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Original Article

Younger tamoxifen-treated breast cancer patients also had higher risk of endometrial cancer and the risk could be reduced by sequenced aromatase inhibitor use: A population-based study in Taiwan

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Abstract

Objective: Previous Western studies reported that older (≥50 years) breast cancer survivors with tamoxifen treatment had higher risk of endometrial cancer. This study aims to disclose whether younger (<50 years) tamoxifen-treated breast cancer patients also had higher risk of endometrial cancer and to examine whether sequenced aromatase inhibitor (AI) use could reduce the risk. **Materials and Methods:** A population-based cohort of 39,216 newly diagnosed breast cancer patients was identified from Taiwan National Health Insurance Database from 1999 to 2012. The risk of endometrial cancer in nonusers (n = 14,588), tamoxifen-only (n = 19,302), and sequenced AI (n = 5326) users was compared with Cox regression analysis and was adjusted with age, diabetes, hypertension, and chemotherapy. **Results:** During the 14-year study period, 133 patients were diagnosed with subsequent endometrial cancers. Compared with nonusers, tamoxifen-only users had higher risk of endometrial cancer (14-year incidence 1.7% vs. 0.3%; adjusted hazard ratio [HR] 3.90; 95% confidence interval [CI], 2.37–6.42). This was observed in both older (≥50 years) and younger (40–50 years) age groups. Adjusted HR (95% CI) for the latter was 3.74 (1.65–8.48). This risk persisted after cessation of tamoxifen use. The risk of endometrial cancer was lower in sequenced AI when compared with tamoxifen-only users (adjusted HR 0.43; 95% CI, 0.25–0.72). **Conclusions:** Not only patients ≥50 years but also younger (40–49 years) patients with tamoxifen treatment had higher risk of subsequent endometrial cancer in this nation-wide cohort. We suggest regular gynecologic monitoring not only during active use but also during follow-up phase. Sequenced AI use may reduce the risk of endometrial cancer in tamoxifen-treated breast cancer patients.

Keywords: *Antiestrogen, Aromatase inhibitor, Breast cancer, Endometrial cancer, Tamoxifen*

Introduction

The International Adjuvant Tamoxifen Longer Against Shorter Breast Cancer Treatment Trial recently reported that for women with estrogen receptor (ER)-positive disease, continuing tamoxifen to 10 years rather than stopping at 5 years produces a further reduction in recurrence and mortality of breast cancer. However, the cumulative risk of subsequently endometrial cancer during 5–14 years was 3.1% (with a mortality rate of 0.4%) for 10 years of tamoxifen versus 1.6% (mortality 0.2%) for 5 years of tamoxifen [1]. Previous Western studies [2,3] reported that only older (≥50 years) but not younger patients taking tamoxifen had higher risk of endometrial cancer when compared with nonusers. The Early Breast Cancer Trialists' Collaborative Group conducted a meta-analysis of 20 trials (n = 21,457) of 5 years of tamoxifen use and revealed increase of endometrial cancer incidence only in women older than 55 years [4]. One systematic review showed that relative risk (RR) for endometrial cancer in women aged under 50 years who take tamoxifen is 1.19 (95% confidence interval [CI], 0.53–2.65; P = 0.6) as compared with the nonusers [2]. Hence, the American College of Obstetricians and Gynecologists committee recently recommends that premenopausal women treated with tamoxifen have no known increased

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risk of uterine cancer and require no additional monitoring beyond routine gynecologic care [3]. However, the median age that East Asian women get a breast cancer diagnosis is about 10 years younger than Western women [5]. It remains uncertain whether younger Asian women treated with tamoxifen also have no increased risk of endometrial cancer.

