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Tamoxifen-Related Optic Neuropathy in Breast Cancer Survivors: A Nationwide Population Study

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Abstract

Background: Breast cancer has overtaken lung cancer as the most prevalent cancer worldwide. The ant i-hormone agent, tamoxifen, could enhance survival. However, tamoxifen-related ocular toxicities, such as optic neuropathy, reported several decades ago, which might cause discontinuation due to possible sight loss. The aim is to implement Taiwan's National Health Insurance Research Database (NHIRD) to probe the incidence of tamoxifen-related optic neuropathy in breast cancer survivors.

Materials and Methods: To use longitudinal NHIRD to investigate the tamoxifen-related optic neuropathy incidence and ophthalmic outpatient use among breast cancer survivors from 1998 to 2012. Differences in the likelihood of developing optic neuropathy between tamoxifen user and non-user groups of breast cancer survivors were analyzed. Results: Between 1998 and 2012, 4890 breast cancer patients were recorded in this NHIRD dataset; 58.2% of them received tamoxifen. The tamoxifen group was significantly younger than counterpart (mean age of 51.3 years versus 53.0 years). The risk of developing optic neuropathy was 0.50% and 0.45% in the tamoxifen group and non-tamoxifen group; this difference was not statistically significant. Discussion: The tamoxifen group was younger. However, the two groups did not differ in the risk of developing optic neuropathy. Our results justify the use of tamoxifen to enhance breast cancer survival.

Conclusions: This study supports tamoxifen use for breast cancer survivors because the risk of development of optic neuropathy is small. However, regular ophthalmic follow-ups are strongly recommended to detect the possible development of ir-

reversible vision-threatening optic neuropathy and the need to discontinue tamoxifen and apply appropriate treatments.

Keywords: Tamoxifen-related optic neuropathy; National Health Insurance Research Database; breast cancer

Introduction

Breast cancer prevalence has been surging for more than four decades worldwide [1]. According to the World Health Organization, 2.3 million breast cancer patients were diagnosed in 2020, among whom 685 000 deaths were noted. In the past five years alone, 7.8 million breast cancer patients were diagnosed. Breast cancer has overtaken lung cancer to become the most prevalent cancer globally [2, 3]. Taiwan is no exception to this trend. According to Chen's 2022 report [4], the rate of breast cancer incidence doubled from 60.35 to 128.20 per 100,000 populations between 1998 and 2016. Furthermore, the trend in breast cancer firstly turned in younger age and later in older age is also evident in Taiwan [4]. Therefore, rigorous interdisciplinary efforts have been made to treat breast cancer to increase survival. In addition to surgical interventions and radiation therapy, many chemotherapeutic agents have been meticulously included in serial clinical trials and later treatment guidelines or suggestions to increase breast cancer survival in the past decades. Among these chemotherapeutic agents, tamoxifen has caught the attention of many oncologists because of its antiestrogen or antihormone effect because tamoxifen could be applied to both the premenopausal and postmenopausal breast cancer survivors [5]. The employment of antihormone regimens, such as tamoxifen as an adjuvant regimen for estrogen-receptor positive breast cancer survivors, could play a role in improving survival in late metastatic breast cancer, as well as in earlier-stage premenopausal breast cancer.

However, tamoxifen-related ocular toxicities [6-7], including whirl-shaped corneal opacity, posterior subcapsular cataract, crystalline retinopathy, cystoid macular edema, macular hole, retinal vein occlusion, and optic neuropathy, have been reported in the literature [8]. Among these ocular toxicities, optic neuropathy and cystoid macular edema are the most worrisome and vision-threatening, and require discontinuation of tamoxifen because of risks to vision and irreversible damage in some cases. While posterior subcapsular cataract might affect visual acuity depending on severity, it can be treated with lensectomy and surgical intraocular lens replacement. Whirl-shaped corneal opacity is the least worrisome, as corneal opacity mostly needs close observation if it does not affect the visual axis. Therefore, the balancing of the risks and benefits of tamoxifen usage in breast cancer is an important topic. The aims or our study were to use data from Taiwan's National Health Insurance Research Database (NHIRD) to probe the incidence of tamoxifen-related optic neuropathy and ophthalmic outpatient use among breast cancer survivors

