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ORIGINAL RESEARCH

Effects of Endocrine Therapy on Cardiovascular Diseases and Type 2 Diabetes Among Breast Cancer Survivors: The National Health Insurance Service Database of Korea

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BACKGROUND: Although endocrine therapy is an effective treatment for breast cancer, its antiestrogen effects are associated with increased risks of cardiovascular diseases and type 2 diabetes. This study aimed to investigate the association between endocrine therapy and the risk of cardiovascular diseases and type 2 diabetes among breast cancer survivors in Korea, in consideration of various age groups.

METHODS AND RESULTS: In the National Health Insurance Service database of Korea, a total of 133 171 patients with breast cancer aged ≥20 years were included in the current study. Endocrine therapy was treated as time-varying exposure, and patients were categorized as nonusers, selective estrogen receptor modulator users, aromatase inhibitor users, and both users. Time-dependent Cox regression models were used to estimate hazard ratios (HRs) and 95% CIs. Age at diagnosis, socioeconomic status, histological type, other treatments, and comorbidities were adjusted in the model. Compared with nonusers, selective estrogen receptor modulator users were associated with higher risks of stroke (HR, 1.20 [95% CI, 1.04–1.40]) and venous thromboembolism (HR, 1.47 [95% CI, 1.13–1.90]), whereas aromatase inhibitor users were associated with a higher risk of coronary heart disease (HR, 1.22 [95% CI, 1.06–1.41]). The risk of type 2 diabetes was associated with selective estrogen receptor modulator users (HR, 1.13 [95% CI, 1.05–1.21]), aromatase inhibitor users (HR, 1.14 [95% CI, 1.05–1.23]), and both users (HR, 1.24 [95% CI, 1.10–1.39]). In particular, the risk of a composite of cardiovascular diseases was higher in younger or premenopausal patients.

CONCLUSIONS: In breast cancer survivors in Korea, endocrine therapy is associated with a higher risk of cardiovascular diseases and type 2 diabetes. Monitoring of cancer comorbidities after endocrine therapy is needed in younger and older patients.

Key Words: breast cancer ■ cardiovascular diseases ■ comorbidities ■ endocrine therapy ■ type 2 diabetes

Breast cancer is the most commonly diagnosed cancer in women, and its prevalence is steadily increasing worldwide.[1,2] The incidence of breast cancer in Korea continues to increase across all age groups. Some of the key features of breast cancer in Korea are its higher incidence in younger women aged 40 to 49 years, an increasing proportion of premenopausal women, and a higher survival rate than in other countries. Improved cancer screening and advanced cancer treatment will further increase the number of breast cancer survivors.[2]

It has been reported that many breast cancer survivors die from noncancer diseases, especially

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CLINICAL PERSPECTIVE

What Is New?

- As a large, longitudinal, population-based study of Korea (N=133 171), endocrine therapy was associated with elevated risks of a composite of cardiovascular diseases and type 2 diabetes in patients with breast cancer diagnosed from 2006 to 2016.
- The increased risk of cardiovascular diseases could be affected by menopausal status and the age of diagnosis among patients with breast cancer, whereas the risk of type 2 diabetes was higher regardless of age.

What Are the Clinical Implications?

- It is necessary to manage cancer comorbidities in younger endocrine therapy users, as well as in older breast cancer survivors.
- Monitoring of cancer comorbidities after endocrine therapy in various age groups may contribute to the healthy prognosis of patients with breast cancer.

Nonstandard Abbreviations and Acronyms

AI	aromatase inhibitor
NHIS	National Health Insurance Service
PSM	propensity score matching
SERM	selective estrogen receptor modulator
T2D	type 2 diabetes

cardiovascular disease (CVD) and diabetes, rather than their diagnosed cancer.[3,4] This is likely to be affected by common risk factors (such as age, alcohol intake, tobacco use, obesity, physical activity, diet, and adverse events caused by cancer treatment) between breast cancer and other non-communicable diseases.[5]

Endocrine therapies used for hormone receptor-positive patients with breast cancer are classified as selective estrogen receptor modulators (SERMs) such as tamoxifen, which are involved in binding to estrogen receptors as an antagonist in breast cancer tissues, and aromatase inhibitors (AIs), which are involved in the inhibition of estrogen production.[5–7] Although endocrine therapy is effective for breast cancer recurrence and mortality, its antiestrogen effects can increase the risk of cancer comorbidities. Previous studies investigating their antiestrogen roles in CVD and type 2 diabetes (T2D) have reported inconsistent results, and the findings on AI uses are relatively insufficient compared with SERM use.[8–13] Furthermore, most of the results were for elderly patients with breast cancer, and studies that reflect the characteristics of patients with breast cancer in Korea are necessary.

The National Health Insurance Service (NHIS) claims database provides information on the entire Korean population; thus, it is possible to identify nationwide patients with breast cancer diagnosed between 2006 and 2016 in Korea. The current study aimed to investigate the association between endocrine therapy and the risk of CVD and T2D among breast cancer survivors in Korea, using the NHIS database.

METHODS

The analytical methods and study material will be available to other researchers on request for purposes of reproducing the results or replicating the procedure. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the NHIS committee.

Data Source and Study Population

The NHIS provides a population-based database of the health information of the entire population in Korea, including insurance eligibility, medical treatment and history, and health screening records. We used the NHIS database between 2002 and 2017, which comprises the qualification and contribution health use database including diagnostic records and prescription records, health check-up, and cancer screening databases. The detailed information of the NHIS database were described in previous studies.[14,15] The institutional review board of Seoul National Hospital, Seoul, Korea approved the current study protocol (C-1905-067-1033). The informed consent was waived because the NHIS provides the database anonymized.

Our study population included patients with newly diagnosed invasive or in situ breast cancer between 2006 and 2016 (N=310 919). The *International Classification of Diseases*, *Tenth Revision* (*ICD-10*) was used to identify the diagnostic diseases. Patients with invasive breast cancer were defined as those with a diagnostic code of C50 and a V193 code. Women who had a diagnostic code of D05 with the V193 code and without a diagnosis of C50 within 90 days were considered patients with in situ breast cancer. The V193 code has been used to identify patients with cancer more definitively.[7] The first diagnosed date of breast cancer between 2006 and 2016 was considered the entry date for the study population. Exclusion criteria were applied from 2002 until before the entry date for the following reasons: (1) subjects who had a history of diseases (any type of cancer, CVD, or T2D), (2) previous prescription records of endocrine therapy, (3) patients who survived ≤1 year after the first diagnosis of

breast cancer, (4) the first diagnosis at age ≤19 years, and (5) patients without a V193 code. After applying the exclusion criteria, a total of 133 171 patients were included in the current study. Patients with breast cancer were categorized as nonusers (N=36 699, 27.6%), SERM users (N=61 195, 46.0%), AI users (N=24 633, 18.5%), and both users (N=10 644, 8.0%; Figure 1).

Definition of Exposure and Outcomes

Exposure was categorized as: (1) nonusers, (2) SERM users, (3) AI users, and (4) both users. According to the *Anatomical Therapeutic Chemical* classification system, those who had at least 1 prescription record of antiestrogen (L02BA: tamoxifen, toremifene) and aromatase inhibitors (L02BG: anastrozole, letrozole, and exemestane) after the first diagnosis of breast cancer were defined as SERM and AI users, respectively. If SERM or AI users switched their regimen types after the first prescription, they were classified as both users to reflect the time-updated definition. Those who had no prescription records of endocrine therapy during the follow-up period were defined as nonusers.

Diagnostic CVDs and T2D were considered as the study outcomes. The CVD event was defined as those with at least 1 inpatient medical record or at least 2 outpatient medical records. The composite of CVDs was divided into stroke (*ICD-10*: I60-64), coronary heart disease (CHD; *ICD-10*: I20-25), venous thromboembolism (VTE; *ICD-10*: I26, I80, I82), heart failure (HF; *ICD-10*: I50), and arrhythmia (*ICD-10*: I47-49).[16,17] The T2D event was defined as having diagnostic codes of E11 to E14 with prescriptions of antidiabetic drugs or at least 2 claims of diagnostic codes of E11 to E14 within 365 days.[18] The follow-up duration was calculated from the entry date until the first diagnosis of interest of outcomes (CVD or T2D), other cancers, all-cause death, or last date of this study (December 31, 2017), whichever came first.

Covariates

Demographic characteristics at baseline were identified using qualification and contribution databases. Age at diagnosis was classified as <40, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, and ≥70 years. Insurance-based income level for socioeconomic status was divided into quartile 1 (lowest), including medical aid beneficiaries, and quartile 2, quartile 3, and quartile 4 (highest). Residential region was classified as metropolitan, urban, or rural. Invasive and in situ breast cancers were considered histological subtypes. Information about patients who underwent surgery and other cancer treatments (chemotherapy, radiotherapy, and trastuzumab) within 1 year of the first diagnosis of breast cancer was included. A detailed definition of breast cancer–related treatments has been provided in a previous study.[7] Comorbidities were identified from medical records 1 year before the

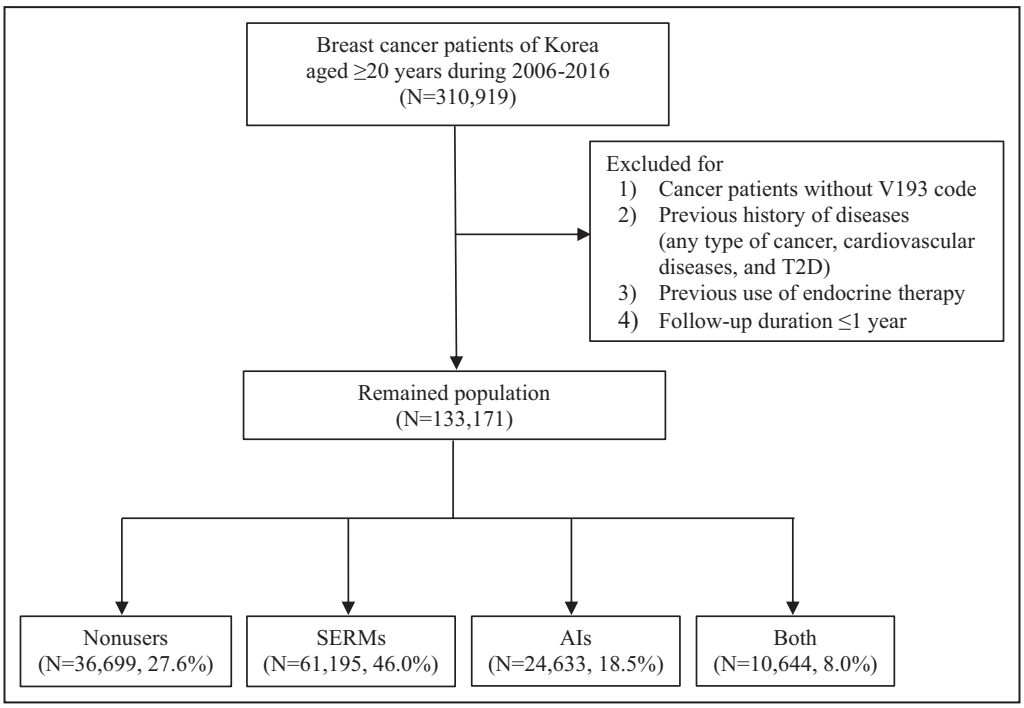

Figure 1. Flowchart for the included study population.
AIs indicates aromatase inhibitors; SERMs, selective estrogen receptor modulators; and T2D, type 2 diabetes.

entry date. Hypertension, dyslipidemia, and osteoporosis were considered as the comorbidities.

Data on body mass index, lifestyle factors (smoking status, alcohol consumption, and physical activity), and menopausal status were available for some patients who underwent health screening before the entry date. Body mass index was categorized as <23 and ≥23.0 kg/m^2. Smoking status, alcohol consumption, and physical activity were classified as never/ever or yes/no. Menopausal status was divided into premenopausal and postmenopausal status.

Statistical Analysis

The χ^2 test for categorical variables and the ANOVA for continuous variables were conducted. Multinomial logistic regression models were used to estimate a mutually adjusted odds ratio and 95% CI for the comparison of the characteristics of the study population according to endocrine therapy. Time-dependent Cox regression models were used to estimate the hazard ratio (HR) and 95% CI for associations between endocrine therapy and the risk of CVDs and T2D compared with nonusers. In a comparative analysis among endocrine therapy users, SERM users were considered as a reference group. Endocrine therapy users may have (the) immortal time between entry date and first prescription date. Thus, it was treated as a nonexposed period to consider time-related bias.[19,20] The multivariable-adjusted model for CVD and T2D included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2D (or CVD).

Subgroup analyses by various age groups (<55 versus ≥55 years, <60 versus ≥60 years; <55 years [40–54 and 45–54 years]; and <60 years [40–59 and 45–59 years]) were performed to investigate further associations in younger and older patients. Subgroup analyses by histological subtype (invasive and in situ), surgery, chemotherapy, radiotherapy, and trastuzumab were conducted to assess the differential effects on CVD or T2D. We also assessed the associations by regimen types of SERMs (tamoxifen and toremifene) and AIs (anastrozole, letrozole, and exemestane).

Various sensitivity analyses were performed to assess the robustness of our results. First, we excluded short-term endocrine therapy users of <6 months or <12 months to consider the depletion of susceptible bias associated with an early increase in acute events.[21] Second, we excluded the patients who were followed-up for <5 years to consider a sufficient time period to identify the incident cases of CVD. Third, the endocrine therapy users were defined as those who had at least 2 prescriptions of regimen to identify the possible misclassification of exposure definition. Fourth, body mass index, lifestyle factors (smoking, alcohol consumption, and physical activity), and menopausal status were further adjusted in patients who underwent health screening because of data availability. In addition, the subgroup analysis by menopausal status was performed in the health screening subjects. Fifth, we compared the results of CVDs in patients with a previous history of CVD at baseline. Lastly, the associations after the propensity score matching (PSM) between 2 groups (SERM users versus nonusers, AI users versus nonusers, and AI users versus SERM users) were also conducted. Each group was matched as the 1:1 ratio according to age at diagnosis (continuous), insurance-based income level, region of residence, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, and osteoporosis. For the comparison of the results before PSM, T2D, or CVD was additionally adjusted for each CVD and T2D outcome. The balance of covariate was checked by standardized mean difference for each comparative group (standardized mean difference <0.1). In addition, a false discovery rate for multiple testing was performed, considering the number of *P* values from the analyses (*P* for false discovery rate <0.5). A heterogeneity test was conducted on the subgroup results. If the *P* value was <0.1 or I^2>50%, we hypothesized that the associations by the stratified factors were significantly heterogeneous. SAS statistical software version 9.4 (SAS Institute, Cary, NC) and the meta package of R version 4.1.0 software (R Foundation for Statistical Computing, Vienna, Austria) were used for all the analyses.

RESULTS

Table 1 shows the baseline characteristics of the included study population for CVD and T2D. The mean (SD) age for nonusers, SERM users, AI users, and both users were 50.1 (10.8), 45.5 (8.3), 58.2 (7.8), and 51.2 (8.7) years, respectively. Compared with nonusers, SERM users were younger, and patients were more likely to have in situ breast cancer. However, the AI users were older and were patients with invasive breast cancer. All of the SERM, AI, and both users underwent surgery, were treated with radiotherapy, and were not treated with trastuzumab compared with nonusers. Although SERM and AI users were treated less with chemotherapy, both users were treated more with chemotherapy than nonusers. In the health screening subjects (N=72 063; 54% of the total population), the SERM users were patients who were premenopausal, and AI users were patients who were postmenopausal and overweight or obese (Table S1).