In recent meta-analysis, Dowsett *et al*. reported that 5 years of aromatase inhibitors (AIs) reduces breast cancer mortality risk by about 15% as compared with 5 years of tamoxifen. Compared to tamoxifen use, there were fewer endometrial cancers in AI user (10-year incidence of 0.4% vs. 1.2%; RR 0.33, 0.21–0.51) [6]. Compared to breast cancer women who received AIs, those taking tamoxifen had higher risk for gynecologic pathologies in both the premenopausal and postmenopausal women groups [7]. Garuti *et al*. reported that when AIs administered as switched therapy after tamoxifen withdrawal, AIs may reverse tamoxifen-associated endometrial thickening [8]. However, the long-term endometrial effect of AIs in tamoxifen-treated patients remains uncertain. The purpose of the study is first to disclose whether younger (<50 years) breast cancer survivors with tamoxifen had higher risk of endometrial cancer in Taiwan and second to examine whether sequenced AI use could reduce the incidence of endometrial cancer in tamoxifen-treated patients.

Materials and Methods

Study population and study design

The Taiwan National Health Insurance (NHI) Research Database is covering approximately 23 million residents and the program covered 99.5% of the population by 2010 [9]. Data for our study were obtained from the Registry for Catastrophic Illness Patient Database (RCIPD) which is a subset of the Taiwan NHI database. RCIPD contains medical records including disease diagnoses, prescription medications, hospitalizations, and outpatient visits of all cancer patients. These databases have been used extensively in researches with reliable quality [9].

In the study, women who were diagnosed with breast cancer and registered in the RCIPD from January 1, 1999, to December 31, 2012, were included. Breast cancer patients were identified by the International Classification of Diseases, 9th Revision (ICD-9) codes of 174.0–174.9. First, we examined antiestrogen use and the risk of subsequent endometrial cancer after adjusting age, hypertension, diabetes, and chemotherapy. To disclose whether younger (<50 years) breast cancer survivors with tamoxifen had higher risk of endometrial cancer, the difference of risk was evaluated by subgroup analysis for age. Second, we restricted the analysis to patients who had used tamoxifen and examined associations of sequenced AI use with endometrial cancer risk.

The schema of study design, status of antiestrogen use, exclusion criteria, and follow-up are shown in Supplementary Figure 1. Males, younger than 18 years, or those with cancers of nonbreast sites were excluded. Considering the need of long-term follow-up and survival, those with distant lymph node or visceral metastasis at diagnosis were also excluded. The primary therapy for breast cancer was defined as primary surgery with or without chemotherapy. Patients who did not undergo primary surgery were excluded. To standardize the therapy, those who used tamoxifen after 1 year of diagnosis were excluded. Short-term cases including those received tamoxifen <180 cumulative defined daily dose (cDDD) or whose follow-up periods <6 months were also excluded.

Antiestrogens defined by this study included tamoxifen and four AIs: letrozole, anastrozole, exemestane, and aminoglutethimide. The defined daily dose (DDD) is a WHO-advocated drug potency unit to assume average maintenance dose. cDDD is the sum of dispensed DDD of any antiestrogens. Tamoxifen user was defined as tamoxifen use >180 cDDD after primary surgery. Tamoxifen users who did not use AI during follow-up were categorized as tamoxifen-only group. Sequenced AI group was defined as AI use after tamoxifen. The compliance of antiestrogens was calculated by dividing cDDD by the period of drug use within the first 5 years.

To avoid immortal time bias, all breast cancer patients were followed after primary therapy. The tamoxifen users were followed after they started tamoxifen. The control nonusers were followed after they had received the last surgery or chemotherapy. The identification of subsequent endometrial cancer was based on a new registration of endometrial cancer in the RCIPD or based on the diagnosis of endometrial cancer using ICD-9 codes (182.0–182.9) during hospitalization. Patients were followed to the occurrence of endometrial cancer during the study period. If no event occurred, they were followed until death or December 31, 2012. Confounding factors including age at diagnosis, diabetes, hypertension, and chemotherapy were controlled. This study was approved by the Research Ethics Committee of Buddhist Tzu Chi General Hospital, Hualien, Taiwan (IRB101-98).

