

Event-free survival following early endometrial events in breast cancer patients treated with anti-hormonal therapy

A nationwide claims data study

Yura Lee, MD, PhD^{a,b}, Yu Rang Park, PhD^{c,*}, Hae Reong Kim, MS^c, Jong Won Lee, MD, PhD^b

Abstract

Tamoxifen, an anti-estrogen agent that can suppress breast cancer, has been reported to increase endometrium-related adverse events. There are no guidelines for screening tamoxifen-treated patients for endometrial disease. We analyzed nationwide claims data related to endometrial diseases to investigate patterns of endometrial disease in breast cancer patients who underwent hormonal treatment.

We sourced claims data from the Health Insurance Review and Assessment Service in South Korea. Patients who made their first claim for an anti-hormonal agent between January 1, 2010 and December 31, 2012 were enrolled retrospectively. We analyzed patient characteristics and all claims related to endometrial disease, stratified by prescribed hormonal agents.

Among a total of 32,496 enrolled patients, 19,603 used tamoxifen only and 10,101 were treated with an aromatase inhibitor (AI) alone. Endometrial events occurred in 15.4% (3028/19603) of the tamoxifen-only patients and 2.0% (201/10101) of the AI-only group. In patients diagnosed with breast cancer at the age of 50 or older, the hazard ratio (HR) of endometrial malignancy in the tamoxifen-only group compared to the AI-only group was 4.13 (95% CI 1.404–12.159, $P = .010$). The HR of curettage in the tamoxifen-only group was 31.0 (95% CI 19.668–48.831, $P < .001$).

The occurrence of endometrial events among tamoxifen-treated breast cancer patients was higher than in patients treated with only AI, similar to previous studies. However, the HR of curettage was uniquely high, despite its invasiveness. Guidelines for screening endometrial disease and improvements of healthcare policy are required to appropriately manage high-risk patients.

Abbreviations: AI = aromatase inhibitor, D&C = dilation and curettage, HR = hazard ratio, ICD = International Classification of Disease, IRB = institutional review board, PAP = Papanicolaou.

Keywords: breast neoplasms, dilatation and curettage, hysterectomy, tamoxifen, uterine diseases

1. Introduction

Early detection and advanced adjuvant treatment have improved survival in breast cancer patients. Research interest has, therefore, turned to strategies for improving quality of life among breast cancer survivors.^[1–3] The health of breast cancer patients is

affected by the treatment processes they undergo and related side effects. Adjuvant hormonal therapy requires a long treatment period, which can extend for up to 10 years and can significantly impact the health of breast cancer survivors.^[4,5] The NSABP B-35, a large-scale randomized controlled trial in a breast cancer cohort, reported side effects of tamoxifen and anastrozole with quality of life impacts.^[6] Such side effects can reduce adherence to adjuvant treatment.^[7] The side effects of tamoxifen have a wide spectrum, ranging from abnormal vaginal bleeding to increased risk of endometrial cancer.^[8–13] In addition, tamoxifen therapy for breast cancer has been reported to cause a higher rate of endometrial disease and to be associated with poorer prognosis in cases of endometrial cancer in numerous previous studies.^[8,12]

The utilization of gynecologic services has increased in tamoxifen-treated breast cancer patients, and it has become apparent that switching from tamoxifen to anastrozole significantly reduces the need for a second hysteroscopy and/or dilation and curettage (D&C), further indicating that there are correlations between tamoxifen and endometrial disease.^[9,14] However, routine transvaginal ultrasonography of patients receiving tamoxifen is not recommended because of the inconsistencies in imaging results and histology, and the invasiveness of the procedure.^[15–17] There are no definitive guidelines for managing breast cancer patients showing no adverse symptoms of tamoxifen other than initial screening and regular Papanicolaou (PAP) smear exams, which are both commonly recommended.^[18–20]

There is also no clear consensus as to when and how tamoxifen regimens should be changed or even discontinued when there are suspected symptoms or signs of adverse effects. Alternative drugs to

Editor: Akif Enes Arikan.

This study was supported by a grant from the Health Insurance Review and Assessment Service (HIRA), Republic of Korea (M20170714715) and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2017R1D1A1B03035762).

The authors have no conflicts of interest to disclose.

The authors of this work have nothing to disclose.

^a Department of Biomedical Informatics, Asan Medical Center, ^b Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine,

^c Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Korea.