Table 1. Baseline Characteristics of Study Population for Cardiovascular Diseases and Type 2 Diabetes

Characteristic	Nonusers, N=36 699, 27.6%		SERM users, N=61 195, 46.0%		SERM users vs nonusers, OR (95% CI)*		AI users, N=24 633, 18.5%		AI users vs nonusers, OR (95% CI)*		Both, N=10 644, 8.0%		Both vs nonusers, OR (95% CI)*	
Age at diagnosis, y														
Mean (SD)	50.1	(10.8)	45.5	(8.3)			58.2	(7.8)			51.2	(8.7)		
<40	6058	(16.5)	11 702	(19.1)	1.89	(1.81–1.98)	90	(0.4)	0.02	(0.01–0.02)	607	(5.7)	0.25	(0.23–0.28)
40–44	5153	(14.0)	16 817	(27.5)	3.08	(2.94–3.23)	257	(1.0)	0.05	(0.04–0.06)	1266	(11.9)	0.63	(0.58–0.68)
45–49	6752	(18.4)	18 856	(30.8)	2.58	(2.47–2.70)	1789	(7.3)	0.27	(0.25–0.28)	3226	(30.3)	1.23	(1.15–1.30)
50–54	7270	(19.8)	8082	(13.2)	1.00	(Reference)	6882	(27.9)	1.00	(Reference)	2651	(24.9)	1.00	(Reference)
55–59	5115	(13.9)	2161	(3.5)	0.38	(0.35–0.40)	6368	(25.9)	1.39	(1.32–1.47)	1259	(11.8)	0.72	(0.66–0.77)
60–64	2941	(8.0)	1410	(2.3)	0.41	(0.38–0.45)	4432	(18.0)	1.64	(1.54–1.74)	752	(7.1)	0.72	(0.66–0.79)
65–69	1623	(4.4)	939	(1.5)	0.50	(0.46–0.55)	2445	(9.9)	1.68	(1.56–1.81)	448	(4.2)	0.78	(0.69–0.88)
≥70	1787	(4.9)	1228	(2.0)	0.56	(0.52–0.61)	2370	(9.6)	1.47	(1.36–1.59)	435	(4.1)	0.69	(0.61–0.77)
Insurance-based income														
Q1 (lowest)	9214	(25.1)	13 924	(22.8)	1.00	(Reference)	6241	(25.3)	1.00	(Reference)	2610	(24.5)	1.00	(Reference)
Q2	7029	(19.2)	11 407	(18.6)	1.02	(0.98–1.07)	4494	(18.2)	1.04	(0.98–1.09)	2034	(19.1)	1.03	(0.97–1.11)
Q3	8686	(23.7)	13 994	(22.9)	1.02	(0.97–1.06)	5719	(23.2)	1.05	(1.00–1.11)	2339	(22.0)	1.01	(0.95–1.08)
Q4 (highest)	11 770	(32.1)	21 870	(35.7)	1.08	(1.04–1.12)	8179	(33.2)	1.01	(0.97–1.06)	3661	(34.4)	1.08	(1.02–1.15)
Region of residence														
Metropolitan	18 619	(50.7)	30 269	(49.5)	1.00	(Reference)	12 662	(51.4)	1.00	(Reference)	5432	(51.0)	1.00	(Reference)
Urban	7736	(21.1)	14 277	(23.3)	1.05	(1.01–1.09)	4747	(19.3)	0.98	(0.93–1.02)	2299	(21.6)	1.01	(0.95–1.07)
Rural	10 244	(27.9)	16 526	(27.0)	1.05	(1.02–1.09)	7189	(29.2)	1.01	(0.97–1.05)	2899	(27.2)	0.96	(0.91–1.01)
Histological type														
Invasive	33 252	(90.6)	52 004	(85.0)	1.00	(Reference)	24 530	(99.6)	1.00	(Reference)	10 459	(98.3)	1.00	(Reference)
In situ	3447	(9.4)	9191	(15.0)	1.29	(1.23–1.36)	103	(0.4)	0.03	(0.02–0.03)	185	(1.7)	0.16	(0.14–0.19)
Surgery														
No	7004	(19.1)	7087	(11.6)	1.00	(Reference)	2587	(10.5)	1.00	(Reference)	1613	(15.2)	1.00	(Reference)
Yes	29695	(80.9)	54 108	(88.4)	1.85	(1.78–1.93)	22 046	(89.5)	1.96	(1.86–2.07)	9031	(84.9)	1.15	(1.08–1.23)
Chemotherapy														
No	11 404	(31.1)	27 663	(45.2)	1.00	(Reference)	8575	(34.8)	1.00	(Reference)	2748	(25.8)	1.00	(Reference)
Yes	25 295	(68.9)	33 532	(54.8)	0.45	(0.44–0.47)	16 058	(65.2)	0.76	(0.73–0.79)	7896	(74.2)	1.09	(1.03–1.15)
Radiotherapy														
No	15 348	(41.8)	18 670	(30.5)	1.00	(Reference)	7292	(29.6)	1.00	(Reference)	3579	(33.6)	1.00	(Reference)
Yes	21 351	(58.2)	42 525	(69.5)	1.60	(1.55–1.65)	17 341	(70.4)	1.84	(1.77–1.91)	7065	(66.4)	1.34	(1.28–1.41)

(*Continued*)

Table 1. Continued

Characteristic	Nonusers, N=36 699, 27.6%		SERM users, N=61 195, 46.0%		SERM users vs nonusers, OR (95% CI)*		AI users, N=24 633, 18.5%		AI users vs nonusers, OR (95% CI)*		Both, N=10 644, 8.0%		Both vs nonusers, OR (95% CI)*	
Trastuzumab														
No	30 794	(83.9)	56 672	(92.6)	1.00	(Reference)	22 283	(90.5)	1.00	(Reference)	9867	(92.7)	1.00	(Reference)
Yes	5905	(16.1)	4523	(7.4)	0.57	(0.54–0.59)	2350	(9.5)	0.45	(0.43–0.48)	777	(7.3)	0.35	(0.33–0.38)
Hypertension														
No	32 012	(87.2)	56 704	(92.7)	1.00	(Reference)	18 591	(75.5)	1.00	(Reference)	9223	(86.7)	1.00	(Reference)
Yes	4687	(12.8)	4491	(7.3)	1.03	(0.98–1.09)	6042	(24.5)	1.15	(1.10–1.21)	1421	(13.4)	1.07	(1.00–1.15)
Dyslipidemia														
No	33 331	(90.8)	57 561	(94.1)	1.00	(Reference)	20 738	(84.2)	1.00	(Reference)	9787	(92.0)	1.00	(Reference)
Yes	3368	(9.2)	3634	(5.9)	0.94	(0.89–0.99)	3895	(15.8)	1.06	(1.00–1.12)	857	(8.1)	0.85	(0.78–0.92)
Osteoporosis														
No	33 696	(91.8)	57 711	(94.3)	1.00	(Reference)	21 617	(87.8)	1.00	(Reference)	9638	(90.6)	1.00	(Reference)
Yes	3003	(8.2)	3484	(5.7)	0.97	(0.92–1.02)	3016	(12.2)	0.94	(0.89–0.99)	1006	(9.5)	1.19	(1.10–1.29)

Data are presented as n (%) unless otherwise indicated. AI indicates aromatase inhibitor; OR, odds ratio; Q, quartile; and SERM, selective estrogen receptor modulator.
*The OR for each covariate was adjusted for other covariates in the multinomial logistic regression model.

Overall Association of CVD and T2D

Table 2 shows the overall association of endocrine therapy on CVD and T2D outcomes. The median follow-up duration was 4.73 years, and the mean follow-up duration was 5.27 (SD, 3.05) years. Compared with nonusers, the higher risks of a composite of CVDs were observed in SERM users (HR, 1.13 [95% CI, 1.05–1.21]), AI users (HR, 1.14 [95% CI, 1.05–1.23]), and both users (HR, 1.24 [95% CI, 1.10–1.39]). For specific CVD outcomes, the risk of stroke was higher in SERM users (HR, 1.20 [95% CI, 1.04–1.40]), the risk of CHD was higher in AI users (HR, 1.22 [95% CI, 1.06–1.41]), and the risk of VTE was higher in SERM (HR, 1.47 [95% CI, 1.13–1.90]) and both users (HR, 1.72 [95% CI, 1.15–2.55]) than in nonusers.

Table 3 shows the associations of CVD and T2D among endocrine therapy users compared with SERM users. Although the risk of CHD was higher in AI than SERM users, there were no significant associations after multiple testing.

Subgroup and Sensitivity Analyses

Summarized results of various subgroup and sensitivity analyses of each outcome were presented as forest plots (Figures 2 and 3, and Figures S1 through S5). More detailed results were presented in Tables S2 through S23.

The risk of composite CVDs was significantly heterogeneous with age at diagnosis in SERM, AI, and both users (Figure 2). Moreover, SERM users have a significant difference by surgery, whereas AI users have significant heterogeneity by histological type, chemotherapy, trastuzumab, and menopausal status. In particular, the risk of composite CVD with AI users was significantly elevated in younger or patients who were premenopausal. The risk of T2D was significantly heterogeneous with age at diagnosis, histological type, and chemotherapy (Figure 3). Unlike CVD, the risk of T2D was higher in older, in situ, and patients who were treated with chemotherapy. Figures S1 through S5 show the summarized forest plots for stroke, CHD, VTE, HF, and arrhythmia. In regimen types, the risk of VTE was higher in tamoxifen, and the risk of T2D was higher in tamoxifen and letrozole, compared with nonusers. Tables S2 through S12 show all of the results of subgroup analyses by age at diagnosis, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, regimen type, and menopausal status.

To assess the robustness of our results, various sensitivity analyses were performed. First, similar associations were observed after excluding users <6 or <12 months; however, the significant association of stroke disappeared in SERM users who were prescribed for >12 months (Table S13). Second, patients who were followed up for >5 years showed stronger

Table 2. Associations of Endocrine Therapy With CVD and T2D Comparison With Nonusers

	Total	No. of events	(%)	1000 PY	Age-adjusted HR (95% CI)		Multivariable-adjusted HR (95% CI)*		*P* value for FDR†
Composite of CVD									
Nonusers	36 699	1339	(3.65)	190.0	1.00	(Reference)	1.00	(Reference)	
SERM users	61 195	1526	(2.49)	318.0	1.05	(0.98–1.13)	1.13	(1.05–1.21)	0.003
AI users	24 633	1159	(4.71)	120.2	1.08	(1.00–1.16)	1.14	(1.05–1.23)	0.003
Both	10 644	377	(3.54)	73.4	1.20	(1.07–1.34)	1.24	(1.10–1.39)	0.002
Stroke									
Nonusers	36 699	335	(0.91)	190.0	1.00	(Reference)	1.00	(Reference)	
SERM users	61 195	356	(0.58)	318.0	1.15	(0.99–1.33)	1.20	(1.04–1.40)	0.048
AI users	24 633	337	(1.37)	120.2	1.09	(0.94–1.26)	1.16	(0.99–1.35)	0.124
Both	10 644	88	(0.83)	73.4	1.11	(0.88–1.41)	1.13	(0.89–1.44)	0.462
CHD									
Nonusers	36 699	414	(1.13)	190.0	1.00	(Reference)	1.00	(Reference)	
SERM users	61 195	465	(0.76)	318.0	1.02	(0.89–1.16)	1.03	(0.90–1.18)	0.679
AI users	24 633	389	(1.58)	120.2	1.18	(1.03–1.35)	1.22	(1.06–1.41)	0.033
Both	10 644	110	(1.03)	73.4	1.12	(0.90–1.39)	1.14	(0.92–1.42)	0.442
VTE									
Nonusers	36 699	96	(0.26)	190.0	1.00	(Reference)	1.00	(Reference)	
SERM users	61 195	154	(0.25)	318.0	1.35	(1.04–1.74)	1.47	(1.13–1.90)	0.012
AI users	24 633	74	(0.30)	120.2	1.10	(0.82–1.49)	1.17	(0.86–1.58)	0.388
Both	10 644	35	(0.33)	73.4	1.65	(1.11–2.45)	1.72	(1.15–2.55)	0.015
HF									
Nonusers	36 699	231	(0.63)	190.0	1.00	(Reference)	1.00	(Reference)	
SERM users	61 195	206	(0.34)	318.0	0.75	(0.63–0.90)	0.98	(0.81–1.18)	0.794
AI users	24 633	156	(0.63)	120.2	0.94	(0.77–1.15)	1.05	(0.85–1.29)	0.794
Both	10 644	60	(0.56)	73.4	1.24	(0.93–1.66)	1.41	(1.05–1.89)	0.065
Arrhythmia									
Nonusers	36 699	263	(0.72)	190.0	1.00	(Reference)	1.00	(Reference)	
SERM users	61 195	346	(0.57)	318.0	1.12	(0.96–1.31)	1.14	(0.97–1.34)	0.244
AI users	24 633	205	(0.83)	120.2	1.07	(0.89–1.28)	1.08	(0.90–1.30)	0.493
Both	10 644	84	(0.79)	73.4	1.28	(1.00–1.64)	1.28	(0.99–1.64)	0.244
T2D									
Nonusers	36 699	1581	(4.31)	190.0	1.00	(Reference)	1.00	(Reference)	
SERM users	61 195	2136	(3.49)	318.0	1.16	(1.09–1.24)	1.22	(1.14–1.30)	<0.001
AI users	24 633	1490	(6.05)	120.2	1.22	(1.14–1.31)	1.22	(1.14–1.31)	<0.001
Both	10 644	477	(4.48)	73.4	1.25	(1.13–1.38)	1.24	(1.12–1.38)	<0.001

AI indicates aromatase inhibitor; CHD, coronary heart disease; CVD, cardiovascular disease; FDR, false discovery rate; HF, heart failure; HR, hazard ratio; PY, person-years; SERM, selective estrogen receptor modulator; T2D, type 2 diabetes; and VTE, venous thromboembolism.

*Multivariable-adjusted model included age at diagnosis (continuous), insurance-based income, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2D (or CVD).

†Significance remained after FDR for multiple test (*P* value for FDR<0.05).

associations of a composite of CVDs, stroke, and CHD in both SERM and AI users; whereas the risk of VTE with SERM users was insignificant (Table S14). Third, the overall associations were not different in the users having at least 2 prescriptions for endocrine therapy (Table S15). Fourth, there was no difference in the results of further adjustments for body mass index, lifestyle factors, and menopausal status, although statistical significance was maintained only in the risk of VTE by SERM users (Table S16). Fifth, in the patients with a previous history of CVD, higher risks of stroke and HF by SERM users were observed (Table S17). Lastly, the results after PSM were compared with the overall findings. The matched covariates achieved the balance in each comparative group (Tables S18 through S20). After PSM, the risks of VTE and T2D remained in SERM users compared with nonusers (Table S21). However, the significance of results by AI

Table 3. Associations of Endocrine Therapy With CVD and T2D Comparison With SERMs

	Total	No. of events	(%)	1000 PY	Age-adjusted HR (95% CI)		Multivariable-adjusted HR (95% CI)*		*P* value for FDR†
Composite of CVD									
SERM users	61 195	1526	(2.49)	318.0	1.00	(Reference)	1.00	(Reference)	
AI users	24 633	1159	(4.71)	120.2	1.02	(0.95–1.11)	1.01	(0.93–1.09)	0.841
Both	10 644	377	(3.54)	73.4	1.14	(1.01–1.27)	1.10	(0.98–1.24)	0.116
Stroke									
SERM users	61 195	356	(0.58)	318.0	1.00	(Reference)	1.00	(Reference)	
AI users	24 633	337	(1.37)	120.2	0.95	(0.82–1.10)	0.96	(0.83–1.12)	0.624
Both	10 644	88	(0.83)	73.4	0.97	(0.76–1.22)	0.94	(0.74–1.19)	0.624
CHD									
SERM users	61 195	465	(0.76)	318.0	1.00	(Reference)	1.00	(Reference)	
AI users	24 633	389	(1.58)	120.2	1.16	(1.01–1.33)	1.19	(1.03–1.37)	0.051
Both	10 644	110	(1.03)	73.4	1.10	(0.89–1.36)	1.11	(0.90–1.37)	0.495
VTE									
SERM users	61 195	154	(0.25)	318.0	1.00	(Reference)	1.00	(Reference)	
AI users	24 633	74	(0.30)	120.2	0.82	(0.62–1.09)	0.80	(0.60–1.06)	0.176
Both	10 644	35	(0.33)	73.4	1.23	(0.85–1.79)	1.17	(0.80–1.71)	0.416
HF									
SERM users	61 195	206	(0.34)	318.0	1.00	(Reference)	1.00	(Reference)	
AI users	24 633	156	(0.63)	120.2	1.25	(1.01–1.54)	1.07	(0.87–1.33)	0.794
Both	10 644	60	(0.56)	73.4	1.66	(1.24–2.22)	1.44	(1.08–1.94)	0.065
Arrhythmia									
SERM users	61 195	346	(0.57)	318.0	1.00	(Reference)	1.00	(Reference)	
AI users	24 633	205	(0.83)	120.2	1.14	(0.90–1.45)	0.95	(0.79–1.14)	0.584
Both	10 644	84	(0.79)	73.4	1.05	(1.04–1.05)	1.12	(0.88–1.43)	0.493
T2D									
SERM users	61 195	2136	(3.49)	318.0	1.00	(Reference)	1.00	(Reference)	
AI users	24 633	1490	(6.05)	120.2	1.08	(0.97–1.19)	1.00	(0.94–1.08)	0.901
Both	10 644	477	(4.48)	73.4	1.05	(1.05–1.05)	1.02	(0.92–1.13)	0.830

AI indicates aromatase inhibitor; CHD, coronary heart disease; CVD, cardiovascular disease; FDR, false discovery rate; HF, heart failure; HR, hazard ratio; PY, person-years; SERM, selective estrogen receptor modulator; T2D, type 2 diabetes; and VTE, venous thromboembolism.