Statistical analysis

The risk of endometrial cancer was compared with Cox regression analysis with competing risk analysis by Fine and Gray method and was adjusted for age at diagnosis, hypertension, diabetes, and chemotherapy. The risk of endometrial cancer in tamoxifen-only and sequenced AI users was compared with Cox regression analysis and adjusted for age, diabetes, hypertension, and chemotherapy. The cumulative incidence of endometrial cancer was plotted using the Kaplan–Meier method, and the difference between the curves was tested with the log-rank test. A two-tailed test at a level of 0.05 was considered statistically significant. Statistical analyses were performed using SAS, version 9.4 (SAS, Inc., Cary, NC, USA).

Results

We identified 105,444 eligible breast cancer patients who were registered for the first time in the RCIPD. After the exclusion criteria were applied, 39,216 patients were included in the study. There were 14,588 (37.2%) nonusers, 19,302 (49.2%) tamoxifen-only users, and 5326 (13.6%) sequenced AI users [Supplementary Figure 1]. The demographic characteristics of the groups are shown in Table 1. A lower proportion of tamoxifen-only users (51.1%) had received chemotherapy when compared with nonusers (66.4%) or sequenced AI users (68.1%). A slightly longer median of follow-up duration

was noted for sequenced AI users (median 6.15 years) than nonusers (4.44 years) or tamoxifen-only users (4.64 years). The medians of tamoxifen cDDD in tamoxifen-only and sequenced AI users were 875 (interquartile range [IQR], 480–1482) and 616 (IQR, 258–1127) days, respectively. The medians of AI cDDD in sequenced AI users were 491 (IQR, 196–968) days. The proportions of adherence to antiestrogen use over 50% in tamoxifen-only and sequenced AI users were 75.0% and 81.7%, respectively. The mortality rate of all patients was 7.6%.

During the 14-year study period, 133 patients were diagnosed with subsequent endometrial cancer. The incidences per 10^5 person-years were 24.8, 91.1, and 48.9 in nonusers, tamoxifen-only users, and sequenced AI users, respectively [Supplementary Table 1]. When compared with nonusers, tamoxifen-only users had a significantly higher risk of endometrial cancer (adjusted hazard ratio [HR] 3.90, 95% CI, 2.37–6.42; $P < 0.0001$), but sequenced AI users had a nonsignificant risk [adjusted HR 1.70, 95% CI, 0.88–3.26; $P = 0.1134$; Table 2]. The Kaplan–Meier analysis revealed that tamoxifen-only users had higher cumulative incidence of endometrial cancer than nonusers [14-year incidence 1.7% vs. 0.3%; $P < 0.0001$; Figure 1a]. Endometrial cancer risk increased with the older age of breast cancer diagnosis. Women diagnosed at the age >60 years had 5.90-fold odds (95% CI, 2. 22–15.69; $P = 0.0004$) of developing endometrial cancer than at the age

Table 1: Demographic data of the breast cancer cohort from National Health Insurance database in Taiwan, 1999-2012