* Correspondence: Yu Rang Park, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, 50-1 Younsei-ro, Seodaemun-gu, Seoul 03722, Korea (e-mail: yurangpark@yuhs.ac).

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Medicine (2019) 98:2(e13976)

Received: 3 June 2018 / Received in final form: 10 December 2018 / Accepted: 12 December 2018

<http://dx.doi.org/10.1097/MD.0000000000013976>

tamoxifen are also limited. The absence of screening guidelines for endometrial disease in patients treated with tamoxifen can also lead to inappropriate investigations. Accurate gynecologic diagnosis and appropriate investigation are therefore important for breast cancer patients treated with tamoxifen in comparison with patients who receive other treatments, especially during early periods of therapy.

Since a patient may be treated at more than 1 hospital, data from medical institutions of various sizes should be included in order to accurately investigate adverse events due to drugs. In South Korea, national insurance claims data cover all medical institutions. We used these data in the present study to investigate the early occurrence of endometrium-related clinical events in breast cancer patients treated with anti-hormonal agents.^[21] Notably, the greatest increases in standardized incidence ratios (SIR) of endometrial cancer in hormone receptor-positive breast cancer have been found in Asian-American and Indian-American patients, but no nationwide studies have been conducted in East Asian countries.^[22] We address this shortfall in the current analysis by analyzing nationwide claims data regarding endometrial exams, procedures, and diagnosis in Korean breast cancer patients.

2. Methods

2.1. Data sources and patient selection

We screened claims data for breast cancer patients provided by the Health Insurance Review and Assessment Service (HIRA) of Korea

for the period from January 1, 2009 to December 31, 2014 to include in our present study cohort. These data indicated that a total of 48,137,244 claims were classified and analyzed for 128,492 patients with main diagnoses of breast cancer. Breast cancer patients who made their first claims for hormonal treatment from January 1, 2010 to December 31, 2012 were included in the analysis. We extracted patient identification numbers, patient age, sex, the start date of the claim, the end date for the claim, main diagnosis codes (International Classification of Disease [ICD]-10), sub-diagnosis codes (also in ICD-10), claimed agent/exam/procedure codes, and additional data frame such as detailed prescription information. To screen for newly diagnosed breast cancer cases during the survey period that was eligible for our analysis, we identified patients who started anti-hormonal treatment within 1-year of breast surgery and had a 1-year wash-out period.

To evaluate the causal effects of the anti-hormonal agents in our study subjects, we excluded patients with total coverage of less than 1-year for these drugs; for whom the insurance claim was not properly processed (i.e., follow-up loss) within 1 year of first making the claim for this treatment; who made a claim for only 1 hormonal agent prescription; or who made any claim related to an endometrial disease at around the same time as the first anti-hormonal agent claim (Fig. 1). We then collected data on the included patients including age at breast cancer diagnosis and claims data for treatment with anti-hormonal agents and against any therapies for endometrial-related events.