*Multivariable-adjusted model included age at diagnosis (continuous), income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2D (or CVD).

†Significance remained after FDR for multiple test (*P* for FDR<0.05).

users compared with nonusers disappeared after PSM (Table S22). In the PSM of SERM users with AI users, a lower risk of T2D in AI users was observed than in SERM users (Table S23).

DISCUSSION

Among Koreans diagnosed with breast cancer from 2006 to 2016 using the NHIS of Korea, SERM users were associated with higher risks of stroke and VTE, whereas AI users were associated with higher risk of CHD, compared with nonusers. Compared with nonusers, the risk of T2D was higher in both SERM and AI users, regardless of age. The higher risks of VTE and T2D in SERM users compared with nonusers still remained after PSM. In addition, from the results considering various age subgroups, our findings suggest that younger patients or patients who are premenopausal should also be monitored for cancer comorbidities.

Previous studies have focused on elderly patients (mean age >65 years)[22,23]; thus, conducting further studies considering various age groups has been suggested.[24] In addition, the incidence of breast cancer in Korea is higher in patients who are young (especially aged 40–49 years) and premenopausal than in Western countries.[2] Thus, we conducted various subgroup analyses including young patients with breast cancer to reflect these characteristics, and also compared AI users with SERM users and compared users (SERM, AI, and both users) with nonusers to investigate the antiestrogen roles of endocrine therapy in CVD and T2D. Consistent with previous studies,[8,23,25] we identified that the VTE risk was higher in SERM users, especially tamoxifen (HR, 1.36 [95% CI, 1.03–1.79]; Table S11),

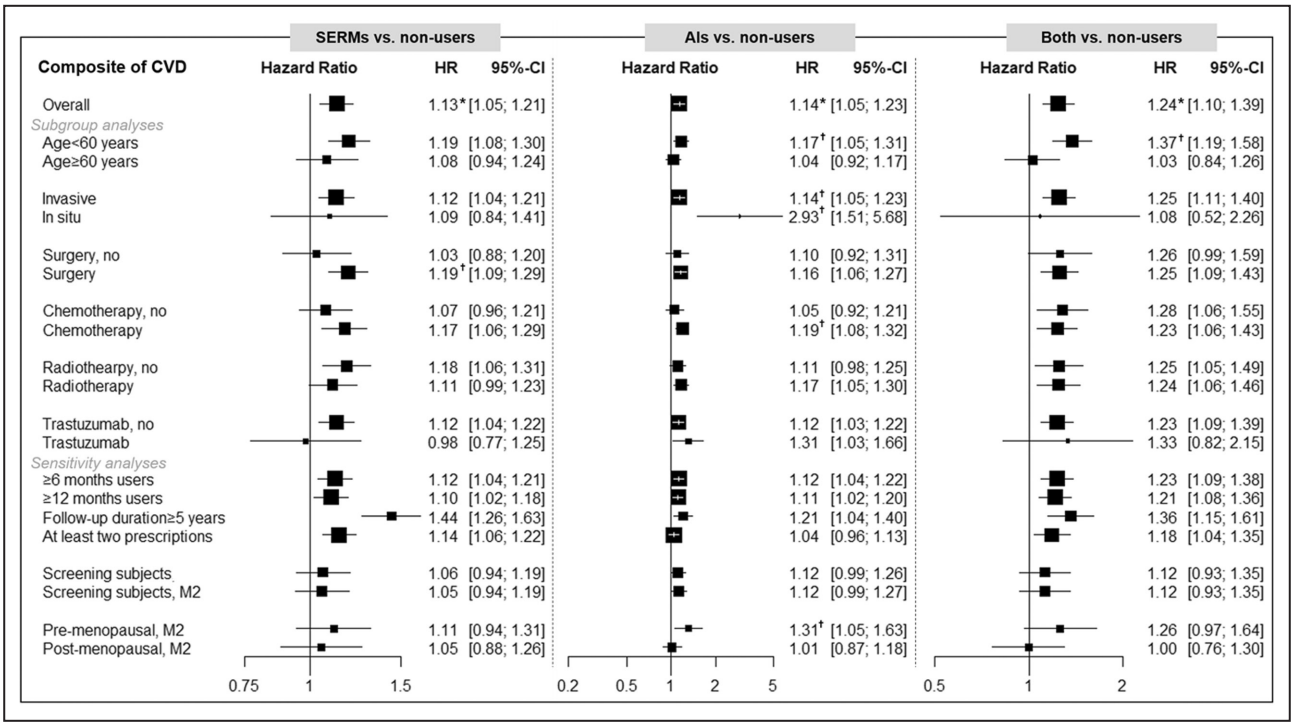

Figure 2. Summary of results for composite of cardiovascular diseases (comparison with nonusers).
The multivariable-adjusted model included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes. However, Model 2 (M2) additionally includes body mass index, lifestyle factors, and menopausal status. The asterisk (*) indicates the significance after multiple testing by a false discovery rate (FDR) (*P* for FDR<0.05) in Table 2. The dagger (†) symbol indicates the results of heterogeneity (*P* <0.1 or I^2>50%) by the stratified factor in the supplementary material. AIs indicates aromatase inhibitors; CVD, cardiovascular disease; HR, hazard ratio; and SERMs, selective estrogen receptor modulators.

compared with nonusers. In contrast, the risks of CHD and stroke were inconsistent,[23,26,27] and we found a higher risk of stroke in SERM users and a higher risk of CHD in AI users compared with nonusers. However, the higher risk of VTE in SERM users compared with nonusers only remained after PSM.

In our subgroup analyses, we identified that a higher risk of CVD outcomes remained in patients who were younger or premenopausal. A possible explanation for our subgroup results is that premenopausal women with a high risk of recurrence can optionally receive ovarian suppression treatments in addition to endocrine therapy.[6] In this case, premenopausal patients with breast cancer may have more severe estrogen deprivation,[6,28] which could be a risk factor for CVD. Further studies are necessary to determine the clinical characteristics of patients with breast cancer.

The evidence of myocardial diseases (HF and arrhythmia) is likely to be more inconclusive than other CVD outcomes.[8,22,23,26,29] Although the current study did not observe an overall association with endocrine therapy, we identified the higher risk of HF by SERM users in sensitivity analyses for patients followed up >5 years and patients with a history of CVD at baseline. Further studies are required to verify this association.

It has been reported that the risk of T2D was higher in tamoxifen users, but the evidence in AI users was insufficient.[12,13,30] Similar to SERMs, AIs can be involved in glucose metabolism by reducing endogenous estrogen levels.[25] Unlike previous studies with small sample sizes (range, 570–22 000),[31] our large population-based study found an elevated risk of T2D among SERM, AI, and both users. In addition, a lower risk of T2D was observed in AI users than SERM users after PSM. Although the subgroup analysis by regimen type did not show difference in the present study, a recent study has suggested the potentially harmful effect of the toremifene regimen type.[32] Further studies based on a larger study population are required to compare with our findings.

This study has several limitations; therefore, our findings should be interpreted with caution. First, the clinical information of patients with breast cancer could not be considered, because the NHIS database was collected for administrative purposes. Although we considered other cancer treatments and histological subtypes in the analyses, insufficient clinical information, such as hormone receptors and cancer stage, may have interfered with the clear associations between endocrine therapy and CVD and T2D risk. CVD and T2D as the

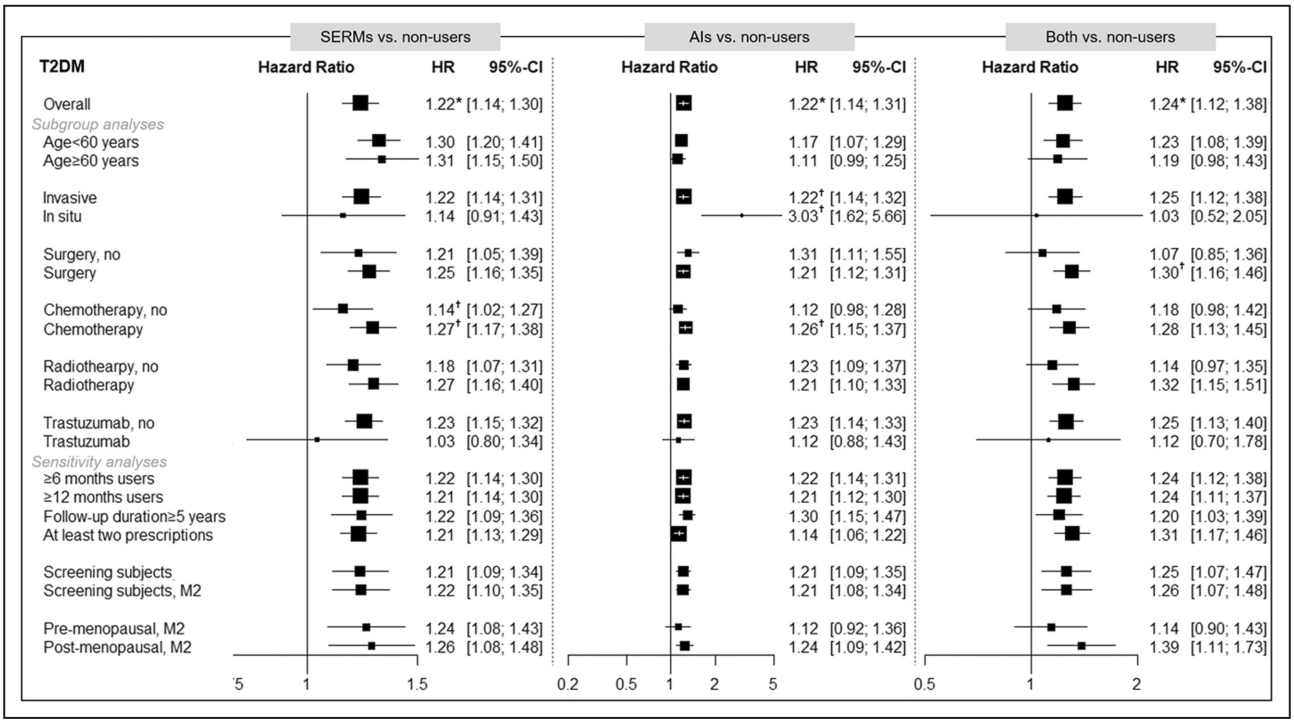

Figure 3. Summary of results for type 2 diabetes (comparison with nonusers).
The multivariable-adjusted model included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and cardiovascular disease. However, Model 2 (M2) additionally includes body mass index, lifestyle factors, and menopausal status. The asterisk (*) indicates the significance after multiple testing by a false discovery rate (FDR) (*P* for FDR<0.05) in Table 2. The dagger (†) symbol indicates the results of heterogeneity (*P*<0.1 or I^2>50%) by the stratified factor in the supplementary material. AIs indicates aromatase inhibitors; HR, hazard ratio; SERMs, selective estrogen receptor modulators; and T2D, type 2 diabetes.

outcomes were defined by both *ICD-10* codes for diseases and *Anatomical Therapeutic Chemical* codes for regimen types based on the previous studies; however, the misclassification bias may still remain. Second, only some health-screening subjects had information on lifestyle factors and menopause status. However, consistent results were identified from the sensitivity analysis after excluding subjects without health checkup information. Third, there was an age difference between the treatment groups, but our results could reflect the real-world clinical practice of prescribing endocrine therapy depending on the menopausal status of the patient. However, these age differences were identified only in younger patients and not in elderly patients. In addition, through various subgroup analyses by age group, we confirmed that our results were comparable with those of previous studies. We also conducted the PSM to determine the robustness of our results. The significance of some results with AI users compared with nonusers disappeared; however, the statistical power was reduced compared with the overall findings. Thus, further studies to assess the AI users with CVD and T2D outcomes are required.

Nevertheless, our study had several strengths. This is a large population-based study including all Korean patients with breast cancer from to 2006 to 2016 in the NHIS database covering the nationwide population of Korea. The definition of the study population was based on a previous study that proved similar to the number of patients with breast cancer in the Korea Central Cancer Registry database.[7] We also identified the differential effects of various age ranges and conducted comparisons of regimen types. By including a large number of AI users compared with previous studies, we could provide evidence of the individual effects of AIs against CVD and T2D. In addition, we attempted to consider the time-related bias in the current study. A time-dependent Cox model was used to consider the immortal time bias. Various sensitivity analyses were conducted to assess the robustness of our findings.