Characteristic	All patients (39,216; 100%), *n* (%)	Nonuser (14,588; 37.2%), *n* (%)	Tamoxifen only (19,302; 49.2%), *n* (%)	Sequenced AI (5326; 13.6%), *n* (%)
Tamoxifen use	24628 (62.8)	—	19302 (100.0)	5326 (100.0)
AI use[a]	5326 (13.6)	—	—	5326 (100.0)
Age at diagnosis				
18-39	5258 (13.4)	2130 (14.6)	2759 (14.3)	369 (6.9)
40-49	13894 (35.4)	4485 (30.7)	7639 (39.6)	1770 (33.2)
50-59	11160 (28.5)	4742 (32.5)	4672 (24.2)	1746 (32.8)
≥60	8904 (22.7)	3231 (22.2)	4232 (21.9)	1441 (27.1)
Follow-up years, median (IQR)	4.81 (2.45-8.11)	4.44 (2.23-7.76)	4.64 (2.36-8.03)	6.15 (3.76-9.14)
Chemotherapy	23181 (59.1)	9688 (66.4)	9867 (51.1)	3626 (68.1)
Diabetes	4418 (11.3)	1631 (11.2)	2109 (10.9)	678 (12.7)
Hypertension	9862 (25.2	3597 (24.7)	4647 (24.1)	1618 (30.4)
cDDD[b], (IQR)				
Tamoxifen	374 (0 to 1036)	—	875 (480 to 1482)	616 (258 to 1127)
AIs	0 (0 to 0)	—	—	491 (196 to 968)
Antiestrogen adherence[c]				
Nonuser	14588 (37.2)	14588 (100.0)	—	—
<0.5	5796 (14.8)	—	4820 (25.0)	976 (18.3)
0.5-0.7	4188 (10.7)	—	3190 (16.5)	998 (18.7)
0.7-0.9	4816 (12.3)	—	3675 (19.0)	1141 (21.4)
≥0.9	9828 (25.1)	—	7617 (39.5)	2211 (41.5)
Mortality	2974 (7.6)	1296 (8.9)	776 (4.0)	902 (16.9)

[a]AI: Exemestane or letrozole or anastrozole or aminoglutethimide, [b]cDDD: cDDD of antiestrogen, [c]Antiestrogen adherence: Cumulative defined daily dose/period of follow-up (day) (within the first 5 years). AI: Aromatase inhibitor, IQR: Interquartile range, cDDD: Cumulative defined daily dose

Table 2: Adjusted hazard ratios for endometrial cancer[a] for breast cancer patients (*n*=39,216) by antiestrogen use in Taiwan, 1999-2012

	Crude HR	95% CI	*P*	Adjusted HR[b]	95% CI	*P*
Antiestrogens use						
Nonuser	1.00			1.00		
Tamoxifen only	3.85	2.35-6.29	<0.0001	3.90	2.37-6.42	<0.0001
Sequenced AI	1.86	0.97-3.59	0.0629	1.70	0.88-3.26	0.1134
Age of breast cancer diagnosis						
18-39	1.00			1.00		
40-49	3.96	1.57-9.96	0.0035	3.85	1.52-9.71	0.0043
50-59	4.77	1.87-12.11	0.0010	5.13	2.00-13.17	0.0007
≥60	5.70	2.24-14.48	0.0003	5.90	2.22-15.69	0.0004
Diabetes (yes vs. no)	1.20	0.70-2.06	0.4982	0.92	0.49-1.72	0.7840
Hypertension (yes vs. no)	1.35	0.93-1.97	0.1141	1.01	0.64-1.60	0.9758
Chemotherapy (yes vs. no)	0.80	0.57-1.12	0.1937	1.14	0.80-1.64	0.4667

[a]ICD-9-CM: Endometrial cancer, 182.xx, [b]Adjusted for age at diagnosis, chemotherapy, hypertension, and diabetes. AI: Aromatase inhibitor, HR: Hazard ratio, CI: Confidence interval, ICD-9: International Classification of Diseases, 9th Revision