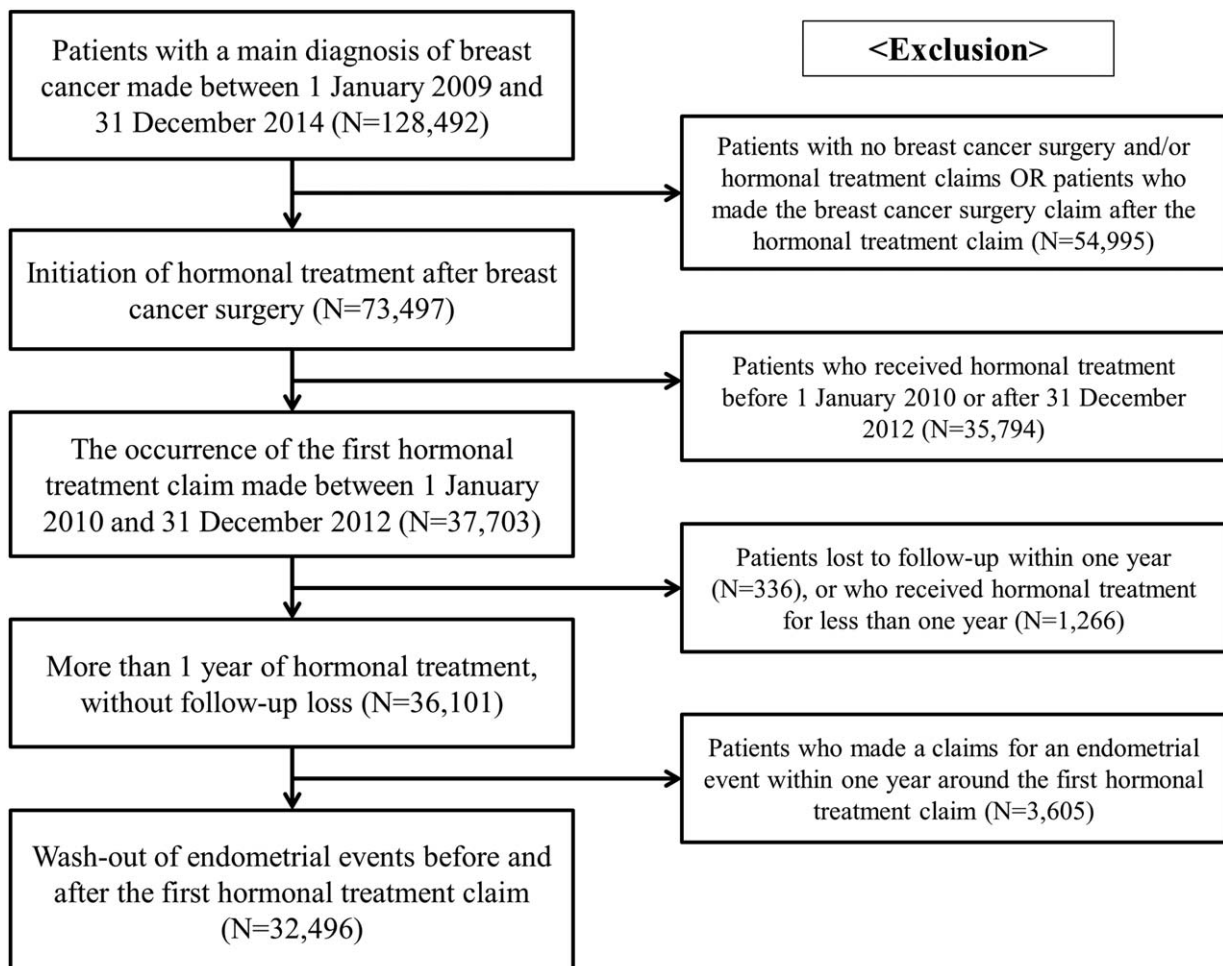


Figure 1. Flow chart of patient selection.

2.2. Definition of endometrial events

We defined endometrial events using both diagnostic and exam/procedural claims data. The codes representing a main diagnosis of abnormal uterine and vaginal bleeding (N93), endometrial hyperplasia (N85) and malignant neoplasm of the uterus (C54, C55, D07, including carcinoma in situ of the endometrium) were taken to indicate an endometrium-related diagnosis. The codes that represented different clinical tests and procedures were sorted into 3 categories:

- (1) exam such as an endometrial biopsy (other than curettage or PAP smear) or pelvic ultrasonography;
- (2) D&C; and
- (3) hysterectomy.

Patients with a history of endometrial events within 1-year of the first anti-hormonal agent claim were excluded to remove cases of underlying or coincident endometrial disease. Only endometrial events that occurred after at least 1-year exposure to an anti-hormonal agent were considered valid for analysis. We adopted this approach to more precisely assess the occurrence of endometrial disease due to anti-hormonal therapy.

2.3. Statistical analysis

The study patients were classified into 3 treatment groups: tamoxifen-only, aromatase inhibitor (AI)-only, and treatment with both agents (both-group). The tamoxifen-only and AI-only patients had no drug changes or switching. The both-group included patients treated with these agents in either order. The patient data included suspected age at breast cancer diagnosis, chemotherapy regimens, treatment adherence during the 3-year study period, in-hospital deaths, and endometrial events. These were evaluated according to the treatment group. Factors related to anti-hormonal agent coverage were presented as the number of patients for whom the total agent coverage was less than 3 years.

Since the indications for AI therapy are limited after menopause, we conducted further analyses of patients in our cohort older than 50 years. In addition, adverse events related to tamoxifen are reported to be correlated with age.^[6,14,23] Differences in endometrial events between the 3 study groups were analyzed using the chi-square test. Survival analysis of

event-free survival outcomes was investigated in the 3 study groups using log-rank tests with a Kaplan–Meier curves and age-adjusted Cox regression analysis. All reported P values were 2-sided, and P values less than .05 were considered significant. R software version 3.2 (<http://cran.r-project.org/>) was used for all statistical analyses.