In conclusion, endocrine therapy is associated with a higher risk of CVD and T2D in breast cancer survivors. CHD risk was higher in AI users, whereas the risks of stroke and VTE were higher in SERM users than in nonusers. The increased risk of CVD could be affected by menopausal status and the age of patients with breast cancer. Although the risk of T2D did not differ between SERM and AI use, the risk was higher regardless of age. Therefore, it is necessary to manage cancer comorbidities in younger endocrine therapy

users, as well as in older breast cancer survivors. Further studies are required to confirm these findings.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S23
Figures S1–S5

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Supplemental Material

Table S1. Baseline characteristics of the health screening subjects

	Non-users (N=18,030, 25.0%)		SERMs (N=33,407, 46.4%)		AIs (N=15,341, 21.3%)		Both (N=5,285, 7.3%)		P-value*
Age at diagnosis [years, mean (SD)]	52.3	(9.0)	47.3	(6.9)	58.3	(7.3)	52.0	(7.7)	<0.001
<40	797	(4.4)	1,782	(5.3)	8	(0.1)	62	(1.2)	<0.001
40-44	2,783	(15.4)	10,344	(31.0)	114	(0.7)	550	(10.4)	
45-49	3,729	(20.7)	12,404	(37.1)	910	(5.9)	1,684	(31.9)	
50-54	4,242	(23.5)	5,549	(16.6)	4,373	(28.5)	1,481	(28.0)	
55-59	2,977	(16.5)	1,315	(3.9)	4,110	(26.8)	680	(12.9)	
60-64	1,720	(9.5)	887	(2.7)	2,968	(19.4)	426	(8.1)	
65-69	937	(5.2)	536	(1.6)	1,517	(9.9)	201	(3.8)	
≥70	845	(4.7)	590	(1.8)	1,341	(8.7)	201	(3.8)	
Insurance based income									
1st (lowest)	4,478	(24.8)	7,912	(23.7)	3,827	(25.0)	1,258	(23.8)	<0.001
2nd	3,644	(20.2)	6,471	(19.4)	2,957	(19.3)	1,078	(20.4)	
3rd	4,114	(22.8)	7,278	(21.8)	3,593	(23.4)	1,132	(21.4)	
4rd (highest)	5,794	(32.1)	11,746	(35.2)	4,964	(32.4)	1,817	(34.4)	
Region of residence									
Metropolitan	9,045	(50.2)	16,441	(49.2)	7,724	(50.4)	2,644	(50.0)	<0.001
Urban	3,849	(21.4)	7,726	(23.1)	2,977	(19.4)	1,154	(21.8)	
Rural	5,135	(28.5)	9,237	(27.7)	4,640	(30.3)	1,486	(28.1)	
Histological type									
Invasive	15,939	(88.4)	27,430	(82.1)	15,269	(99.5)	5,174	(97.9)	<0.001
In situ	2,091	(11.6)	5,977	(17.9)	72	(0.5)	111	(2.1)	
Surgery									
No	2,523	(14.0)	3,110	(9.3)	1,060	(6.9)	534	(10.1)	<0.001
Yes	15,507	(86.0)	30,297	(90.7)	14,281	(93.1)	4,751	(89.9)	
Chemotherapy									
No	5,465	(30.3)	16,633	(49.8)	5,422	(35.3)	1,416	(26.8)	<0.001
Yes	12,565	(69.7)	16,774	(50.2)	9,919	(64.7)	3,869	(73.2)	
Radiotherapy									

No	6,876	(38.1)	9,279	(27.8)	3,876	(25.3)	1,539	(29.1)	<0.001
Yes	11,154	(61.9)	24,128	(72.2)	11,465	(74.7)	3,746	(70.9)	
Trastuzumab									
No	14,543	(80.7)	30,957	(92.7)	13,687	(89.2)	4,827	(91.3)	<0.001
Yes	3,487	(19.3)	2,450	(7.3)	1,654	(10.8)	458	(8.7)	
Hypertension									
No	15,385	(85.3)	30,679	(91.8)	11,576	(75.5)	4,533	(85.8)	<0.001
Yes	2,645	(14.7)	2,728	(8.2)	3,765	(24.5)	752	(14.2)	
Dyslipidemia									
No	15,914	(88.3)	31,059	(93.0)	12,615	(82.2)	4,762	(90.1)	<0.001
Yes	2,116	(11.7)	2,348	(7.0)	2,726	(17.8)	523	(9.9)	
Osteoporosis									
No	16,304	(90.4)	31,364	(93.9)	13,335	(86.9)	4,739	(89.7)	<0.001
Yes	1,726	(9.6)	2,043	(6.1)	2,006	(13.1)	546	(10.3)	
Body mass index (kg/m^2)									
<23	8,681	(48.2)	19,041	(57.0)	5,715	(37.3)	2,534	(48.0)	<0.001
≥23	9,349	(51.9)	14,366	(43.0)	9,626	(62.8)	2,751	(52.1)	
Smoking									
Never	17,005	(94.3)	31,312	(93.7)	14,557	(94.9)	5,027	(95.1)	<0.001
Ever	1,025	(5.7)	2,095	(6.3)	784	(5.1)	258	(4.9)	
Alcohol consumption									
Never	13,859	(76.9)	23,786	(71.2)	12,645	(82.4)	4,083	(77.3)	<0.001
Ever	4,171	(23.1)	9,621	(28.8)	2,696	(17.6)	1,202	(22.7)	
Physical activity									
No	5,151	(28.6)	8,771	(26.3)	4,363	(28.4)	1,754	(33.2)	<0.001
Yes	12,879	(71.4)	24,636	(73.8)	10,978	(71.6)	3,531	(66.8)	
Menopausal status									
Pre-menopausal	9,324	(51.7)	27,801	(83.2)	3,107	(20.3)	3,240	(61.3)	<0.001
Post-menopausal	8,706	(48.3)	5,606	(16.8)	12,234	(79.8)	2,045	(38.7)	

AIs, aromatase inhibitors; SERMs, selective estrogen receptors modulators. *P-value by chi-square test for categorical variables and ANOVA for continuous variable.

Table S2. The subgroup analyses by age at diagnosis (<55 vs. ≥55 years)

	Age <55 years						Age ≥55 years							
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		P-value	I^2
Composite of CVD														
Non-users	25,233	600	(2.38)	136.0	1.00	(Reference)	11,466	739	(6.45)	53.9	1.00	(Reference)		
SERMs	55,457	1,113	(2.01)	290.1	1.16	(1.05-1.28)	5,738	413	(7.20)	27.9	1.15	(1.02-1.29)	0.90	0.0%
AIs	9,018	288	(3.19)	49.3	1.21	(1.05-1.39)	15,615	871	(5.58)	70.9	1.07	(0.97-1.18)	0.17	47.0%
Both	7,750	203	(2.62)	56.4	1.36	(1.15-1.60)	2,894	174	(6.01)	17.0	1.13	(0.96-1.34)	0.12	58.0%
Stroke														
Non-users	25,233	100	(0.40)	136.0	1.00	(Reference)	13,671	235	(1.72)	53.9	1.00	(Reference)		
SERMs	55,457	215	(0.39)	290.1	1.46	(1.15-1.85)	7,009	141	(2.01)	27.9	1.11	(0.90-1.36)	0.09	65.0%
AIs	9,018	69	(0.77)	49.3	1.43	(1.05-1.96)	19,093	268	(1.40)	70.9	1.04	(0.87-1.24)	0.08	68.0%
Both	7,750	38	(0.49)	56.4	1.42	(0.96-2.08)	3,618	50	(1.38)	17.0	0.99	(0.73-1.35)	0.15	51.0%
CHD														
Non-users	25,233	191	(0.76)	136.0	1.00	(Reference)	13,671	223	(1.63)	53.9	1.00	(Reference)		
SERMs	55,457	336	(0.61)	290.1	1.11	(0.93-1.34)	7,009	129	(1.84)	27.9	1.13	(0.91-1.40)	0.91	0.0%
AIs	9,018	106	(1.18)	49.3	1.22	(0.96-1.54)	19,093	283	(1.48)	70.9	1.13	(0.94-1.35)	0.62	0.0%
Both	7,750	61	(0.79)	56.4	1.14	(0.85-1.53)	3,618	49	(1.35)	17.0	1.06	(0.78-1.45)	0.75	0.0%
VTE														
Non-users	25,233	45	(0.18)	136.0	1.00	(Reference)	13,671	51	(0.37)	53.9	1.00	(Reference)		
SERMs	55,457	127	(0.23)	290.1	1.65	(1.17-2.32)	7,009	27	(0.39)	27.9	1.31	(0.84-2.05)	0.43	0.0%
AIs	9,018	15	(0.17)	49.3	1.07	(0.61-1.89)	19,093	59	(0.31)	70.9	1.11	(0.76-1.63)	0.91	0.0%
Both	7,750	18	(0.23)	56.4	1.90	(1.08-3.36)	3,618	17	(0.47)	17.0	1.66	(0.95-2.90)	0.73	0.0%
HF														
Non-users	25,233	129	(0.51)	136.0	1.00	(Reference)	13,671	102	(0.75)	53.9	1.00	(Reference)		
SERMs	55,457	156	(0.28)	290.1	0.84	(0.66-1.05)	7,009	50	(0.71)	27.9	1.18	(0.85-1.65)	0.09	65.0%
AIs	9,018	43	(0.48)	49.3	1.13	(0.81-1.58)	19,093	113	(0.59)	70.9	1.09	(0.83-1.44)	0.88	0.0%
Both	7,750	39	(0.50)	56.4	1.69	(1.16-2.46)	3,618	21	(0.58)	17.0	1.15	(0.71-1.85)	0.22	35.0%
Arrhythmia														
Non-users	25,233	135	(0.54)	136.0	1.00	(Reference)	13,671	128	(0.94)	53.9	1.00	(Reference)		
SERMs	55,457	279	(0.50)	290.1	1.17	(0.95-1.44)	7,009	67	(0.96)	27.9	1.20	(0.90-1.60)	0.90	0.0%
AIs	9,018	55	(0.61)	49.3	1.08	(0.79-1.48)	19,093	150	(0.79)	70.9	1.03	(0.81-1.30)	0.80	0.0%
Both	7,750	47	(0.61)	56.4	1.33	(0.94-1.87)	3,618	37	(1.02)	17.0	1.28	(0.88-1.86)	0.90	0.0%

T2DM														
Non-users	25,233	808	(3.20)	136.0	1.00	(Reference)	12,648	773	(6.11)	53.9	1.00	(Reference)		
SERMs	55,457	1,630	(2.94)	290.1	1.24	(1.14-1.35)	6,368	506	(7.95)	27.9	1.41	(1.26-1.58)	0.06	71.0%
AIs	9,018	440	(4.88)	49.3	1.13	(1.01-1.27)	17,184	1,050	(6.11)	70.9	1.19	(1.08-1.30)	0.56	0.0%
Both	7,750	273	(3.52)	56.4	1.19	(1.03-1.37)	3,282	204	(6.22)	17.0	1.21	(1.04-1.42)	0.83	0.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S3. The subgroup analyses by age at diagnosis (<60 vs. ≥60 years)

	Age <60years						Age ≥60 years							
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		P-value	I^2
Composite of CVD														
Non-users	30,348	808	(2.66)	160.7	1.00	(Reference)	6,351	531	(8.36)	29.3	1.00	(Reference)		
SERMs	57,618	1,214	(2.11)	300.7	1.19	(1.08-1.30)	3,577	312	(8.72)	17.4	1.08	(0.94-1.24)	0.25	24.0%
AIs	15,386	510	(3.31)	78.5	1.17	(1.05-1.31)	9,247	649	(7.02)	41.7	1.04	(0.92-1.17)	0.15	53.0%
Both	9,009	260	(2.89)	64.0	1.37	(1.19-1.59)	1,635	117	(7.16)	9.5	1.03	(0.84-1.26)	0.02	81.0%
Stroke														
Non-users	30,348	150	(0.49)	160.7	1.00	(Reference)	6,351	185	(2.91)	29.3	1.00	(Reference)		
SERMs	57,618	245	(0.43)	300.7	1.41	(1.14-1.74)	3,577	111	(3.10)	17.4	1.05	(0.83-1.32)	0.06	71.0%
AIs	15,386	113	(0.73)	78.5	1.21	(0.95-1.55)	9,247	224	(2.42)	41.7	1.05	(0.86-1.28)	0.37	0.0%
Both	9,009	48	(0.53)	64.0	1.29	(0.92-1.79)	1,635	40	(2.45)	9.5	0.99	(0.70-1.40)	0.28	14.0%
CHD														
Non-users	30,348	256	(0.84)	160.7	1.00	(Reference)	6,351	158	(2.49)	29.3	1.00	(Reference)		
SERMs	57,618	369	(0.64)	300.7	1.17	(0.99-1.38)	3,577	96	(2.68)	17.4	1.07	(0.83-1.37)	0.54	0.0%
AIs	15,386	187	(1.22)	78.5	1.24	(1.02-1.50)	9,247	202	(2.18)	41.7	1.02	(0.82-1.26)	0.19	42.0%
Both	9,009	78	(0.87)	64.0	1.24	(0.96-1.61)	1,635	32	(1.96)	9.5	0.93	(0.63-1.36)	0.22	34.0%
VTE														
Non-users	30,348	67	(0.22)	160.7	1.00	(Reference)	6,351	29	(0.46)	29.3	1.00	(Reference)		
SERMs	57,618	137	(0.24)	300.7	1.49	(1.11-2.02)	3,577	17	(0.48)	17.4	1.40	(0.79-2.48)	0.85	0.0%
AIs	15,386	30	(0.19)	78.5	0.98	(0.64-1.49)	9,247	44	(0.48)	41.7	1.38	(0.86-2.22)	0.28	14.0%
Both	9,009	25	(0.28)	64.0	1.75	(1.09-2.81)	1,635	10	(0.61)	9.5	1.76	(0.85-3.65)	0.99	0.0%
HF														
Non-users	30,348	159	(0.52)	160.7	1.00	(Reference)	6,351	72	(1.13)	29.3	1.00	(Reference)		
SERMs	57,618	168	(0.29)	300.7	0.90	(0.72-1.11)	3,577	38	(1.06)	17.4	1.07	(0.72-1.58)	0.44	0.0%
AIs	15,386	73	(0.47)	78.5	1.11	(0.85-1.47)	9,247	83	(0.90)	41.7	1.05	(0.76-1.46)	0.80	0.0%
Both	9,009	47	(0.52)	64.0	1.67	(1.19-2.35)	1,635	13	(0.80)	9.5	0.97	(0.54-1.77)	0.12	58.0%
Arrhythmia														
Non-users	30,348	176	(0.58)	160.7	1.00	(Reference)	6,351	87	(1.37)	29.3	1.00	(Reference)		
SERMs	57,618	296	(0.51)	300.7	1.19	(0.99-1.44)	3,577	50	(1.40)	17.4	1.08	(0.77-1.53)	0.63	0.0%
AIs	15,386	109	(0.71)	78.5	1.15	(0.90-1.47)	9,247	96	(1.04)	41.7	0.93	(0.69-1.25)	0.27	19.0%
Both	9,009	62	(0.69)	64.0	1.38	(1.02-1.85)	1,635	22	(1.35)	9.5	1.09	(0.68-1.75)	0.41	0.0%

T2DM														
Non-users	30,348	1,063	(3.50)	160.7	1.00	(Reference)	6,351	518	(8.16)	29.3	1.00	(Reference)		
SERMs	57,618	1,782	(3.09)	300.7	1.30	(1.20-1.41)	3,577	354	(9.90)	17.4	1.32	(1.15-1.50)	0.89	0.0%
AIs	15,386	772	(5.02)	78.5	1.17	(1.07-1.29)	9,247	718	(7.76)	41.7	1.11	(0.99-1.25)	0.47	0.0%
Both	9,009	339	(3.76)	64.0	1.23	(1.08-1.39)	1,635	138	(8.44)	9.5	1.19	(0.98-1.43)	0.77	0.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S4. The subgroup analyses by age at diagnosis (<55 year; 40-54 and 45-54 years)