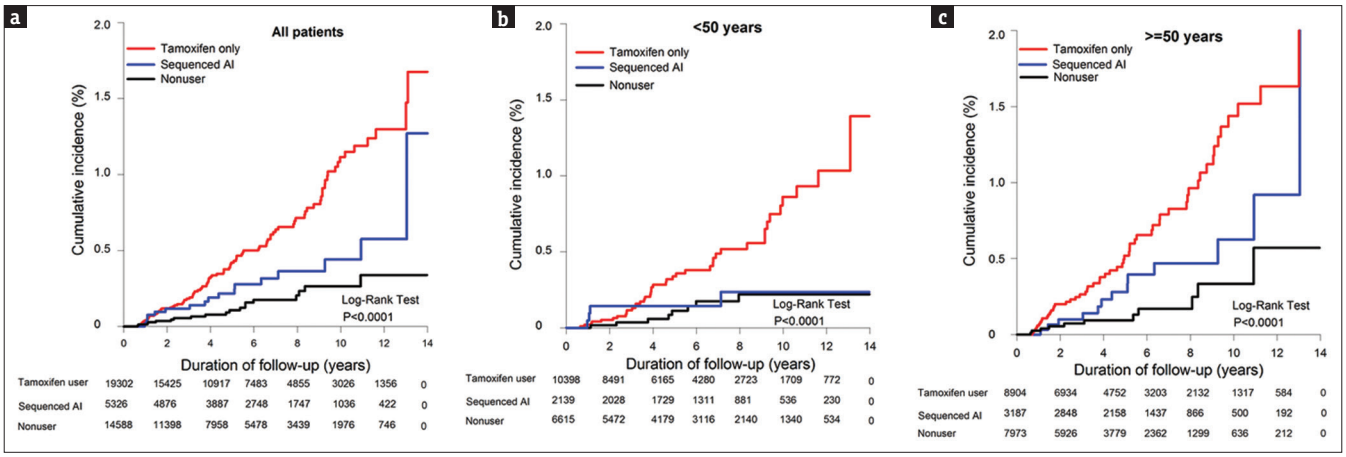

Figure 1: Cumulative incidences of endometrial cancer in nonusers, tamoxifen-only users, and sequenced AI users. (a) all patients; the 14-year incidence in nonusers, tamoxifen-only users, and sequenced AI users was 0.3%, 1.7%, and 1.3%, respectively, (b) <50 years old; the 14-year incidence in nonusers, tamoxifen-only users, and sequenced AI users was 0.2%, 1.4%, and 0.2%, respectively, and (c) ≥50 years old; the 14-year incidence in nonusers, tamoxifen-only users, and sequenced AI users was 0.6%, 2.3%, and 2.0%, respectively, (Kaplan–Meier method). AI: Aromatase inhibitor

group of 18–39 years [Table 2]. To clarify whether the risk of endometrial cancer in younger women, we did subgroup analysis for age. As shown in Table 3 and Figure 1b and c, younger (40–49 years) patients with tamoxifen only also had higher risk of endometrial cancer than nonusers (adjusted HR 3.74; 95% CI, 1.65–8.48; P = 0.0015). Meanwhile, although the cDDD of tamoxifen use was <5 years in most of the young and old patients, the difference of cumulative incidences of endometrial cancer had been persistently increasing even after patients had discontinued tamoxifen [Figure 1a-c].

To disclose whether sequenced AI use could reduce the incidence of endometrial cancer, tamoxifen-only users (n = 19,302) were compared with sequenced AI users (n = 5326). Comparing to the tamoxifen-only group, the sequenced AI group had a lower risk for endometrial cancer (adjusted HR 0.43; 95% CI, 0.25–0.72; P = 0.0014) after adjusting age at diagnosis, diabetes, hypertension, and chemotherapy [Table 4]. Kaplan–Meier analysis revealed that the cumulative incidence of endometrial cancer was lower in sequenced AI users [Figure 1a-c].

Discussion

Our cohort with a 14-year study period included 39,216 survivors of nonmetastatic breast cancer with long-term survival. 62.8% of them had used antiestrogen for a median (IQR) cDDD of 875 (480–1482) days in tamoxifen-only users and 980 (532–1593) in tamoxifen-AI sequential users. Most of them had well compliance of medication.