2.4. Ethics

This study was approved by the institutional review board (IRB) of Asan Medical Center, Korea (IRB no. 2017–0654). The requirement for informed consent was waived by our IRB, as this study involved routinely collected medical data that were anonymously managed at all stages, including during data cleaning and statistical analysis.

3. Results

We enrolled a total of 32,496 breast cancer patients treated with an anti-hormonal agent and for whom 2-year wash-out was performed. Of these cases, 19,603 patients (60.3%) had only received tamoxifen and 10,101 (31.1%) were administered AI alone (Table 1). More than 50% of the patients on tamoxifen alone (14,351/19,603, 73.2%) were less than 50 years of age. Of the total patient cohort, 4.3% (1413/32,496) also underwent chemotherapy. During the study period, 33.8% (10,972/32,496) of these patients received an anti-hormonal agent for less than 3 years and were also analyzed.

Among the total of 9306 endometrial events in 3582 of our study patients, 84.1% (7825/9306) occurred in the tamoxifen-only group, and 4.2% (392/9306) occurred in the AI-only group. This compares with a rate of endometrial events in the total cohort of 15.4% (3028/19,603) in the tamoxifen-only group and 2.0% (201/10,101) in the AI-only group. Among the claims with endometrium-related main diagnoses, bleeding (3333 claims) was the most frequent, followed by hyperplasia (2184 claims) and malignancy (572 claims). Among claims made for tests and procedures, curettage (1625 claims) was the most frequent followed by exam (1193 claims) and hysterectomy (399 claims).

A total of 16,753 patients in the total cohort were diagnosed with breast cancer when older than 50 (Table 2). Of these, 5252 patients (31.3%) were in the tamoxifen-only group, and 9559

Table 1

Patient characteristics and endometrial events.

Characteristics	Tamoxifen only N = 19,603 (60.32%)	AI only N = 10,101 (31.08%)	Both N = 2,792 (8.59%)	Total N = 32,496
Median age at breast cancer diagnosis, Range	46 (18~90)	58 (37~91)	53 (29~96)	50 (18~96)
Age under 50	14,351	542	850	15,743
Age range of 50~59	3,580	5,043	1,187	9,810
60 and above	1,672	4,516	755	6,943
Adjuvant chemotherapy	642 (3.28)	588 (5.82)	183 (6.55)	1,413 (4.35)
Medication coverage < 3yr	6,424 (32.77)	3,654 (36.17)	894 (32.02)	10,972 (33.76)
In-hospital death	149 (0.76)	141 (1.40)	155 (5.55)	445 (1.37)
No. of patients with any claims related to endometrial events, %	3,028 (15.4)	201 (2.0)	353 (12.6)	3,582 (11.0)
Abnormal vaginal bleeding	1,366	112	134	1,612
Endometrial hyperplasia	731	23	88	842
Endometrial malignancy	28	7	7	42
Endometrial exam	826	50	106	982
Dilation and curettage	1,258	22	137	1,417
Hysterectomy	305	27	67	399

AI = aromatase Inhibitor.

Table 2
Endometrial events for patients diagnosed with breast cancer at the age of 50 and above.

Endometrial events	Tamoxifen only N = 5,252 (31.3%)	AI only N = 9,559 (57.1%)	Both N = 1,942 (11.6%)	Total N = 16,753
No. of claims (Number of patients)				
Any events	1941 (719)	334 (181)	571 (201)	2846 (1101)
Tamoxifen only		<i>P</i> < .001	<i>P</i> = .029	
AI only			<i>P</i> < .001	
Abnormal vaginal bleeding	647 (312)	154 (99)	197 (90)	998 (501)
Tamoxifen only		<i>P</i> < .001	<i>P</i> = .203	
AI only			<i>P</i> < .001	
Endometrial hyperplasia	517 (199)	36 (22)	174 (55)	727 (276)
Tamoxifen only		<i>P</i> < .001	<i>P</i> = .639	
AI only			<i>P</i> < .001	
Endometrial malignancy	92 (11)	42 (5)	6 (1)	140 (17)
Tamoxifen only		<i>P</i> = .088	<i>P</i> = .062	
AI only			<i>P</i> = .759	
Endometrial exam	265 (210)	55 (46)	63 (50)	383 (306)
Tamoxifen only		<i>P</i> < .001	<i>P</i> = .004	
AI only			<i>P</i> < .001	
Dilation and curettage	355 (314)	22 (20)	107 (93)	484 (427)
Tamoxifen only		<i>P</i> < .001	<i>P</i> = .081	
AI only			<i>P</i> < .001	
Hysterectomy	65 (65)	25 (25)	24 (24)	114 (114)
Tamoxifen only		<i>P</i> < .001	<i>P</i> = .995	
AI only			<i>P</i> < .001	

AI = aromatase Inhibitor.