	Age 40-54 years					Age 45-54 years				
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*
Composite of CVD										
Non-users	19,175	515	(2.69)	101.8	1.00 (Reference)	14,022	414	(2.95)	74.5	1.00 (Reference)
SERMs	43,755	938	(2.14)	223.1	1.18 (1.05-1.31)	26,938	665	(2.47)	133.2	1.24 (1.09-1.40)
AIs	8,928	288	(3.23)	48.8	1.19 (1.03-1.37)	8,671	279	(3.22)	47.1	1.20 (1.04-1.40)
Both	7,143	192	(2.69)	52.2	1.33 (1.12-1.57)	5,877	163	(2.77)	42.6	1.31 (1.09-1.58)
Stroke										
Non-users	19,175	90	(0.47)	101.8	1.00 (Reference)	14,022	75	(0.53)	74.5	1.00 (Reference)
SERMs	43,755	186	(0.43)	223.1	1.48 (1.14-1.91)	26,938	140	(0.52)	133.2	1.60 (1.20-2.13)
AIs	8,928	69	(0.77)	48.8	1.39 (1.01-1.91)	8,671	66	(0.76)	47.1	1.40 (1.00-1.96)
Both	7,143	36	(0.50)	52.2	1.37 (0.92-2.04)	5,877	33	(0.56)	42.6	1.44 (0.94-2.19)
CHD										
Non-users	19,175	178	(0.93)	101.8	1.00 (Reference)	14,022	156	(1.11)	74.5	1.00 (Reference)
SERMs	43,755	303	(0.69)	223.1	1.08 (0.89-1.31)	26,938	220	(0.82)	133.2	1.02 (0.82-1.26)
AIs	8,928	106	(1.19)	48.8	1.21 (0.95-1.54)	8,671	104	(1.20)	47.1	1.19 (0.93-1.52)
Both	7,143	60	(0.84)	52.2	1.13 (0.84-1.53)	5,877	55	(0.94)	42.6	1.12 (0.82-1.54)
VTE										
Non-users	19,175	35	(0.18)	101.8	1.00 (Reference)	14,022	25	(0.18)	74.5	1.00 (Reference)
SERMs	43,755	101	(0.23)	223.1	1.76 (1.18-2.62)	26,938	71	(0.26)	133.2	2.05 (1.28-3.29)
AIs	8,928	15	(0.17)	48.8	1.05 (0.58-1.89)	8,671	15	(0.17)	47.1	1.27 (0.68-2.38)
Both	7,143	15	(0.21)	52.2	1.69 (0.91-3.16)	5,877	13	(0.22)	42.6	2.05 (1.02-4.11)
HF										
Non-users	19,175	102	(0.53)	101.8	1.00 (Reference)	14,022	80	(0.57)	74.5	1.00 (Reference)
SERMs	43,755	119	(0.27)	223.1	0.83 (0.64-1.08)	26,938	78	(0.29)	133.2	0.89 (0.65-1.22)
AIs	8,928	43	(0.48)	48.8	1.10 (0.78-1.56)	8,671	40	(0.46)	47.1	1.01 (0.70-1.45)
Both	7,143	36	(0.50)	52.2	1.63 (1.10-2.43)	5,877	24	(0.41)	42.6	1.31 (0.81-2.11)
Arrhythmia										
Non-users	19,175	110	(0.57)	101.8	1.00 (Reference)	14,022	78	(0.56)	74.5	1.00 (Reference)
SERMs	43,755	229	(0.52)	223.1	1.20 (0.95-1.52)	26,938	156	(0.58)	133.2	1.40 (1.06-1.84)
AIs	8,928	55	(0.62)	48.8	1.08 (0.78-1.50)	8,671	54	(0.62)	47.1	1.21 (0.85-1.72)

Both	7,143	45	(0.63)	52.2	1.34	(0.94-1.91)	5,877	38	(0.65)	42.6	1.42	(0.96-2.12)
T2DM												
Non-users	19,175	726	(3.79)	101.8	1.00	(Reference)	14,022	589	(4.20)	74.5	1.00	(Reference)
SERMs	43,755	1,429	(3.27)	223.1	1.22	(1.12-1.34)	26,938	1,022	(3.79)	133.2	1.28	(1.16-1.42)
AIs	8,928	439	(4.92)	48.8	1.14	(1.01-1.28)	8,671	425	(4.90)	47.1	1.14	(1.00-1.29)
Both	7,143	264	(3.70)	52.2	1.18	(1.02-1.36)	5,877	232	(3.95)	42.6	1.19	(1.02-1.39)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs).

Table S5. The subgroup analyses by age at diagnosis (<60 years;40-59 and 45-59 years)

	Age 40-59 years						Age 45-59 years					
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*	
Composite of CVD												
Non-users	24,290	723	(2.98)	126.5	1.00	(Reference)	19,137	622	(3.25)	74.5	1.00	(Reference)
SERMs	45,916	1,039	(2.26)	233.6	1.21	(1.09-1.33)	29,099	766	(2.63)	133.2	1.26	(1.13-1.41)
AIs	15,296	510	(3.33)	78.0	1.16	(1.04-1.30)	15,039	501	(3.33)	47.1	1.17	(1.04-1.32)
Both	8,402	249	(2.96)	59.8	1.35	(1.17-1.57)	7,136	220	(3.08)	42.6	1.34	(1.15-1.57)
Stroke												
Non-users	24,290	140	(0.58)	126.5	1.00	(Reference)	19,137	125	(0.65)	74.5	1.00	(Reference)
SERMs	45,916	216	(0.47)	233.6	1.41	(1.13-1.76)	29,099	170	(0.58)	133.2	1.48	(1.16-1.88)
AIs	15,296	113	(0.74)	78.0	1.19	(0.93-1.53)	15,039	110	(0.73)	47.1	1.20	(0.93-1.55)
Both	8,402	46	(0.55)	59.8	1.25	(0.89-1.76)	7,136	43	(0.60)	42.6	1.27	(0.89-1.81)
CHD												
Non-users	24,290	243	(1.00)	126.5	1.00	(Reference)	19,137	221	(1.15)	74.5	1.00	(Reference)
SERMs	45,916	336	(0.73)	233.6	1.13	(0.95-1.34)	29,099	253	(0.87)	133.2	1.08	(0.90-1.31)
AIs	15,296	187	(1.22)	78.0	1.24	(1.02-1.51)	15,039	185	(1.23)	47.1	1.23	(1.01-1.50)
Both	8,402	77	(0.92)	59.8	1.22	(0.94-1.59)	7,136	72	(1.01)	42.6	1.21	(0.92-1.59)
VTE												
Non-users	24,290	57	(0.23)	126.5	1.00	(Reference)	19,137	47	(0.25)	74.5	1.00	(Reference)
SERMs	45,916	111	(0.24)	233.6	1.60	(1.14-2.24)	29,099	81	(0.28)	133.2	1.75	(1.20-2.55)
AIs	15,296	30	(0.20)	78.0	0.94	(0.61-1.45)	15,039	30	(0.20)	47.1	1.02	(0.65-1.60)
Both	8,402	22	(0.26)	59.8	1.63	(0.98-2.71)	7,136	20	(0.28)	42.6	1.82	(1.06-3.13)
HF												
Non-users	24,290	132	(0.54)	126.5	1.00	(Reference)	19,137	110	(0.57)	74.5	1.00	(Reference)
SERMs	45,916	131	(0.29)	233.6	0.91	(0.71-1.17)	29,099	90	(0.31)	133.2	1.00	(0.75-1.33)
AIs	15,296	73	(0.48)	78.0	1.10	(0.83-1.46)	15,039	70	(0.47)	47.1	1.05	(0.78-1.42)
Both	8,402	44	(0.52)	59.8	1.64	(1.15-2.33)	7,136	32	(0.45)	42.6	1.39	(0.92-2.10)
Arrhythmia												
Non-users	24,290	151	(0.62)	126.5	1.00	(Reference)	19,137	119	(0.62)	74.5	1.00	(Reference)
SERMs	45,916	246	(0.54)	233.6	1.24	(1.01-1.53)	29,099	173	(0.59)	133.2	1.43	(1.12-1.81)
AIs	15,296	109	(0.71)	78.0	1.15	(0.90-1.48)	15,039	108	(0.72)	47.1	1.23	(0.94-1.60)
Both	8,402	60	(0.71)	59.8	1.41	(1.04-1.91)	7,136	53	(0.74)	42.6	1.49	(1.07-2.08)
T2DM												

Non-users	24,290	981	(4.04)	126.5	1.00	(Reference)	19,137	844	(4.41)	74.5	1.00	(Reference)
SERMs	45,916	1,581	(3.44)	233.6	1.28	(1.18-1.39)	29,099	1,174	(4.03)	133.2	1.34	(1.22-1.47)
AIs	15,296	771	(5.04)	78.0	1.18	(1.08-1.30)	15,039	757	(5.03)	47.1	1.19	(1.08-1.32)
Both	8,402	330	(3.93)	59.8	1.21	(1.06-1.37)	7,136	298	(4.18)	42.6	1.21	(1.06-1.39)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs).

Table S6. The subgroup analysis by histological types

	Invasive						*In situ*						P-value	I^2
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*			
Composite of CVD														
Non-users	33,252	1,251	(3.76)	173.1	1.00	(Reference)	3,447	88	(2.55)	16.9	1.00	(Reference)		
SERMs	52,004	1,324	(2.55)	275.2	1.12	(1.04-1.22)	9,191	202	(2.20)	42.8	1.09	(0.84-1.41)	0.82	0.0%
AIs	24,530	1,156	(4.71)	119.7	1.14	(1.05-1.23)	103	3	(2.91)	0.5	2.93	(1.51-5.68)	<0.01	87.0%
Both	10,459	369	(3.53)	72.2	1.25	(1.11-1.40)	185	8	(4.32)	1.2	1.08	(0.52-2.26)	0.71	0.0%
Stroke														
Non-users	33,252	311	(0.94)	173.1	1.00	(Reference)	3,447	24	(0.70)	16.9	1.00	(Reference)		
SERMs	52,004	309	(0.59)	275.2	1.21	(1.04-1.42)	9,191	47	(0.51)	42.8	1.07	(0.64-1.78)	0.64	0.0%
AIs	24,530	336	(1.37)	119.7	1.17	(1.00-1.37)	103	1	(0.97)	0.5	1.82	(0.43-7.75)	0.55	0.0%
Both	10,459	86	(0.82)	72.2	1.14	(0.90-1.46)	185	2	(1.08)	1.2	0.79	(0.18-3.41)	0.62	0.0%
CHD														
Non-users	33,252	377	(1.13)	173.1	1.00	(Reference)	3,447	37	(1.07)	16.9	1.00	(Reference)		
SERMs	52,004	397	(0.76)	275.2	1.05	(0.91-1.21)	9,191	68	(0.74)	42.8	0.84	(0.55-1.27)	0.32	0.0%
AIs	24,530	388	(1.58)	119.7	1.24	(1.07-1.43)	103	1	(0.97)	0.5	2.02	(0.61-6.68)	0.43	0.0%
Both	10,459	108	(1.03)	72.2	1.18	(0.95-1.47)	185	2	(1.08)	1.2	0.63	(0.15-2.65)	0.40	0.0%
VTE														
Non-users	33,252	90	(0.27)	173.1	1.00	(Reference)	3,447	6	(0.17)	16.9	1.00	(Reference)		
SERMs	52,004	137	(0.26)	275.2	1.47	(1.12-1.93)	9,191	17	(0.18)	42.8	1.35	(0.51-3.56)	0.86	0.0%
AIs	24,530	74	(0.30)	119.7	1.16	(0.85-1.58)	103	0	0.00	0.5	4.47	(0.49-40.62)	0.23	29.0%
Both	10,459	34	(0.33)	72.2	1.70	(1.13-2.54)	185	1	(0.54)	1.2	2.78	(0.31-24.83)	0.66	0.0%
HF														
Non-users	33,252	225	(0.68)	173.1	1.00	(Reference)	3,447	6	(0.17)	16.9	1.00	(Reference)		
SERMs	52,004	191	(0.37)	275.2	0.95	(0.78-1.16)	9,191	15	(0.16)	42.8	1.37	(0.52-3.62)	0.48	0.0%
AIs	24,530	155	(0.63)	119.7	1.03	(0.84-1.27)	103	1	(0.97)	0.5	11.86	(2.89-48.67)	<0.01	91.0%
Both	10,459	58	(0.55)	72.2	1.38	(1.02-1.85)	185	2	(1.08)	1.2	4.19	(0.81-21.78)	0.19	41.0%
Arrhythmia														
Non-users	33,252	248	(0.75)	173.1	1.00	(Reference)	3,447	15	(0.44)	16.9	1.00	(Reference)		
SERMs	52,004	291	(0.56)	275.2	1.11	(0.93-1.31)	9,191	55	(0.60)	42.8	1.54	(0.86-2.77)	0.29	12.0%
AIs	24,530	205	(0.84)	119.7	1.06	(0.88-1.27)	103	0	0.00	0.5	2.40	(0.31-18.38)	0.43	0.0%
Both	10,459	83	(0.79)	72.2	1.26	(0.98-1.62)	185	1	(0.54)	1.2	1.12	(0.15-8.65)	0.91	0.0%

T2DM														
Non-users	33,252	1,469	(4.42)	173.1	1.00	(Reference)	3,447	112	(3.25)	16.9	1.00	(Reference)		
SERMs	52,004	1,857	(3.57)	275.2	1.22	(1.14-1.31)	9,191	279	(3.04)	42.8	1.14	(0.91-1.43)	0.57	0.0%
AIs	24,530	1,484	(6.05)	119.7	1.22	(1.14-1.32)	103	6	(5.83)	0.5	3.03	(1.62-5.66)	<0.01	87.0%
Both	10,459	468	(4.47)	72.2	1.25	(1.12-1.39)	185	9	(4.86)	1.2	1.03	(0.52-2.06)	0.60	0.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S7. The subgroup analysis by surgery

	No surgery						Surgery							
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		P-value	I^2
Composite of CVD														
Non-users	7,004	405	(5.78)	38.1	1.00	(Reference)	29,695	934	(3.15)	151.8	1.00	(Reference)		
SERMs	7,087	274	(3.87)	41.2	1.03	(0.88-1.20)	54,108	1,252	(2.31)	276.8	1.19	(1.09-1.29)	0.12	59.0%
AIs	2,587	161	(6.22)	13.9	1.10	(0.92-1.31)	22,046	998	(4.53)	106.3	1.16	(1.06-1.27)	0.58	0.0%
Both	1,613	88	(5.46)	11.2	1.26	(0.99-1.59)	9,031	289	(3.20)	62.2	1.25	(1.09-1.43)	0.97	0.0%
Stroke														
Non-users	7,004	129	(1.84)	38.1	1.00	(Reference)	29,695	206	(0.69)	151.8	1.00	(Reference)		
SERMs	7,087	74	(1.04)	41.2	0.92	(0.69-1.22)	54,108	282	(0.52)	276.8	1.40	(1.17-1.68)	0.02	83.0%
AIs	2,587	48	(1.86)	13.9	0.87	(0.62-1.20)	22,046	289	(1.31)	106.3	1.30	(1.08-1.55)	0.03	78.0%
Both	1,613	21	(1.30)	11.2	0.96	(0.60-1.53)	9,031	67	(0.74)	62.2	1.25	(0.95-1.66)	0.33	0.0%
CHD														
Non-users	7,004	127	(1.81)	38.1	1.00	(Reference)	29,695	287	(0.97)	151.8	1.00	(Reference)		
SERMs	7,087	97	(1.37)	41.2	1.12	(0.86-1.46)	54,108	368	(0.68)	276.8	1.03	(0.88-1.21)	0.61	0.0%
AIs	2,587	61	(2.36)	13.9	1.37	(1.01-1.86)	22,046	328	(1.49)	106.3	1.20	(1.03-1.42)	0.47	0.0%
Both	1,613	25	(1.55)	11.2	1.12	(0.73-1.74)	9,031	85	(0.94)	62.2	1.16	(0.91-1.49)	0.90	0.0%
VTE														
Non-users	7,004	33	(0.47)	38.1	1.00	(Reference)	29,695	63	(0.21)	151.8	1.00	(Reference)		
SERMs	7,087	20	(0.28)	41.2	0.96	(0.56-1.64)	54,108	134	(0.25)	276.8	1.70	(1.25-2.32)	0.07	70.0%
AIs	2,587	10	(0.39)	13.9	1.12	(0.59-2.12)	22,046	64	(0.29)	106.3	1.22	(0.86-1.74)	0.82	0.0%
Both	1,613	11	(0.68)	11.2	1.98	(0.98-4.03)	9,031	24	(0.27)	62.2	1.65	(1.02-2.67)	0.67	0.0%
HF														
Non-users	7,004	51	(0.73)	38.1	1.00	(Reference)	29,695	180	(0.61)	151.8	1.00	(Reference)		
SERMs	7,087	29	(0.41)	41.2	0.86	(0.55-1.34)	54,108	177	(0.33)	276.8	1.00	(0.81-1.23)	0.56	0.0%
AIs	2,587	22	(0.85)	13.9	1.22	(0.75-1.99)	22,046	134	(0.61)	106.3	1.03	(0.82-1.28)	0.52	0.0%
Both	1,613	12	(0.74)	11.2	1.38	(0.72-2.64)	9,031	48	(0.53)	62.2	1.41	(1.02-1.96)	0.95	0.0%
Arrhythmia														
Non-users	7,004	65	(0.93)	38.1	1.00	(Reference)	29,695	198	(0.67)	151.8	1.00	(Reference)		
SERMs	7,087	54	(0.76)	41.2	1.22	(0.85-1.74)	54,108	292	(0.54)	276.8	1.15	(0.96-1.39)	0.80	0.0%
AIs	2,587	20	(0.77)	13.9	1.02	(0.63-1.63)	22,046	185	(0.84)	106.3	1.10	(0.90-1.35)	0.76	0.0%
Both	1,613	19	(1.18)	11.2	1.70	(1.00-2.87)	9,031	65	(0.72)	62.2	1.21	(0.91-1.61)	0.27	19.0%

