiovascular events.
The results of log-rank test and Kaplan-Meier survival analyses of AMI, ischemic stroke, hemorrhagic stroke and total cardiovascular events are shown in Figure 1. Treatment with tamoxifen was significantly associated with less risk of AMI (log-rank P=0.008) (Figure 1A), ischemic stroke (log-rank P=0.008) (Figure 1B), hemorrhagic stroke (log-rank P=0.029) (Figure 1C) and total cardiovascular events (log-rank P<0.001) (Figure 1D) than in the subjects in the non-exposed group. In addition, 432 deaths, including 4 cardiovascular deaths (tamoxifen, 3; control, 1) and 428 (tamoxifen, 215; control, 213) breast cancer-related deaths occurred. There was no significant difference in cardiovascular deaths between the tamoxifen and non-exposure groups. However, treatment with tamoxifen was associated with less cancer mortality (n=215, 10.5%) than in the non-exposure group (n=213, 13.2%) (P<0.05) (Figure 2). After adjusting for baseline characteristics including age, hypertension medication, diabetes mellitus, hyperlipidemia, arrhythmia, and chronic kidney disease. AMI, acute myocardial infarction.

Figure 2. Breast cancer-related mortality between tamoxifen (Tam) use and controls in Asian patients with breast cancer.

Figure 3. Association between tamoxifen (Tam) use and cardiovascular events by proportional hazards regression analysis, adjusted for age, history of hypertension, diabetes mellitus, hyperlipidemia, arrhythmia, and chronic kidney disease. AMI, acute myocardial infarction.
treatment was independently associated with a lower risk of developing future MI (HR 0.22; 95% CI 0.07–0.70), ischemic stroke (HR 0.52; 95% CI 0.35–0.78), hemorrhagic stroke (HR 0.25; 95% CI 0.07–0.92) and total cardiovascular events (HR 0.54; 95% CI 0.37–0.78, P<0.001) (Table 2, Figure 3).

Discussion
In this study, we demonstrated that treatment with tamoxifen was significantly associated with a reduced risk of developing future MI, ischemic stroke, hemorrhagic stroke and total cardiovascular events in female patients with breast cancer. During a mean follow-up of 6.9 years, exposure to tamoxifen was associated with a 78%, 48% and 75% absolute risk reduction for AMI, ischemic stroke and hemorrhagic stroke, respectively, suggesting the cardiovascular protective effect of tamoxifen in female patients with breast cancer.

Malignancy development, progression or chemotherapeutic treatment of breast cancer may result in a chronic inflammatory status that could be linked to cardiovascular disease. Tamoxifen, an estrogen-competitive antagonist, has been proven to prolong survival of node-negative, estrogen-receptor-positive breast cancer in premenopausal female patients. In addition to therapeutic effects on breast cancer, tamoxifen has long been observed to exert a favorable effect on lipid profiles. It has been reported that tamoxifen may increase the serum level of HDL and decrease that of LDL-C as well. Estrogenic effects of tamoxifen have been proposed to ameliorate the risks of adverse cardiovascular events. The effect of tamoxifen on cardiovascular risk reduction had been investigated in several pioneer studies. In 1988, Bruning et al revealed the LDL-lowering and HDL-increasing properties of tamoxifen. In 1991, Love et al further elucidated tamoxifen’s favorable effects on lipid and lipoprotein profiles, from which a mean decrease of 12% in total cholesterol and a mean decrease of 20% in calculated LDL-C levels were detected at the end of a 24-month follow-up, even though plasma glucose levels, reported exercise and work activity, weight, and systolic and diastolic blood pressures did not change with tamoxifen treatment. In the late 1990s, Joseph et al demonstrated that tamoxifen treatment among breast cancer patients reduced coronary artery disease alongside a reduction of the risk of heart-related death for 0.32/1,000 patients in the B-14 study. Nordenskjöld et al also reported better cardiovascular outcomes with longer use of tamoxifen compared with short-term use (5 vs. 2 years). However, the association between tamoxifen use and cardiovascular protection is inconsistent and sometimes conflicting. In the early 2000s, Steven et al discovered that tamoxifen was not associated with either beneficial or adverse cardiovascular effects. Our data revealed that, from a median follow-up of 6.9 years, tamoxifen was associated with a lowered incidence of the composite endpoint of total cardiovascular events for female breast cancer patients in an Asian population. Furthermore, a significant survival benefit was also detected in this study, with a mortality hazard reduction of 22% after a mean follow-up of 6.9 years. However, the survival benefit mainly derived from a reduction in cancer-related deaths. The survival benefit had been reported previously. Our current study is concordance with a recently published study of mortality reduction benefit of tamoxifen among women with breast cancer. As to the insignificant difference in the cardiovascular mortality between the tamoxifen and control groups, it is considered reasonable because the study population was breast cancer patients whose mortality is mainly determined by the underlying malignancy. In addition, our study subjects were relatively young female patients (mean age =50 years) and did not have multiple risk factors. That is a possible explanation for why there were only a few cases of cardiovascular mortality in both groups. Further larger studies with long-term follow-up may be needed to assess the beneficial cardiovascular mortality reduction of tamoxifen.