(57.1%) were in the AI-only group. Of the 2864 claims made by patients over 50 years of age, 68.2% (1941/2846) occurred in the tamoxifen-only group and 11.7% (334/2846) in the AI-only group. Endometrial event variables showed a significantly higher frequency in the tamoxifen-only group compared with the AI-only group (*P* < .05). In the tamoxifen-only group, there were more claims related to exams, malignancy, and D&C compared to the both-group (*P* = .004, *P* = .062, *P* = .080). The both-group claims data also indicated that all endometrial events except for

malignancy (*P* = .759) had a significantly higher occurrence compared with the AI-only group (*P* < .001).

Log-rank tests and Kaplan–Meier curve analysis of event-free survival following endometrial events in patients over 50 showed distinct differences between the 3 treatment groups (Figs. 2–4). In all survival curves, the AI-only group showed better event-free survival outcomes than the tamoxifen-only group. However, claims associated with malignancy showed no significant difference between the AI-only group

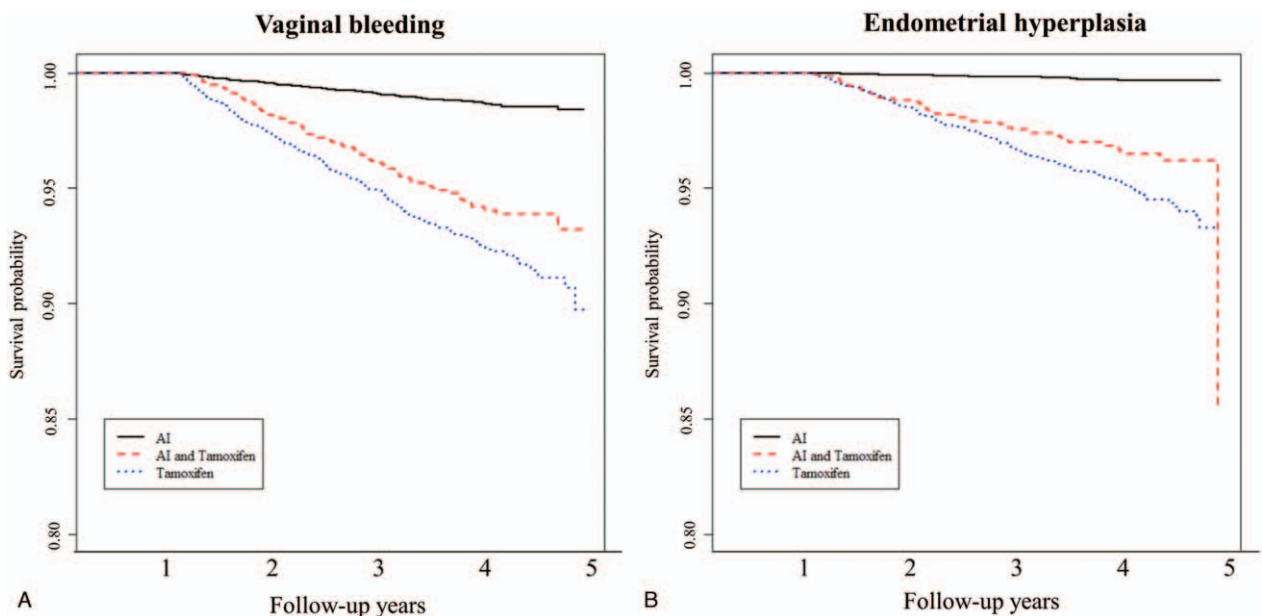


Figure 2. Unadjusted Kaplan–Meier curves for (a) abnormal vaginal bleeding and (b) endometrial hyperplasia.