In contrast to reports in the Western world, this population-based study in Taiwan revealed that not only older (≥50 years) patients but also younger (40–49 years) patients with tamoxifen also had higher risk (adjusted HR 3.74; P = 0.0015) of endometrial cancer than nonusers. It is reasoned that ER-agonist and oncogenic effects of tamoxifen on uterine tissue are mitigated by cyclic shedding of endometrium in premenopausal women. The different risks of endometrial cancer in younger tamoxifen user between Western studies and ours might result from the racial difference in natural menopause and chemotherapy-related menopause. The median age at natural menopause in Taiwanese women is 49.5 years [10], which is about 2 years earlier than Western countries such as America [11], Finland [12], and Australia [13]. Women in developing countries such as India and the Philippines still have younger age (44 years) of menopause [14]. Liem *et al.* reported that the majority (91.1%) of young (≤45) Chinese breast cancer patients developed chemotherapy-related amenorrhea (CRA) [15], which is much higher than that 68% (95% CI, 66%–70%) reported in a systemic review of Western countries [16]. The CRA incidence varies with age, cytotoxic agent, and cumulative dose of chemotherapy [16]. The earlier age of menopause in Asian women may partly explain the higher risk of endometrial cancer in young tamoxifen users in Taiwan.

Previous studies showed an increasing endometrial cancer risk not only in the active treatment phase but also in the follow-up phase after 3 years or longer tamoxifen use [17-19]. The median of tamoxifen cDDD in tamoxifen-only users was 875 (IQR, 480–1482) days. Our patients with cDDD as short as 730 days also had higher risk of endometrial cancer (data not shown). The tamoxifen cDDD of most patients was <5 years, and our findings also revealed that the risk of endometrial cancer did not decrease from the active to follow-up phase of tamoxifen treatment [Figure 1a-c]. Hence, we suggest regular surveillance of endometrial cancer not only during active phase but also in the follow-up phase of tamoxifen treatment. The surveillance is also indicated for patients with <2 years of cDDD use or whose age over 40 years.

There are also significant racial and environmental differences in characteristics of breast cancers in Taiwan. The incidence peak of Taiwanese female breast cancer is younger than Western countries, and a rapid surge of young-female breast cancer (YFBC) has been observed in Taiwan and other East Asian countries [5]. In contrast to the predominance of triple-negative basal type of YFBC in Western countries [20,21], those in East Asia are more ER/progesterone receptor (PR)-positive luminal A type [5]. The dominant ER/PR-positive histology of YFBC also means that a higher proportion of younger patients in Taiwan are using antiestrogens.

Table 3: Adjusted hazard ratios for endometrial cancer[a] in the multivariable models using Cox regression by the age of breast diagnosis in Taiwan, 1999-2012

Cancer site	Endometrial cancer		
	Nonuser	Tamoxifen only	Sequenced AI
Age: 18-39			
Number of patients	2130	2759	369
Patients with event	1	3	1
Antiestrogen cDDD, median (IQR)			
Tamoxifen	—	930 (532-1480)	896 (494-1505)
AIs	—	—	419 (168-773)
Adjusted HR[b] (95% CI)	1.0	2.48 (0.26-23.63)	5.63 (0.41-76.65)
P		0.4285	0.1946
Age: 40-49			
Number of patients	4485	7639	1770
Patients with event	7	38	3
Antiestrogen cDDD, median (IQR)			
Tamoxifen	—	900 (504-1506)	770 (392-1266)
AIs	—	—	457 (175-946)
Adjusted HR[b] (95% CI)	1.0	3.74 (1.65-8.48)	0.82 (0.21-3.21)
P		0.0015	0.7786
Age: 50-59			
Number of patients	4742	4672	1746
Patients with event	10	24	6
Antiestrogen cDDD, median (IQR)			
Tamoxifen	—	862 (470-1463)	528 (224-1001)
AIs	—	—	518 (210-980)
Adjusted HR[b] (95% CI)	1.0	2.34 (1.09-5.01)	1.20 (0.44-3.30)
P		0.0287	0.7227
Age: ≥0.60			
Number of patients	3231	4232	1441
Patients with event	1	32	7
Antiestrogen cDDD, median (IQR)			
Tamoxifen	—	812 (449-1440)	469 (172-976)
AIs	—	—	529 (215-1015)
Adjusted HR[b] (95% CI)	1.0	21.38 (2.96-154.75)	11.06 (1.37-89.58)
P		0.0024	0.0243