T2DM														
Non-users	7,004	423	(6.04)	38.1	1.00	(Reference)	29,695	1,158	(3.90)	151.8	1.00	(Reference)		
SERMs	7,087	377	(5.32)	41.2	1.21	(1.05-1.39)	54,108	1,759	(3.25)	276.8	1.25	(1.16-1.35)	0.64	0.0%
AIs	2,587	213	(8.23)	13.9	1.31	(1.11-1.55)	22,046	1,277	(5.79)	106.3	1.21	(1.12-1.31)	0.42	0.0%
Both	1,613	85	(5.27)	11.2	1.07	(0.85-1.36)	9,031	392	(4.34)	62.2	1.30	(1.16-1.46)	0.16	50.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S8. The subgroup analysis by chemotherapy

	No chemotherapy						Chemotherapy						P-value	I^2
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*			
Composite of CVD														
Non-users	11,404	539	(4.73)	61.2	1.00	(Reference)	25,295	800	(3.16)	128.8	1.00	(Reference)		
SERMs	27,663	701	(2.53)	137.9	1.07	(0.96-1.21)	33,532	825	(2.46)	180.1	1.17	(1.06-1.29)	0.29	11.0%
AIs	8,575	433	(5.05)	39.5	1.06	(0.92-1.21)	16,058	726	(4.52)	80.6	1.19	(1.08-1.32)	0.16	50.0%
Both	2,748	143	(5.20)	18.1	1.28	(1.06-1.55)	7,896	234	(2.96)	55.4	1.23	(1.06-1.43)	0.76	0.0%
Stroke														
Non-users	11,404	169	(1.48)	61.2	1.00	(Reference)	25,295	166	(0.66)	128.8	1.00	(Reference)		
SERMs	27,663	170	(0.61)	137.9	0.94	(0.76-1.17)	33,532	186	(0.55)	180.1	1.50	(1.21-1.85)	<0.01	89.0%
AIs	8,575	151	(1.76)	39.5	1.03	(0.81-1.29)	16,058	186	(1.16)	80.6	1.27	(1.03-1.56)	0.18	45.0%
Both	2,748	35	(1.27)	18.1	0.96	(0.67-1.40)	7,896	53	(0.67)	55.4	1.29	(0.94-1.77)	0.24	28.0%
CHD														
Non-users	11,404	183	(1.60)	61.2	1.00	(Reference)	25,295	231	(0.91)	128.8	1.00	(Reference)		
SERMs	27,663	237	(0.86)	137.9	0.99	(0.81-1.21)	33,532	228	(0.68)	180.1	1.11	(0.92-1.34)	0.41	0.0%
AIs	8,575	155	(1.81)	39.5	1.16	(0.92-1.47)	16,058	234	(1.46)	80.6	1.25	(1.04-1.50)	0.63	0.0%
Both	2,748	47	(1.71)	18.1	1.27	(0.92-1.77)	7,896	63	(0.80)	55.4	1.09	(0.82-1.45)	0.49	0.0%
VTE														
Non-users	11,404	38	(0.33)	61.2	1.00	(Reference)	25,295	58	(0.23)	128.8	1.00	(Reference)		
SERMs	27,663	66	(0.24)	137.9	1.08	(0.74-1.56)	33,532	88	(0.26)	180.1	1.59	(1.13-2.23)	0.13	57.0%
AIs	8,575	22	(0.26)	39.5	0.84	(0.55-1.29)	16,058	52	(0.32)	80.6	1.28	(0.88-1.86)	0.15	52.0%
Both	2,748	12	(0.44)	18.1	1.02	(0.55-1.89)	7,896	23	(0.29)	55.4	1.73	(1.06-2.84)	0.19	42.0%
HF														
Non-users	11,404	56	(0.49)	61.2	1.00	(Reference)	25,295	175	(0.69)	128.8	1.00	(Reference)		
SERMs	27,663	67	(0.24)	137.9	1.08	(0.74-1.56)	33,532	139	(0.41)	180.1	0.87	(0.70-1.09)	0.34	0.0%
AIs	8,575	37	(0.43)	39.5	0.84	(0.55-1.29)	16,058	119	(0.74)	80.6	1.18	(0.93-1.49)	0.18	44.0%
Both	2,748	13	(0.47)	18.1	1.02	(0.55-1.89)	7,896	47	(0.60)	55.4	1.60	(1.14-2.23)	0.21	36.0%
Arrhythmia														
Non-users	11,404	93	(0.82)	61.2	1.00	(Reference)	25,295	170	(0.67)	128.8	1.00	(Reference)		
SERMs	27,663	161	(0.58)	137.9	1.30	(1.00-1.70)	33,532	185	(0.55)	180.1	1.09	(0.88-1.34)	0.30	7.0%
AIs	8,575	69	(0.80)	39.5	1.15	(0.83-1.60)	16,058	136	(0.85)	80.6	1.07	(0.85-1.34)	0.70	0.0%
Both	2,748	36	(1.31)	18.1	1.95	(1.31-2.90)	7,896	48	(0.61)	55.4	1.03	(0.74-1.42)	0.01	83.0%

T2DM														
Non-users	11,404	563	(4.94)	61.2	1.00	(Reference)	25,295	1,018	(4.02)	128.8	1.00	(Reference)		
SERMs	27,663	919	(3.32)	137.9	1.14	(1.02-1.27)	33,532	1,217	(3.63)	180.1	1.27	(1.17-1.38)	0.12	59.0%
AIs	8,575	496	(5.78)	39.5	1.12	(0.99-1.28)	16,058	994	(6.19)	80.6	1.26	(1.15-1.37)	0.15	52.0%
Both	2,748	145	(5.28)	18.1	1.18	(0.98-1.42)	7,896	332	(4.20)	55.4	1.28	(1.13-1.45)	0.48	0.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S9. The subgroup analysis by radiotherapy

	No radiotherapy						Radiotherapy							
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		P-value	I^2
Composite of CVD														
Non-users	15,348	712	(4.64)	81.5	1.00	(Reference)	21,351	627	(2.94)	108.5	1.00	(Reference)		
SERMs	18,670	626	(3.35)	101.9	1.18	(1.06-1.31)	42,525	900	(2.12)	216.1	1.11	(1.00-1.23)	0.41	0.0%
AIs	7,292	436	(5.98)	36.9	1.11	(0.98-1.25)	17,341	723	(4.17)	83.3	1.17	(1.05-1.30)	0.52	0.0%
Both	3,579	161	(4.50)	24.9	1.25	(1.05-1.49)	7,065	216	(3.06)	48.6	1.24	(1.06-1.46)	0.97	0.0%
Stroke														
Non-users	15,348	202	(1.32)	81.5	1.00	(Reference)	21,351	133	(0.62)	108.5	1.00	(Reference)		
SERMs	18,670	182	(0.97)	101.9	1.25	(1.02-1.52)	42,525	174	(0.41)	216.1	1.18	(0.93-1.49)	0.71	0.0%
AIs	7,292	146	(2.00)	36.9	1.09	(0.88-1.35)	17,341	191	(1.10)	83.3	1.25	(1.00-1.57)	0.39	0.0%
Both	3,579	37	(1.03)	24.9	0.97	(0.68-1.38)	7,065	51	(0.72)	48.6	1.31	(0.94-1.83)	0.21	35.0%
CHD														
Non-users	15,348	217	(1.41)	81.5	1.00	(Reference)	21,351	197	(0.92)	108.5	1.00	(Reference)		
SERMs	18,670	180	(0.96)	101.9	1.10	(0.90-1.34)	42,525	285	(0.67)	216.1	1.01	(0.84-1.23)	0.57	0.0%
AIs	7,292	143	(1.96)	36.9	1.28	(1.03-1.59)	17,341	246	(1.42)	83.3	1.16	(0.96-1.41)	0.49	0.0%
Both	3,579	46	(1.29)	24.9	1.21	(0.87-1.67)	7,065	64	(0.91)	48.6	1.09	(0.82-1.45)	0.64	0.0%
VTE														
Non-users	15,348	51	(0.33)	81.5	1.00	(Reference)	21,351	45	(0.21)	108.5	1.00	(Reference)		
SERMs	18,670	54	(0.29)	101.9	1.32	(0.90-1.94)	42,525	100	(0.24)	216.1	1.69	(1.17-2.44)	0.37	0.0%
AIs	7,292	29	(0.40)	36.9	1.27	(0.80-2.01)	17,341	45	(0.26)	83.3	1.14	(0.75-1.73)	0.74	0.0%
Both	3,579	13	(0.36)	24.9	1.54	(0.82-2.86)	7,065	22	(0.31)	48.6	1.94	(1.15-3.27)	0.58	0.0%
HF														
Non-users	15,348	114	(0.74)	81.5	1.00	(Reference)	21,351	117	(0.55)	108.5	1.00	(Reference)		
SERMs	18,670	86	(0.46)	101.9	1.07	(0.81-1.42)	42,525	120	(0.28)	216.1	0.91	(0.70-1.18)	0.40	0.0%
AIs	7,292	51	(0.70)	36.9	0.89	(0.65-1.23)	17,341	105	(0.61)	83.3	1.19	(0.91-1.56)	0.18	45.0%
Both	3,579	26	(0.73)	24.9	1.42	(0.92-2.20)	7,065	34	(0.48)	48.6	1.40	(0.95-2.08)	0.96	0.0%
Arrhythmia														
Non-users	15,348	128	(0.83)	81.5	1.00	(Reference)	21,351	135	(0.63)	108.5	1.00	(Reference)		
SERMs	18,670	125	(0.67)	101.9	1.20	(0.94-1.53)	42,525	221	(0.52)	216.1	1.11	(0.89-1.38)	0.64	0.0%
AIs	7,292	69	(0.95)	36.9	1.07	(0.80-1.43)	17,341	136	(0.78)	83.3	1.12	(0.87-1.42)	0.82	0.0%
Both	3,579	39	(1.09)	24.9	1.55	(1.08-2.24)	7,065	45	(0.64)	48.6	1.12	(0.79-1.58)	0.20	38.0%

T2DM														
Non-users	15,348	781	(5.09)	81.5	1.00	(Reference)	21,351	800	(3.75)	108.5	1.00	(Reference)		
SERMs	18,670	766	(4.10)	101.9	1.18	(1.07-1.31)	42,525	1,370	(3.22)	216.1	1.28	(1.16-1.40)	0.28	15.0%
AIs	7,292	511	(7.01)	36.9	1.23	(1.09-1.37)	17,341	979	(5.65)	83.3	1.21	(1.10-1.33)	0.88	0.0%
Both	3,579	176	(4.92)	24.9	1.14	(0.97-1.35)	7,065	301	(4.26)	48.6	1.32	(1.15-1.51)	0.20	39.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S10. The subgroup analysis by trastuzumab

	No trastuzumab						Trastuzumab						P-value	I^2
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*			
Composite of CVD														
Non-users	30,794	1,146	(3.72)	165.8	1.00	(Reference)	5,905	193	(3.27)	24.2	1.00	(Reference)		
SERMs	56,672	1,410	(2.49)	298.8	1.13	(1.04-1.22)	4,523	116	(2.56)	19.2	0.98	(0.77-1.25)	0.30	7.0%
AIs	22,283	1,055	(4.73)	110.5	1.12	(1.03-1.22)	2,350	104	(4.43)	9.7	1.31	(1.03-1.66)	0.21	35.0%
Both	9,867	358	(3.63)	69.1	1.23	(1.09-1.39)	777	19	(2.45)	4.3	1.33	(0.82-2.15)	0.75	0.0%
Stroke														
Non-users	30,794	306	(0.99)	165.8	1.00	(Reference)	5,905	29	(0.49)	24.2	1.00	(Reference)		
SERMs	56,672	335	(0.59)	298.8	1.16	(0.99-1.35)	4,523	21	(0.46)	19.2	1.67	(0.93-3.02)	0.24	28.0%
AIs	22,283	313	(1.40)	110.5	1.11	(0.95-1.30)	2,350	24	(1.02)	9.7	1.77	(1.03-3.06)	0.11	62.0%
Both	9,867	84	(0.85)	69.1	1.10	(0.86-1.41)	777	4	(0.51)	4.3	1.38	(0.48-3.97)	0.69	0.0%
CHD														
Non-users	30,794	375	(1.22)	165.8	1.00	(Reference)	5,905	39	(0.66)	24.2	1.00	(Reference)		
SERMs	56,672	438	(0.77)	298.8	1.01	(0.88-1.16)	4,523	27	(0.60)	19.2	1.28	(0.76-2.17)	0.39	0.0%
AIs	22,283	368	(1.65)	110.5	1.21	(1.04-1.40)	2,350	21	(0.89)	9.7	1.32	(0.79-2.20)	0.75	0.0%
Both	9,867	104	(1.05)	69.1	1.11	(0.89-1.38)	777	6	(0.77)	4.3	1.91	(0.80-4.61)	0.24	29.0%
VTE														
Non-users	30,794	77	(0.25)	165.8	1.00	(Reference)	5,905	19	(0.32)	24.2	1.00	(Reference)		
SERMs	56,672	149	(0.26)	298.8	1.62	(1.22-2.14)	4,523	5	(0.11)	19.2	0.51	(0.19-1.36)	0.03	80.0%
AIs	22,283	65	(0.29)	110.5	1.20	(0.86-1.67)	2,350	9	(0.38)	9.7	1.16	(0.53-2.55)	0.94	0.0%
Both	9,867	33	(0.33)	69.1	1.80	(1.18-2.73)	777	2	(0.26)	4.3	1.49	(0.34-6.59)	0.81	0.0%
HF														
Non-users	30,794	154	(0.50)	165.8	1.00	(Reference)	5,905	77	(1.30)	24.2	1.00	(Reference)		
SERMs	56,672	158	(0.28)	298.8	0.99	(0.79-1.23)	4,523	48	(1.06)	19.2	0.82	(0.56-1.20)	0.41	0.0%
AIs	22,283	125	(0.56)	110.5	1.03	(0.81-1.30)	2,350	31	(1.32)	9.7	1.16	(0.76-1.75)	0.62	0.0%
Both	9,867	54	(0.55)	69.1	1.35	(0.99-1.86)	777	6	(0.77)	4.3	1.79	(0.77-4.20)	0.54	0.0%
Arrhythmia														
Non-users	30,794	234	(0.76)	165.8	1.00	(Reference)	5,905	29	(0.49)	24.2	1.00	(Reference)		
SERMs	56,672	331	(0.58)	298.8	1.16	(0.98-1.38)	4,523	15	(0.33)	19.2	0.77	(0.40-1.48)	0.23	30.0%
AIs	22,283	186	(0.83)	110.5	1.07	(0.88-1.30)	2,350	19	(0.81)	9.7	1.38	(0.76-2.51)	0.42	0.0%
Both	9,867	83	(0.84)	69.1	1.33	(1.03-1.72)	777	1	(0.13)	4.3	0.31	(0.04-2.31)	0.16	50.0%

T2DM														
Non-users	30,794	1,390	(4.51)	165.8	1.00	(Reference)	5,905	191	(3.23)	24.2	1.00	(Reference)		
SERMs	56,672	2,038	(3.60)	298.8	1.23	(1.15-1.32)	4,523	98	(2.17)	19.2	1.04	(0.80-1.34)	0.20	39.0%
AIs	22,283	1,392	(6.25)	110.5	1.23	(1.14-1.33)	2,350	98	(4.17)	9.7	1.12	(0.88-1.43)	0.47	0.0%
Both	9,867	457	(4.63)	69.1	1.25	(1.13-1.40)	777	20	(2.57)	4.3	1.12	(0.70-1.78)	0.64	0.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. [1]Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S11. The subgroup analysis by regimen types