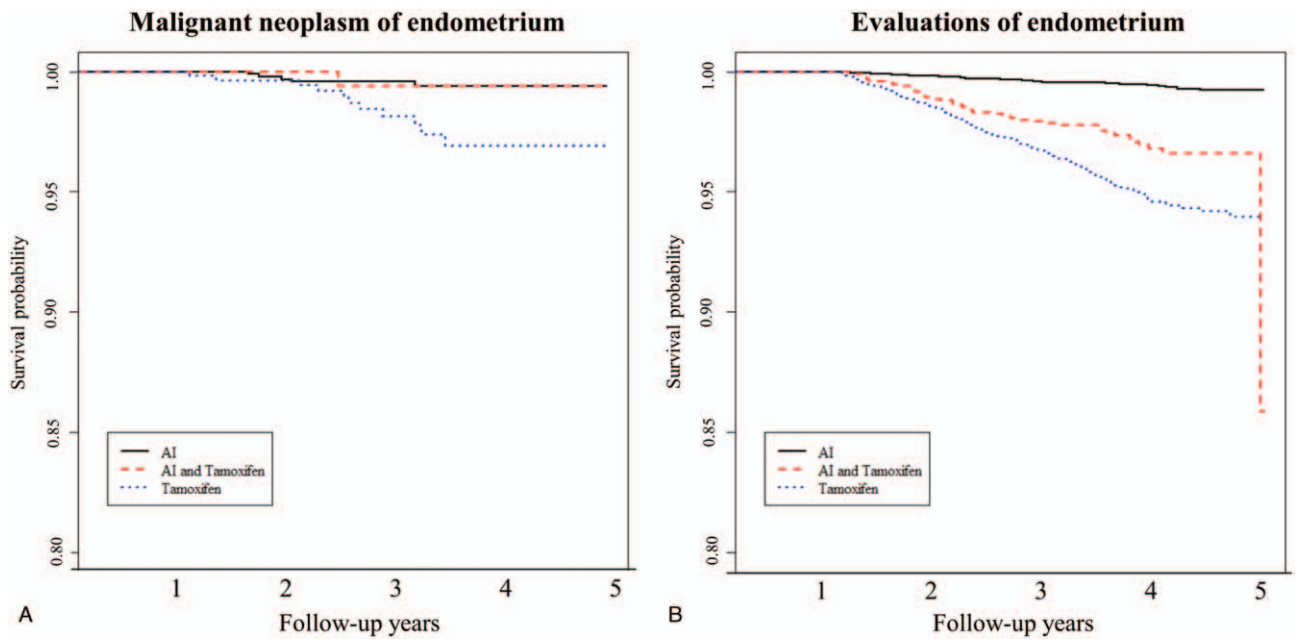


Figure 3. Unadjusted Kaplan-Meier curves for (a) malignant neoplasm of endometrium and (b) exams to evaluate the endometrium.

and both-group, and there was no significant difference between the both-group and tamoxifen-only group in the curve for hysterectomy claims (Figs. 3 and 4). In age-adjusted Cox regression analysis, the tamoxifen-only group showed a hazard ratio (HR) of 7.62 (95% CI 6.459–9.004, $P < .001$) for all endometrial events compared to the AI-only group, (95% CI 19.668–48.831, $P < .001$) and 4.13 (95% CI 1.404–12.159, $P = .010$) for malignancy. The HR for D&C in the tamoxifen-only group, compared to the AI-only group was 30.78 (95% CI 19.668–48.831, $P < .001$).

4. Discussion

We found that early endometrial events are more frequent in breast cancer patients treated with tamoxifen than in those treated with other anti-hormonal therapies. The lower incidence (15.4%) of endometrial events in the tamoxifen-only group compared with rates reported in previous studies of 20% to 60% may be due to the 2-year wash-out period before and after the day of the first anti-hormonal agent claim in our patient series.^[14,24,25] In all of the claims types in our current cohort