Materials and Methods

Database

Taiwan launched mandatory National Health Insurance (NHI) on March 1, 1994. Since then, coverage has been more than 99%, and as of 2023, the population covered is around 23 million. In addition, the Bureau of NHI in Taiwan has been maintaining a National Health Insurance Research Database (NHIRD) since 1997 [9]. The NHIRD were owned by Taiwan's NHI which was subordinated of Ministry of Health and Welfare. This dataset is representative as it includes almost all nationals i.e.99% of Taiwan's population

Taiwan's Bureau of NHI has released NHIRD data for research since 1997. Before releasing NHIRD data, the Bureau of NHI anonymizes the data. The NHIRD includes claims data comprising diagnosis codes, medications, and interventions, as well as the expenditure for outpatient, emergent, and inpatient care. Therefore, we employed the longitudinal one-million NHIRD data set to investigate tamoxifen use and tamoxifen-related optic neuropathy in breast cancer, i.e. the proportion of patients using tamoxifen after breast cancer diagnosis and treatment, and most importantly, to determine the tamoxifen-related optic neuropathy incidence rate.

The breast cancer patients treated with tamoxifen were denoted the tamoxifen group and those not treated with tamoxifen as the non-tamoxifen group. This study was an observational retrospective cohort study. It was approved by the institutional review board (IRB) of Taipei Medical University (TMU-JIRB N201602088), which acts in accordance with the Declaration of Helsinki. The IRB waived the need for informed consent given that the study used retrospective administrative claims data.

Identification of Cases and Cohort

In this study, we included breast cancer patients with the diagnosis code of ICD-9-CM 174 from January 1, 1998, to December 31, 2012. The index date was defined as the first date of diagnosis of breast cancer.

Exposure Assessment (Tamoxifen)

To be included in the study as a breast cancer case, the patient had to make at least three outpatient visits or have one admission with the breast cancer diagnosis code of ICD-9-CM 174; the tamoxifen group had to have initiated tamoxifen after the index date. We calculated the interval between surgical intervention and tamoxifen therapy as well as the presenting age of breast cancer of patients in the two groups, i.e., the tamoxifen group and the non-tamoxifen group.

We also considered data on additional outpatient visits, inpatient services, or emergent care sought after the index date by both groups. The exposure inclusion criterion was whether there had ever been three outpatient visits or one inpatient service with the diagnosis code of ICD-9-CM 377 for optic neuropathy. The exposure date of optic neuropathy had to be after the index date. Moreover, we excluded optic neuropathy exposure dates if they were later than December 31, 2011, as well as patients aged < 20 years and > 90 years. In addition, the use of ophthalmic outpatient services as counts per year was compared between the two groups for the next 10 years.

Statistical Analysis

Statistical Analysis System (SAS) for Windows 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for statistical analysis. Descriptive statistical analyses were carried out to compare the demographic features and the risk of developing optic neuropathy of the two groups (tamoxifen group and non-tamoxifen group) using the t-test for continuous variables and the chi-square test for categorical variables. Two-tailed tests were performed, with the level of statistical significance set at $p < 0.05$.

Results

This study initially included 5728 breast cancer patients with the diagnosis code of ICD-9-CM 174 from January 1, 1998, to December 31, 2012. It excluded 448 patients as their breast cancer diagnosis was made before January 1, 1998; 187 patients were excluded due to use of tamoxifen before breast cancer diagnosis, and another 143 patients were excluded because of incomplete demographic data such as the date of birth. In total, 4950 breast cancer patients were finally included in the study (Figure 1).