	No. of total	No. of events	(%)	1,000 PY	Age-adjusted HR (95% CI)		Adjusted HR (95% CI)*	
Composite of CVD								
Non-users	36,699	1,399	(3.81)	190.0	1.00	(Reference)	1.00	(Reference)
Tamoxifen	58,809	1,341	(2.28)	299.0	0.96	(0.89-1.04)	1.04	(0.96-1.13)
Toremifene	1,502	138	(9.19)	11.7	1.22	(1.02-1.46)	1.20	(1.00-1.43)
Anastrozole	9,173	475	(5.18)	47.2	0.99	(0.89-1.10)	1.04	(0.93-1.15)
Letrozole	14,495	642	(4.43)	68.1	0.98	(0.89-1.08)	1.04	(0.94-1.15)
Stroke								
Non-users	36,699	335	(0.91)	190.0	1.00	(Reference)	1.00	(Reference)
Tamoxifen	58,809	307	(0.52)	299.0	1.07	(0.91-1.25)	1.14	(0.97-1.34)
Toremifene	1,502	42	(2.80)	11.7	1.28	(0.93-1.77)	1.19	(0.86-1.65)
Anastrozole	9,173	142	(1.55)	47.2	1.04	(0.85-1.26)	1.11	(0.91-1.35)
Letrozole	14,495	186	(1.28)	68.1	1.02	(0.85-1.22)	1.10	(0.91-1.32)
CHD								
Non-users	36,699	414	(1.13)	190.0	1.00	(Reference)	1.00	(Reference)
Tamoxifen	58,809	400	(0.68)	299.0	0.92	(0.79-1.05)	0.93	(0.80-1.08)
Toremifene	1,502	46	(3.06)	11.7	1.32	(0.97-1.79)	1.24	(0.91-1.69)
Anastrozole	9,173	156	(1.70)	47.2	1.06	(0.88-1.27)	1.09	(0.90-1.32)
Letrozole	14,495	225	(1.55)	68.1	1.13	(0.96-1.33)	1.18	(1.00-1.40)
VTE								
Non-users	36,699	96	(0.26)	190.0	1.00	(Reference)	1.00	(Reference)
Tamoxifen	58,809	140	(0.24)	299.0	1.24	(0.95-1.62)	1.36	(1.03-1.79)
Toremifene	1,502	11	(0.73)	11.7	1.51	(0.81-2.83)	1.51	(0.80-2.83)
Anastrozole	9,173	31	(0.34)	47.2	1.00	(0.66-1.50)	1.05	(0.69-1.59)
Letrozole	14,495	37	(0.26)	68.1	0.86	(0.59-1.26)	0.90	(0.61-1.33)
HF								
Non-users	36,699	231	(0.63)	190.0	1.00	(Reference)	1.00	(Reference)
Tamoxifen	58,809	191	(0.32)	299.0	0.71	(0.59-0.87)	0.94	(0.77-1.16)
Toremifene	1,502	12	(0.80)	11.7	0.71	(0.39-1.26)	0.83	(0.46-1.49)
Anastrozole	9,173	67	(0.73)	47.2	0.90	(0.68-1.18)	1.02	(0.77-1.35)
Letrozole	14,495	74	(0.51)	68.1	0.71	(0.55-0.93)	0.78	(0.60-1.03)
Arrhythmia								
Non-users	36,699	263	(0.72)	190.0	1.00	(Reference)	1.00	(Reference)
Tamoxifen	58,809	304	(0.52)	299.0	0.99	(0.83-1.17)	0.99	(0.83-1.17)
Toremifene	1,502	27	(1.80)	11.7	1.28	(0.86-1.90)	1.28	(0.86-1.90)
Anastrozole	9,173	80	(0.87)	47.2	0.93	(0.72-1.20)	0.93	(0.72-1.20)
Letrozole	14,495	121	(0.83)	68.1	1.04	(0.84-1.30)	1.04	(0.84-1.30)
T2DM								
Non-users	36,699	1,581	(4.31)	190.0	1.00	(Reference)	1.00	(Reference)
Tamoxifen	58,809	1,910	(3.25)	299.0	1.08	(1.01-1.16)	1.14	(1.07-1.23)
Toremifene	1,502	157	(10.45)	11.7	1.22	(1.04-1.44)	1.15	(0.97-1.35)
Anastrozole	9,173	591	(6.44)	47.2	1.10	(1.00-1.21)	1.10	(1.00-1.21)
Letrozole	14,495	834	(5.75)	68.1	1.14	(1.05-1.24)	1.14	(1.05-1.25)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs).

Table S12. The subgroup analysis by menopausal status in the health screening subjects

	Pre-menopausal						Post-menopausal						P-value	I^2
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*			
Composite of CVD														
Non-users	9,324	218	(2.34)	45.5	1.00	(Reference)	8,706	322	(3.70)	35.6	1.00	(Reference)		
SERMs	27,801	478	(1.72)	127.8	1.11	(0.94-1.31)	5,606	194	(3.46)	24.1	1.05	(0.88-1.26)	0.66	0.0%
AIs	3,107	126	(4.06)	17.5	1.31	(1.05-1.63)	12,234	435	(3.56)	48.8	1.02	(0.88-1.18)	0.06	72.0%
Both	3,240	78	(2.41)	22.7	1.26	(0.97-1.64)	2,045	68	(3.33)	11.0	1.00	(0.76-1.30)	0.22	33.0%
Stroke														
Non-users	9,324	41	(0.44)	45.5	1.00	(Reference)	8,706	88	(1.01)	35.6	1.00	(Reference)		
SERMs	27,801	94	(0.34)	127.8	1.28	(0.88-1.87)	5,606	45	(0.80)	24.1	0.82	(0.58-1.18)	0.09	64.0%
AIs	3,107	30	(0.97)	17.5	1.35	(0.84-2.16)	12,234	122	(1.00)	48.8	1.07	(0.81-1.42)	0.42	0.0%
Both	3,240	14	(0.43)	22.7	1.15	(0.62-2.15)	2,045	19	(0.93)	11.0	0.97	(0.59-1.61)	0.67	0.0%
CHD														
Non-users	9,324	68	(0.73)	45.5	1.00	(Reference)	8,706	108	(1.24)	35.6	1.00	(Reference)		
SERMs	27,801	141	(0.51)	127.8	1.03	(0.77-1.39)	5,606	74	(1.32)	24.1	1.02	(0.75-1.37)	0.93	0.0%
AIs	3,107	44	(1.42)	17.5	1.49	(1.03-2.16)	12,234	135	(1.10)	48.8	0.91	(0.70-1.18)	0.03	78.0%
Both	3,240	26	(0.80)	22.7	1.33	(0.83-2.11)	2,045	22	(1.08)	11.0	0.91	(0.57-1.46)	0.27	19.0%
VTE														
Non-users	9,324	12	(0.13)	45.5	1.00	(Reference)	8,706	24	(0.28)	35.6	1.00	(Reference)		
SERMs	27,801	58	(0.21)	127.8	2.59	(1.36-4.90)	5,606	12	(0.21)	24.1	1.04	(0.53-2.06)	0.06	72.0%
AIs	3,107	6	(0.19)	17.5	1.22	(0.47-3.18)	12,234	30	(0.25)	48.8	0.93	(0.54-1.61)	0.63	0.0%
Both	3,240	8	(0.25)	22.7	2.58	(1.03-6.48)	2,045	6	(0.29)	11.0	1.24	(0.50-3.09)	0.27	19.0%
HF														
Non-users	9,324	43	(0.46)	45.5	1.00	(Reference)	8,706	47	(0.54)	35.6	1.00	(Reference)		
SERMs	27,801	56	(0.20)	127.8	0.75	(0.51-1.12)	5,606	24	(0.43)	24.1	1.40	(0.86-2.29)	0.05	73.0%
AIs	3,107	21	(0.68)	17.5	1.51	(0.90-2.53)	12,234	64	(0.52)	48.8	1.11	(0.76-1.64)	0.35	0.0%
Both	3,240	13	(0.40)	22.7	1.43	(0.75-2.74)	2,045	7	(0.34)	11.0	0.97	(0.43-2.19)	0.47	0.0%
Arrhythmia														
Non-users	9,324	54	(0.58)	45.5	1.00	(Reference)	8,706	55	(0.63)	35.6	1.00	(Reference)		
SERMs	27,801	129	(0.46)	127.8	1.02	(0.74-1.41)	5,606	39	(0.70)	24.1	1.26	(0.84-1.90)	0.43	0.0%
AIs	3,107	25	(0.80)	17.5	1.01	(0.62-1.63)	12,234	85	(0.69)	48.8	1.14	(0.81-1.62)	0.67	0.0%
Both	3,240	17	(0.52)	22.7	0.96	(0.55-1.68)	2,045	14	(0.68)	11.0	1.08	(0.60-1.96)	0.78	0.0%

T2DM														
Non-users	9,324	284	(3.05)	45.5	1.00	(Reference)	8,706	375	(4.31)	35.6	1.00	(Reference)		
SERMs	27,801	720	(2.59)	127.8	1.24	(1.08-1.43)	5,606	267	(4.76)	24.1	1.27	(1.08-1.48)	0.87	0.0%
AIs	3,107	162	(5.21)	17.5	1.12	(0.92-1.36)	12,234	590	(4.82)	48.8	1.24	(1.09-1.42)	0.38	0.0%
Both	3,240	99	(3.06)	22.7	1.14	(0.90-1.43)	2,045	107	(5.23)	11.0	1.39	(1.11-1.73)	0.22	33.0%

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, T2DM (or CVDs), BMI, smoking, alcohol consumption, and physical activity. If the P-value was <0.1 or I^2>50% in the heterogeneity test, then we hypothesized a significant difference by the stratified factor.

Table S13. The sensitivity analysis after excluding short-term users; ≥6 or ≥12 month use)

	≥6 months use (N=130,696)					≥12 months use (N=125,555)				
	No. of total	No. of events	(%)	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	Adjusted HR (95% CI)*	
Composite of CVD										
Non-users	36,699	1,339	(3.65)	1.00	(Reference)	36,699	1,339	(3.65)	1.00	(Reference)
SERMs	59,417	1,475	(2.48)	1.12	(1.04-1.21)	55,949	1,405	(2.51)	1.10	(1.02-1.18)
AIs	24,044	1,140	(4.74)	1.13	(1.04-1.22)	22,692	1,109	(4.89)	1.11	(1.02-1.20)
Both	10,536	373	(3.54)	1.23	(1.09-1.38)	10,215	365	(3.57)	1.21	(1.08-1.36)
Stroke										
Non-users	36,699	335	(0.91)	1.00	(Reference)	36,699	335	(0.91)	1.00	(Reference)
SERMs	59,417	336	(0.57)	1.18	(1.01-1.37)	55,949	312	(0.56)	1.13	(0.97-1.32)
AIs	24,044	330	(1.37)	1.14	(0.98-1.33)	22,692	326	(1.44)	1.15	(0.99-1.34)
Both	10,536	87	(0.83)	1.12	(0.88-1.42)	10,215	85	(0.83)	1.10	(0.87-1.41)
CHD										
Non-users	36,699	414	(1.13)	1.00	(Reference)	36,699	414	(1.13)	1.00	(Reference)
SERMs	59,417	447	(0.75)	1.01	(0.88-1.16)	55,949	431	(0.77)	1.01	(0.88-1.16)
AIs	24,044	384	(1.60)	1.21	(1.05-1.40)	22,692	376	(1.66)	1.20	(1.04-1.38)
Both	10,536	108	(1.03)	1.13	(0.91-1.40)	10,215	106	(1.04)	1.12	(0.90-1.39)
VTE										
Non-users	36,699	96	(0.26)	1.00	(Reference)	36,699	96	(0.26)	1.00	(Reference)
SERMs	59,417	152	(0.26)	1.49	(1.15-1.94)	55,949	143	(0.26)	1.43	(1.10-1.87)
AIs	24,044	72	(0.30)	1.15	(0.85-1.57)	22,692	66	(0.29)	1.08	(0.79-1.47)
Both	10,536	35	(0.33)	1.72	(1.16-2.55)	10,215	34	(0.33)	1.66	(1.11-2.48)
HF										
Non-users	36,699	231	(0.63)	1.00	(Reference)	36,699	231	(0.63)	1.00	(Reference)
SERMs	59,417	202	(0.34)	0.99	(0.81-1.20)	55,949	189	(0.34)	0.95	(0.78-1.15)
AIs	24,044	154	(0.64)	1.04	(0.85-1.28)	22,692	146	(0.64)	1.01	(0.82-1.24)
Both	10,536	60	(0.57)	1.41	(1.05-1.89)	10,215	59	(0.58)	1.39	(1.04-1.87)
Arrhythmia										
Non-users	36,699	263	(0.72)	1.00	(Reference)	36,699	263	(0.72)	1.00	(Reference)
SERMs	59,417	339	(0.57)	1.14	(0.97-1.34)	55,949	331	(0.59)	1.14	(0.97-1.34)
AIs	24,044	202	(0.84)	1.08	(0.89-1.30)	22,692	197	(0.87)	1.06	(0.88-1.28)
Both	10,536	83	(0.79)	1.26	(0.98-1.62)	10,215	81	(0.79)	1.24	(0.96-1.60)

T2DM										
Non-users	36,699	1,581	(4.31)	1.00	(Reference)	36,699	1,581	(4.31)	1.00	(Reference)
SERMs	59,417	2,076	(3.49)	1.22	(1.14-1.30)	55,949	2,007	(3.59)	1.21	(1.14-1.30)
AIs	24,044	1,478	(6.15)	1.22	(1.14-1.31)	22,692	1,445	(6.37)	1.21	(1.13-1.30)
Both	10,536	476	(4.52)	1.24	(1.12-1.38)	10,215	469	(4.59)	1.24	(1.12-1.38)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs).

Table S14. The sensitivity analysis in patients with a followed-up duration ≥5 years

	No. of total	No. of events	(%)	1,000 PY	Age adjusted HR (95% CI)		Adjusted HR (95% CI)*	
Composite of CVD								
Non-users	16,678	399	(2.39)	135.5	1.00	(Reference)	1.00	(Reference)
SERMs	28,314	501	(1.77)	224.7	1.39	(1.23-1.58)	1.44	(1.26-1.63)
AIs	10,375	318	(3.07)	80.7	1.17	(1.02-1.35)	1.21	(1.04-1.40)
Both	7,566	210	(2.78)	63.2	1.33	(1.12-1.57)	1.36	(1.15-1.61)
Stroke								
Non-users	16,678	97	(0.58)	135.5	1.00	(Reference)	1.00	(Reference)
SERMs	28,314	110	(0.39)	224.7	1.42	(1.09-1.85)	1.48	(1.13-1.94)
AIs	10,375	105	(1.01)	80.7	1.36	(1.03-1.78)	1.42	(1.07-1.87)
Both	7,566	44	(0.58)	63.2	1.18	(0.83-1.69)	1.23	(0.86-1.76)
CHD								
Non-users	16,678	122	(0.73)	135.5	1.00	(Reference)	1.00	(Reference)
SERMs	28,314	173	(0.61)	224.7	1.45	(1.15-1.82)	1.45	(1.15-1.83)
AIs	10,375	106	(1.02)	80.7	1.34	(1.04-1.73)	1.42	(1.10-1.84)
Both	7,566	60	(0.79)	63.2	1.24	(0.91-1.70)	1.30	(0.95-1.78)
VTE								
Non-users	16,678	28	(0.17)	135.5	1.00	(Reference)	1.00	(Reference)
SERMs	28,314	40	(0.14)	224.7	1.41	(0.88-2.26)	1.50	(0.93-2.41)
AIs	10,375	21	(0.20)	80.7	1.29	(0.75-2.21)	1.39	(0.80-2.40)
Both	7,566	18	(0.24)	63.2	1.59	(0.88-2.88)	1.66	(0.91-3.02)
HF								
Non-users	16,678	45	(0.27)	135.5	1.00	(Reference)	1.00	(Reference)
SERMs	28,314	56	(0.20)	224.7	1.44	(1.00-2.09)	**1.55**	**(1.06-2.25)**
AIs	10,375	37	(0.36)	80.7	1.35	(0.89-2.05)	1.41	(0.92-2.16)
Both	7,566	36	(0.48)	63.2	1.98	(1.28-3.08)	2.09	(1.34-3.26)
Arrhythmia								
Non-users	16,678	107	(0.64)	135.5	1.00	(Reference)	1.00	(Reference)
SERMs	28,314	122	(0.43)	224.7	1.25	(0.97-1.61)	1.28	(0.99-1.65)
AIs	10,375	49	(0.47)	80.7	0.72	(0.52-0.99)	0.68	(0.49-0.95)
Both	7,566	52	(0.69)	63.2	1.21	(0.87-1.69)	1.17	(0.84-1.64)
T2DM								
Non-users	16,678	548	(3.29)	135.5	1.00	(Reference)	1.00	(Reference)
SERMs	28,314	626	(2.21)	224.7	1.18	(1.05-1.31)	1.22	(1.09-1.37)
AIs	10,375	480	(4.63)	80.7	1.30	(1.16-1.47)	1.30	(1.15-1.47)
Both	7,566	268	(3.54)	63.2	1.20	(1.03-1.39)	1.20	(1.03-1.39)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs).