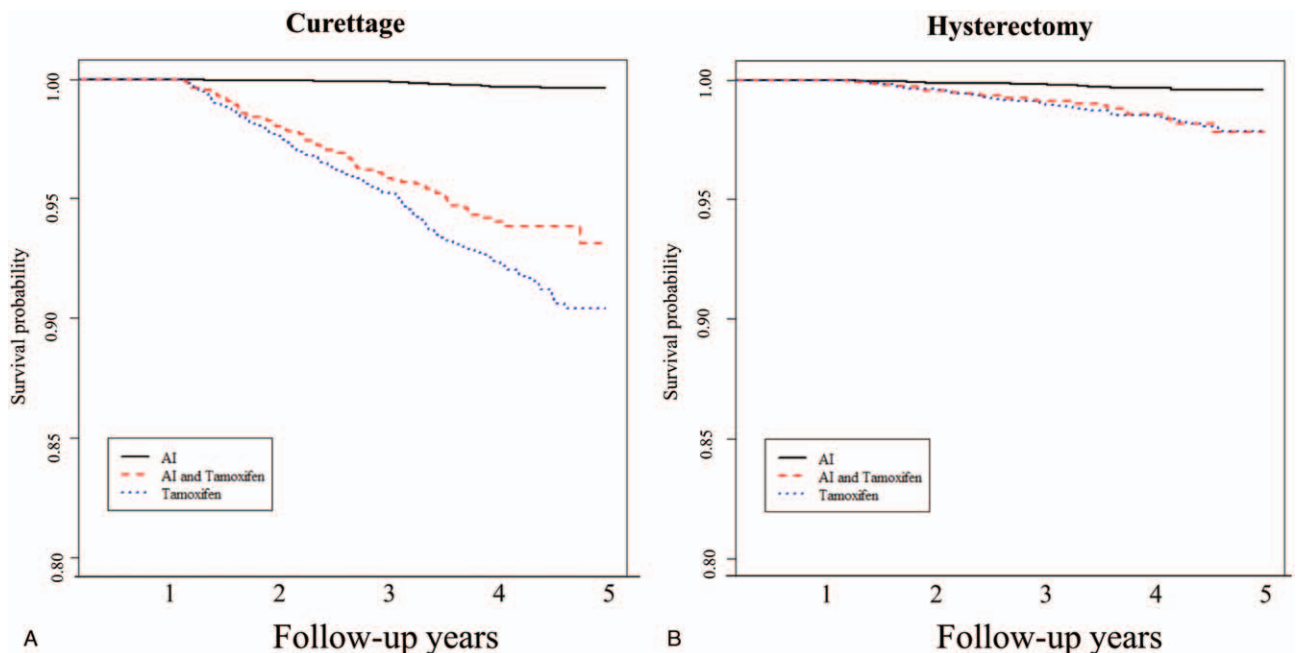


Figure 4. Unadjusted Kaplan-Meier curves for (a) dilation and curettage and (b) hysterectomy.

except for malignancy, the tamoxifen-treated group (tamoxifen-only group and both-group) showed higher risk of endometrial events than the AI-only group. In addition, D&C claims showed the highest HR in the tamoxifen-only group (HR=30.78). The HR of endometrial malignancy was significantly higher only in the tamoxifen-only treated patients in our series.

We found no differences in risk for malignancy between the AI-only group and both-group (HR=0.97, 95% CI 0.113–8.348, $P=.978$). Due to the study period, we adopted for patient enrollment (from 1 January 2010 with data collection to December 31, 2014), the duration of hormone treatment coverage did not exceed 5 years in any of the patients we analyzed. In the both-group patients, who had shorter periods of tamoxifen exposure, our findings supported previous results indicating that the prolonged use of tamoxifen increases the risk of endometrial cancer.^[8,12] Hence, more frequent gynecologic investigations and more detection efforts should be considered in tamoxifen-treated patients due to the increased risk of endometrial malignancy.

Our age-adjusted risk analysis and Kaplan–Meier curves indicated that the risk of endometrial events increased with the duration of tamoxifen exposure. This suggests that the need for gynecological investigations in these patients has not been overestimated. However, with reference to the AI-only group, the D&C claims showed a significantly higher HR in the tamoxifen-only group. This finding is likely to the dual functionality of D&C as an investigation and treatment procedure. The rate of intra-operative complications of non-obstetric D&C, such as uterine perforation, false passage, severe hemorrhage, and vaginal/cervical laceration, have been reported at 1.9%, which is similar to the proportion of claims for D&C and to the number of patients with endometrial malignancy in the tamoxifen-only group (28/1441, 1.9%).^[15] Although latent complications such as infection or adhesion can occur, adverse events arising from diagnostic D&C have been reported at lower rates (1.4%).^[26] However, we found in our current analysis that the HR of D&C claims was remarkably higher than that for bleeding (5.9), hyperplasia (18.1), or malignancy (4.1). In addition to less invasive investigations such as transvaginal/pelvic USG, non-invasive exams such as magnetic resonance imaging are viable methods of evaluating the endometrium.^[27] However, these alternative procedures are not currently covered by national health insurance in Korea.