The group of breast cancer patients that used tamoxifen after cancer diagnosis included 2882 (58.22%) individuals and the group that did not use tamoxifen included 2068 (41.78%) individuals

The mean age (mean ± standard deviation) of breast cancer patients was 53.0 ± 12.2 years, and the median age (Q1, Q3) was 51.3 (44.8, 60.3) years. The mean (± standard deviation) drug lag was 164.0 ± 32.3.9 days, while the median (Q1, Q3) was 95.0 (17.0, 200.0) days

The tamoxifen group was significantly younger than the non-tamoxifen group (52.26 ±11.59 years versus the 53.78 ± 12.20 years; paired t-test: $p < 0.0001$; Table 1). The likelihood of developing optic neuropathy was 13/2597 (0.50%) in the tamoxifen group and

8/1751 (0.45%) in the non-tamoxifen group. This difference was not statistically significant (chi-square test: p = 0.84; Table 1) Lastly, the tamoxifen group had a slightly higher frequency of using ophthalmic services than the non-tamoxifen group in the following 10 years (Table 3). The frequency of use of ophthalmic services was 0.94–1.93 counts per year in the tamoxifen group and 0.82–1.88 counts per year in the non-tamoxifen group, and both groups showed a higher frequency of use than the average count (0.7) for outpatient services in Taiwan previously reported by us [10]. However, the frequency of use of ophthalmic services did not differ significantly between the two groups (Wilcoxon rank-sum test: p-value is only significant in the fourth year (0.049), otherwise the p-value is insignificant, ranging from 0.1 to 0.82.)

	Tamoxifen group		Non-Tamoxifen group		
	n = 2610		n = 1759		
	Mean	std	Mean	std	*p*-value
Age at index date Optic neuropathy	52.26	11.59	53.78	12.2	<.0001 t-test
No	2597	99.50%	1751	99.55%	0.84 Chisq
Yes	13	0.50%	8	0.45%	
Count of ophthalmic outpatient service use					
1st year (n=4369)	0.94	2.4	0.82	2.14	0.1 Wilcoxon
2nd year (n=3931)	1.88	4.21	1.71	4.1	0.14
3rd year (n=3498)	1.81	3.85	1.71	4	0.15
4th year (n=3091)	1.92	4.05	1.64	3.85	0.049
5th year (n=2714)	1.94	4.11	1.76	3.92	0.31
6th year (n=2381)	1.91	4.13	1.67	3.45	0.23
7th year (n=2071)	1.92	4.18	1.71	3.52	0.56
8th year (n=1769)	1.93	4.23	1.72	4.1	0.19
9th year (n=1486)	1.92	3.82	1.65	3.58	0.12
10th year (n=1227)	1.93	3.96	1.88	3.73	0.82

Table 1: The likelihood of the tamoxifen group and the non-tamoxifen group developing optic neuropathy and using ophthalmic services.

t-test: paired t-test; chisq: chi-square test; Wilcoxon: Wilcoxon rank-sum test

Discussion

The incidence of breast cancer in the present study was 489 per 100,000 populations between 1998 and 2011 in Taiwan. The mean age of breast cancer patients was 53.0 ± 12.2 years and the median was 51.3 (44.8, 60.3) years in this study. This mean age is lower than the 65 years worldwide [11]. This younger age trend in breast cancer in Taiwan outpaces the trend in other parts of the world and warrants further investigation, especially of factors such as lifestyle and genetics.

Breast cancer has become the most prevalent malignancy globally. In Taiwan, breast cancer tops female malignancies and currently accounts for the third malignancy in the population [4]. Due to revolutionary chemotherapeutic agents, cancer survival has improved in the recent decades. The younger age trend in breast cancer justifies the use of antihormone medication, such as tamoxifen, for premenopausal female breast cancer survivors. Consequently, the use of tamoxifen as an antiestrogen therapy has increased. However, ocular toxicity still remains a concern because of the risks to vision or visual quality, which might compromise patients' quality of life. Most types of ocular toxicity need medications to treat symptoms, but other types warrant adjustments to medication, such as dosage reduction, drug holidays, and discontinuation of the regimen in extreme situations.