The reasons behind tamoxifen’s beneficial effects on heart protection have yet to be elucidated. Breast cancer patients taking tamoxifen have lower serum cholesterol and other lipid levels than those not taking tamoxifen, which suggests that it might prevent atherosclerotic events. Borgo et al discovered attenuated acetylcholine-induced coronary vasoconstriction and enhanced adenosine-induced coronary vasodilatation after tamoxifen administration, which suggested a beneficial effect of tamoxifen therapy on coronary vascular reactivity. El Gebily et al demonstrated that tamoxifen could possibly reduce cardiac arrhythmia by interfering with the potassium channel current, which also implied the protective potential of tamoxifen. Zhao et al revealed that by improving mitochondrial function in an animal model, tamoxifen protected against cardiac-injuring tumor necrosis factor α, which was a novel potential therapeutic target for atrial fibrillation. In another subcellular study, tamoxifen was found to induce manganese superoxide dismutase, a mitochondrial antioxidant enzyme, which protected mouse cardiomyocytes from adriamycin injury.

The strength of the present study was the database that spans the entire population nationwide and could trace nearly all breast cancer cases in Taiwan over the study period. Every resident in Taiwan is requested to join the public health program, and >99% of Taiwanese people have joined the NHI service, which is a complete and thorough health research surveillance system. Additionally, the large sample size and cohort study design with controls provided considerable statistical advantages for detecting real, even subtle, differences between the 2 cohorts.

Study Limitations
Breast cancer patients were identified using the ICD-9 code from the catastrophic illness database and information on various organs involved was not available in this database. The NHI database specifically identifies 31 illnesses as “catastrophic,” such as cancers, hemophilia, systemic sclerosis, autoimmune diseases and chronic renal failure, because they may lead to catastrophic financial burden and subsequent impoverishment. Patients with catastrophic illness need to be reviewed by specialists on the Committee of the Bureau of National Insurance, and are then exempted from co-payment for catastrophic expenditures if they are approved. Breast cancer is listed in the category of catastrophic illness, and all patients in this study were identified as those with catastrophic illness certificates in the Taiwan National insurance dataset. Therefore, the diagnosis of breast cancer could be confirmed. Personal information, including body mass index and smoking status, was not available in the administrative data, which could have prevented accurate assessment of the contributory and confounding effects of these factors. Cardiac toxicity of certain chemotherapies for breast cancer (eg, doxorubicin) could not be assessed in our study, which requires more sophisticated evaluation.

In conclusion, treatment with tamoxifen was significantly associated with a reduced risk of the future development of MI, ischemic stroke, and hemorrhagic stroke in female Asian patients with breast cancer. A larger randomized and prospective study is needed to further delineate and confirm our findings and explain the mechanism of the cardiovascular benefits of tamoxifen.
Acknowledgments

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Disclosures
None.

References