Based on previous study findings that the risk of tamoxifen-induced endometrial cancer is significantly increased in older patients, we conducted a chi-square test and survival analysis in cases who had a diagnosis breast cancer at the age of 50 or older, a group that comprised only 26.8% of the total tamoxifen-only patients.^[23] This is consistent with the high incidence of young breast cancer patients reported in countries.^[28] In our sub-analysis of patients aged 50 and above, the proportion of cases with an endometrial malignancy showed the smallest decrease (11/28, remain 39.3% after age limitation), while the hysterectomy claims showed the greatest decrease (65/305, remain 21.3%). This is presumably because a hysterectomy is performed only once in a lifetime. In the sub-groups of patients over 50, the percentage of patients with an endometrial malignancy who had undergone a hysterectomy was 14.9% (17/114). This suggests that most of the hysterectomies in this group had been performed due to a benign disease of the endometrium. Similarly, the event-free survival curves for hysterectomy between the tamoxifen-treated and AI-only groups diverged at the early stage of treatment. The survival curves for endometrial malignancy showed a long latency period in our analysis.

The medication coverage index indicated that the majority of the patients in our analysis complied with the anti-hormonal treatment regimens within the 3-year study period. However, prescription claims for anti-hormonal agents do not necessarily indicate adherence. The adverse effects of anti-hormonal agents are also known to cause non-adherence.^[7] However, patients who experience endometrial events may have continued taking tamoxifen, as this is recommended to them when discussing possible side effects. Further investigations are needed to evaluate the level of adherence to tamoxifen and other anti-hormonal regimens before and after the occurrence of an endometrial event. Longer-term follow-up of tamoxifen-taking patients with endometrial events is also needed.

Early recognition of the side effects of a drug facilitates the consideration of treatment changes or even discontinuation. Moreover, by considering the timing of an adverse event from the beginning of a particular drug regimen, the appropriateness of this intervention can be more adequately assessed. The gradual increase in the number or intensity of follow-up assessments in accordance with degree of tamoxifen exposure will enable a more accurate assessment of whether the accumulated dose is the cause of an adverse event.^[29] The observation that risk increases with the duration of tamoxifen suggests that side effects increase with exposure to tamoxifen.

Some details of the patients included in the present study are not included in claims data (e.g., weight and height, menopause status, breast cancer stage and subtype, pathology results of hysterectomy) and therefore could not be assessed. However, the national claims data we used provided far more generic information on the use of medications than the records of any single institution. To enable early detection of adverse events following hormone therapy, we focused on early endometrial events in our study. Further evaluation studies that include real-time and long-term research, such as risk prediction model analysis of endometrial events, are needed.

The present study is the first to use national data from an East Asian country to analyze the occurrence of endometrial events in breast cancer patients receiving anti-hormonal therapy. The use of such data, rather than relying on subjective reporting of symptoms by patients themselves, could provide a far more reliable and useful guide for the use of these treatments. With the lack of current screening guidelines for endometrial disease in breast cancer patients receiving anti-hormonal therapy, proper patient education is crucial. Our study approach and findings will assist with the drafting of recommendations for evaluating endometrial events, development of screening guidelines for breast cancer patients with or without symptoms, and establishment of health policies for breast cancer survivors with histories of anti-hormone treatment.

5. Conclusions

The early detection of any side effects from a medication is important for determining the most appropriate treatment direction. It is also necessary to identify patterns of side effects that occur during a particular treatment. As found in previous studies, the results of our current analysis indicate that patients treated with tamoxifen have significantly increased risk of developing endometrial events. In the case of malignancy, the only difference between AI-only treated patients and the tamoxifen-only group was likely due to the latency period for malignancy caused by tamoxifen exposure. The appropriateness of using curettage and hysterectomy cannot be confirmed by our

present investigation and we did not include histology information. However, it is clear that guidelines for the screening of endometrial diseases and improvements in healthcare policy are required for appropriate management of high-risk patients. Additional research is thus needed to determine the long-term effects of hormonal therapy, compliance with medication, and the effectiveness of curettage and hysterectomy, including more detailed information on breast cancer patients undergoing such therapies.

Author contributions

Conceptualization: Yura Lee, Jong Won Lee.

Data curation: Hae Reong Kim.

Formal analysis: Yura Lee, Hae Reong Kim.

Methodology: Yura Lee, Yurang Park.

Supervision: Yurang Park, Jong Won Lee.

Validation: Hae Reong Kim.

Visualization: Yura Lee.

Writing – original draft: Yura Lee.

Writing – review & editing: Yurang Park, Jong Won Lee.

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