The ocular toxicities of tamoxifen include whirl-shaped corneal opacity, subcapsular lens opacity, retinal crystalline deposits, macular hole, retinal vein occlusion, cystoid macular edema, and optic neuropathy [6,7,8]. Among the types of ocular toxicity, optic neuropathy is highly concerning for patients, ophthalmologists, and oncologists, as it can be vision-threatening and irreversible if intervention is not timely. One of the possible treatments for tamoxifen-related optic neuropathy is steroids, including oral and pulse therapy, a subjective decision for ophthalmologists as well as oncologists. The present study demonstrated that there is no statistically significant difference in the incidence of optic neuropathy between the tamoxifen group (0.50%) and the non-tamoxifen group (0.45%) of breast cancer patients. This result is similar to a previous report of 0.6–0.9% of all ocular toxicities related to tamoxifen following its use after breast cancer diagnosis [12]. Therefore, we validated the justification for tamoxifen use after breast cancer diagnosis. On the other hand, we also highlight the need for awareness of the occurrence of optic neuropathy after tamoxifen use.

We also examined the interval between surgical intervention and tamoxifen therapy. Its mean and median were 164 and 95.0 days, respectively, which are quite reasonable as most breast cancer patients would initially receive surgical intervention, if indicated, and it may take several months for patients to recover from the surgery before receiving chemotherapy regimens that include anti-hormone treatment.

The use of ophthalmic outpatient services was employed as a surrogate in this study to explore possible ocular toxicity, i.e., optic neuropathy, as the presenting symptoms could have been blurred vision or change of color sense that prompted the patients to seek ophthalmic medical attention. To our surprise, there was only a small or subtle increase in ophthalmic outpatient service use, which might have been due to low incidence of tamoxifen-related optic neuropathy. In addition, there was no statistically significant difference in ophthalmic outpatient service use between the two groups, paralleling the lack of statistically significant differences in tamoxifen-related optic neuropathy.

Because of the stealthy onset of tamoxifen-related optic neuropathy, the symptoms mostly present as blurred vision, which could be subtle in the beginning. Moreover, the occurrence of tamoxifen-related optic neuropathy is not dose-dependent [13-21]. Therefore, we propose regular ophthalmic examinations that include pre-medication ophthalmic services to provide baseline data and post-medication services every six months to monitor the emergence of visual symptoms like blurred vision and color sense change. The ophthalmic service should include examinations of visual acuity, pupillary light reflexes, optic nerve head, and color sense (such as Ishihara color plate examinations), as well as visual evoked potential and visual fields, if indicated.

Strength and Limitations

This population-based study used data from the NHIRD in Taiwan. Therefore, it was robust and selection bias is minimized. However, the NHIRD records data for reimbursement purposes; therefore, the diagnosis codes are selected by physicians and cannot be verified. Moreover, other important data on ophthalmic examinations, such as visual acuity, pupillary light reflexes, and optic nerve findings, could not be accessed. Furthermore, as this study was based on the NHIRD of Taiwan, caution is necessary to generalize its findings to other populations.

Conclusion

Data from the NHIRD of Taiwan were used to investigate tamoxifen-related optic neuropathy in breast cancer patients. The rates of optic neuropathy were 0.5% and 0.45% in the tamoxifen group and the non-tamoxifen group, respectively; the difference was not statistically significant. In terms of optic neuropathy risk, Tamoxifen is relatively safe for breast cancer because of low incidence of optic neuropathy and if the precaution is taken to perform an ophthalmic examination before tamoxifen use and regular follow-ups every six months after its use.

The findings of this study could ultimately lead us to understand the incidence of breast cancer and tamoxifen-related ocular toxicity manifested as optic neuropathy. We believe that the results could help oncologists and ophthalmologists in their decision-making to continue or discontinue tamoxifen use to optimize breast cancer treatment outcomes.

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