[a]ICD-9-CM: Endometrial cancer, 182.xx, [b]Adjusted for chemotherapy, hypertension, and diabetes. AI: Aromatase inhibitor, HR: Hazard ratio, CI: Confidence interval, ICD-9: International Classification of Diseases, 9th Revision

Meanwhile, although when compared with nonusers, tamoxifen had a significantly higher risk of endometrial cancer (14-year incidence 1.7% vs. 0.3%), the clinical benefit of tamoxifen on breast cancer survival still outweighs the increased incidence from endometrial cancer.

Latest studies show that the extension of adjuvant AI to 10 years resulted in significantly higher rates of disease-free survival of breast cancer [22] and there were fewer endometrial cancers with AIs than tamoxifen treatment [6,23]. Previous studies revealed that AIs may reverse tamoxifen-induced endometrial changes in postmenopausal breast cancer patients [8,24]. In a 5-year study in South Korea, Lee *et al*. reported that breast cancer patients over 50 years of age who ever taking tamoxifen and AIs had lower incidence of endometrial malignancy when compared with those taking tamoxifen only [25]. However, the long-term carcinogenic effect of using sequenced AIs after tamoxifen remains uncertain. Our study disclosed that sequenced AI use could reduce the risk of endometrial cancer in tamoxifen users (adjusted HR 0.43). In postmenopausal women, the ovaries cease to produce estrogen. Estrogen synthesized at extragonadal tissues such as adipocytes in mammary gland contributes to the proliferation of uterine endometrium, and it may lead to endometrial hyperplasia and neoplasia. Aromatase is the principle enzyme for estrogen synthesis in the postmenopausal women. It is theorized that inhibiting the aromatase would extenuate the carcinogenic effect of tamoxifen in the uterine endometrium. Our study supports this theory and indicates that the use of AIs after tamoxifen may attenuate the risk of endometrial cancer.

The present study has a few limitations. This was a retrospective study without the prospectively defined protocol of adjuvant treatment. Moreover, information regarding cancer stage, histology subtypes, ER status, menopausal status, parity, oral contraceptive use, and obesity are absent.

Conclusions

Not only patients aged ≥50 years but also younger (40–49 years) patients with tamoxifen treatment had higher

Table 4: Adjusted hazard ratios for endometrial cancer[a] in tamoxifen-only (*n*=19,302) and sequenced aromatase inhibitor users (*n*=5326)

Antiestrogens use	*n*	Adjusted HR[b]	95% CI	*P*
Age: all				
Tamoxifen only	19,302	1.00	0.25-0.72	0.0014
Tamoxifen and sequenced AI	5326	0.43		
Age: 18-49				
Tamoxifen only	10,398	1.00	0.09-0.82	0.0197
Tamoxifen and sequenced AI	2139	0.28		
Age: ≥50				
Tamoxifen only	8904	1.00	0.28-0.94	0.0303
Tamoxifen and sequenced AI	3187	0.51		

[a]ICD-9-CM: Endometrial cancer , 182.xx, [b]Adjusted for age at diagnosis, chemotherapy, hypertension, and diabetes. AI: Aromatase inhibitor, HR: Hazard ratio, CI: Confidence interval, ICD-9: International Classification of Diseases, 9th Revision

risk of subsequent endometrial cancer in Taiwan. We suggest regular gynecologic monitoring during both the active use of tamoxifen and the follow-up phase. Sequenced AI use may reduce endometrial cancer risk in tamoxifen-treated breast cancer patients.

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Conflicts of interest

There are no conflicts of interest.

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