Table S15. The sensitivity analysis; the users having at least two prescriptions

	No. of total	No. of events	(%)	1,000 PY	Age-adjusted HR (95% CI)		Adjusted HR (95% CI)*	
Composite of CVD								
Non-users	38,519	1,399	(3.63)	198.6	1.00	(Reference)	1.00	(Reference)
SERMs	61,457	1,612	(2.62)	320.5	1.07	(0.99-1.14)	1.14	(1.06-1.23)
AIs	24,714	1,118	(4.52)	121.9	0.99	(0.92-1.07)	1.04	(0.96-1.13)
Both	8,481	272	(3.21)	60.6	1.15	(1.01-1.32)	1.18	(1.04-1.35)
Stroke								
Non-users	38,519	352	(0.91)	198.6	1.00	(Reference)	1.00	(Reference)
SERMs	61,457	369	(0.60)	320.5	1.13	(0.98-1.31)	1.18	(1.02-1.37)
AIs	24,714	330	(1.34)	121.9	1.03	(0.89-1.20)	1.10	(0.95-1.29)
Both	8,481	65	(0.77)	60.6	1.11	(0.85-1.45)	1.12	(0.86-1.47)
CHD								
Non-users	38,519	434	(1.13)	198.6	1.00	(Reference)	1.00	(Reference)
SERMs	61,457	482	(0.78)	320.5	1.01	(0.89-1.15)	1.02	(0.89-1.16)
AIs	24,714	382	(1.55)	121.9	1.10	(0.96-1.27)	1.14	(0.99-1.31)
Both	8,481	80	(0.94)	60.6	1.08	(0.85-1.37)	1.08	(0.85-1.38)
VTE								
Non-users	38,519	99	(0.26)	198.6	1.00	(Reference)	1.00	(Reference)
SERMs	61,457	168	(0.27)	320.5	1.44	(1.12-1.85)	1.58	(1.22-2.04)
AIs	24,714	67	(0.27)	121.9	0.92	(0.68-1.25)	0.98	(0.71-1.33)
Both	8,481	25	(0.29)	60.6	1.57	(1.00-2.45)	1.62	(1.03-2.54)
HF								
Non-users	38,519	241	(0.63)	198.6	1.00	(Reference)	1.00	(Reference)
SERMs	61,457	220	(0.36)	320.5	0.79	(0.66-0.95)	1.02	(0.85-1.23)
AIs	24,714	145	(0.59)	121.9	0.85	(0.69-1.04)	0.94	(0.76-1.16)
Both	8,481	47	(0.55)	60.6	1.33	(0.97-1.83)	1.49	(1.08-2.05)
Arrhythmia								
Non-users	38,519	274	(0.71)	198.6	1.00	(Reference)	1.00	(Reference)
SERMs	61,457	373	(0.61)	320.5	1.02	(0.85-1.23)	1.16	(0.99-1.37)
AIs	24,714	196	(0.79)	121.9	0.94	(0.76-1.16)	0.96	(0.79-1.15)
Both	8,481	55	(0.65)	60.6	1.49	(1.08-2.05)	1.09	(0.81-1.46)
T2DM								
Non-users	38,519	1,659	(4.31)	198.6	1.00	(Reference)	1.00	(Reference)
SERMs	61,457	2,203	(3.58)	320.5	1.14	(0.98-1.34)	1.21	(1.13-1.29)
AIs	24,714	1,445	(5.85)	121.9	0.95	(0.79-1.14)	1.14	(1.06-1.22)
Both	8,481	377	(4.45)	60.6	1.10	(0.82-1.47)	1.31	(1.17-1.46)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs).

Table S16. The sensitivity analysis in the health screening subjects

	No. of total	No. of events	(%)	1,000 PY	Age-adjusted HR (95% CI)		Adjusted HR (95% CI)*		Adjusted HR (95% CI)†	
Composite of CVD										
Non-users	18,030	540	(3.00)	81.0	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
SERMs	33,407	672	(2.01)	151.9	0.99	(0.89-1.11)	1.06	(0.94-1.19)	1.06	(0.94-1.19)
AIs	15,341	561	(3.66)	66.3	1.08	(0.96-1.21)	1.12	(0.99-1.26)	1.12	(0.99-1.27)
Both	5,285	146	(2.76)	33.7	1.10	(0.91-1.33)	1.12	(0.93-1.36)	1.12	(0.93-1.36)
Stroke										
Non-users	18,030	129	(0.72)	81.0	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
SERMs	33,407	139	(0.42)	151.9	1.01	(0.79-1.28)	1.03	(0.81-1.32)	1.02	(0.80-1.31)
AIs	15,341	152	(0.99)	66.3	1.09	(0.87-1.38)	1.15	(0.90-1.46)	1.16	(0.91-1.48)
Both	5,285	33	(0.62)	33.7	1.04	(0.71-1.54)	1.04	(0.71-1.54)	1.04	(0.71-1.54)
CHD										
Non-users	18,030	176	(0.98)	81.0	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
SERMs	33,407	215	(0.64)	151.9	0.96	(0.79-1.18)	0.94	(0.77-1.16)	0.96	(0.78-1.18)
AIs	15,341	179	(1.17)	66.3	1.09	(0.89-1.34)	1.10	(0.89-1.36)	1.09	(0.88-1.35)
Both	5,285	48	(0.91)	33.7	1.11	(0.80-1.53)	1.10	(0.79-1.52)	1.11	(0.80-1.54)
VTE										
Non-users	18,030	36	(0.20)	81.0	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
SERMs	33,407	70	(0.21)	151.9	1.56	(1.04-2.34)	1.70	(1.11-2.59)	1.66	(1.09-2.54)
AIs	15,341	36	(0.23)	66.3	1.07	(0.68-1.69)	1.11	(0.70-1.77)	1.13	(0.71-1.81)
Both	5,285	14	(0.26)	33.7	1.67	(0.89-3.13)	1.74	(0.92-3.27)	1.73	(0.92-3.25)
HF										
Non-users	18,030	90	(0.50)	81.0	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
SERMs	33,407	80	(0.24)	151.9	0.65	(0.48-0.87)	0.94	(0.69-1.28)	0.91	(0.66-1.25)
AIs	15,341	85	(0.55)	66.3	1.04	(0.78-1.40)	1.20	(0.88-1.62)	1.22	(0.90-1.65)
Both	5,285	20	(0.38)	33.7	1.04	(0.63-1.70)	1.22	(0.74-2.01)	1.21	(0.73-1.99)
Arrhythmia										
Non-users	18,030	109	(0.60)	81.0	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
SERMs	33,407	168	(0.50)	151.9	1.10	(0.86-1.40)	1.12	(0.87-1.44)	1.12	(0.87-1.44)
AIs	15,341	110	(0.72)	66.3	1.11	(0.85-1.45)	1.09	(0.83-1.43)	1.09	(0.83-1.43)
Both	5,285	31	(0.59)	33.7	1.06	(0.70-1.58)	1.02	(0.68-1.53)	1.02	(0.68-1.53)
T2DM										
Non-users	18,030	659	(3.66)	81.0	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)

SERMs	33,407	987	(2.95)	151.9	1.16	(1.05-1.28)	1.21	(1.10-1.34)	1.22	(1.10-1.35)
AIs	15,341	752	(4.90)	66.3	1.22	(1.10-1.35)	1.21	(1.09-1.35)	1.21	(1.08-1.34)
Both	5,285	206	(3.90)	33.7	1.25	(1.07-1.47)	1.26	(1.07-1.47)	1.26	(1.07-1.48)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and (T2DM or CVDs). †Additionally adjusted for BMI, smoking, alcohol consumption, physical activity, and menopausal status.

Table S17. The sensitivity analysis in patients with previous history of CVDs

	Overall						with previous history of CVD					
	No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	Adjusted HR (95% CI)*	
Composite of CVD												
Non-users	36,699	1,339	(3.65)	190.0	1.00	(Reference)	1,583	333	(21.04)	6.4	1.00	(Reference)
SERMs	61,195	1,526	(2.49)	318.0	1.13	(1.05-1.21)	1,728	356	(20.60)	7.3	1.18	(1.02-1.38)
AIs	24,633	1,159	(4.71)	120.2	1.14	(1.05-1.23)	1,858	383	(20.61)	7.5	1.06	(0.91-1.23)
Both	10,644	377	(3.54)	73.4	1.24	(1.10-1.39)	431	76	(17.63)	2.3	1.10	(0.85-1.42)
Stroke												
Non-users	36,699	335	(0.91)	190.0	1.00	(Reference)	1,583	80	(5.05)	6.4	1.00	(Reference)
SERMs	61,195	356	(0.58)	318.0	1.20	(1.04-1.40)	1,728	88	(5.09)	7.3	1.41	(1.03-1.92)
AIs	24,633	337	(1.37)	120.2	1.16	(0.99-1.35)	1,858	99	(5.33)	7.5	1.19	(0.88-1.60)
Both	10,644	88	(0.83)	73.4	1.13	(0.89-1.44)	431	21	(4.87)	2.3	1.31	(0.80-2.14)
CHD												
Non-users	36,699	414	(1.13)	190.0	1.00	(Reference)	1,583	146	(9.22)	6.4	1.00	(Reference)
SERMs	61,195	465	(0.76)	318.0	1.03	(0.90-1.18)	1,728	126	(7.29)	7.3	0.98	(0.77-1.26)
AIs	24,633	389	(1.58)	120.2	1.22	(1.06-1.41)	1,858	165	(8.88)	7.5	1.03	(0.82-1.29)
Both	10,644	110	(1.03)	73.4	1.14	(0.92-1.42)	431	32	(7.42)	2.3	1.03	(0.70-1.52)
VTE												
Non-users	36,699	96	(0.26)	190.0	1.00	(Reference)	1,583	14	(0.88)	6.4	1.00	(Reference)
SERMs	61,195	154	(0.25)	318.0	1.47	(1.13-1.90)	1,728	8	(0.46)	7.3	0.67	(0.26-1.69)
AIs	24,633	74	(0.30)	120.2	1.17	(0.86-1.58)	1,858	10	(0.54)	7.5	0.82	(0.37-1.83)
Both	10,644	35	(0.33)	73.4	1.72	(1.15-2.55)	431	2	(0.46)	2.3	0.84	(0.19-3.77)
HF												
Non-users	36,699	231	(0.63)	190.0	1.00	(Reference)	1,583	26	(1.64)	6.4	1.00	(Reference)
SERMs	61,195	206	(0.34)	318.0	0.98	(0.81-1.18)	1,728	29	(1.68)	7.3	1.78	(1.03-3.07)
AIs	24,633	156	(0.63)	120.2	1.05	(0.85-1.29)	1,858	27	(1.45)	7.5	0.90	(0.51-1.57)
Both	10,644	60	(0.56)	73.4	1.41	(1.05-1.89)	431	4	(0.93)	2.3	0.82	(0.28-2.40)

Arrhythmia												
Non-users	36,699	263	(0.72)	190.0	1.00	(Reference)	1,583	68	(4.30)	6.4	1.00	(Reference)
SERMs	61,195	346	(0.57)	318.0	1.14	(0.97-1.34)	1,728	105	(6.08)	7.3	1.21	(0.88-1.67)
AIs	24,633	205	(0.83)	120.2	1.08	(0.90-1.30)	1,858	83	(4.47)	7.5	1.18	(0.85-1.64)
Both	10,644	84	(0.79)	73.4	1.28	(0.99-1.64)	431	17	(3.94)	2.3	1.18	(0.69-2.03)

AIs, aromatase inhibitors; CHD, coronary heart diseases; CI, confidence intervals; CVD, cardiovascular diseases; HF, heart failure; HR, hazard ratio; PY, person-years; SERMs, selective estrogen receptor modulators; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism. *Adjusted for age at diagnosis, income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs).

Table S18. Baseline characteristics of study population after PSM; SERMs vs. non-users

	Non-users (N=31,022, 50.0%)		SERMs (N=31,022, 50.0%)		SMD
Age at diagnosis (mean, SD)	48.0	(9.8)	47.3	(9.8)	-0.08
<40	6,038	(19.5)	5,800	(18.7)	
40-49	11,652	(37.6)	15,192	(49.0)	
50-59	9,948	(32.1)	6,789	(21.9)	
60-69	2,578	(8.3)	2,032	(6.6)	
≥70	806	(2.6)	1,209	(3.9)	
Insurance based income					
1st (lowest)	7,565	(24.4)	7,652	(24.7)	0.01
2nd	5,991	(19.3)	6,011	(19.4)	
3rd	7,358	(23.7)	7,486	(24.1)	
4rd (highest)	10,108	(32.6)	9,873	(31.8)	
Region of residence					
Metropolitan	15,387	(49.6)	15,094	(48.7)	-0.02
Urban	6,866	(22.1)	6,996	(22.6)	
Rural	8,684	(28.0)	8,842	(28.5)	
Histological type					
Invasive	27,661	(89.2)	27,367	(88.2)	-0.03
In situ	3,361	(10.8)	3,655	(11.8)	
Surgery					
No	5,185	(16.7)	5,180	(16.7)	0.00
Yes	25,837	(83.3)	25,842	(83.3)	
Chemotherapy					
No	10,286	(33.2)	9,626	(31.0)	0.05
Yes	20,736	(66.8)	21,396	(69.0)	
Radiotherapy					
No	12,035	(38.8)	12,491	(40.3)	-0.03
Yes	18,987	(61.2)	18,531	(59.7)	
Trastuzumab					
No	27,653	(89.1)	27,035	(87.1)	0.06
Yes	3,369	(10.9)	3,987	(12.9)	
Hypertension					
No	27,887	(89.9)	27,964	(90.1)	-0.01
Yes	3,135	(10.1)	3,058	(9.9)	
Dyslipidemia					
No	28,701	(92.5)	28,681	(92.5)	<0.01
Yes	2,321	(7.5)	2,341	(7.5)	
Osteoporosis					
No	28,964	(93.4)	28,956	(93.3)	<0.01
Yes	2,058	(6.6)	2,066	(6.7)	

PSM, propensity score matching; SERMs, selective estrogen receptor modulators; SMD, standardized mean difference. If SMD >0.1, the covariate has the poor balance.

Table S19. Baseline characteristics of study population after PSM; AIs vs. non-users

	Non-users (N=17,336, 50.0%)		AIs (N=17,336, 50.0%)		SMD
Age at diagnosis (mean, SD)	57.5	(8.8)	56.6	(7.5)	-0.06
<40	179	(1.0)	90	(0.5)	
40-49	2,605	(15.0)	2,036	(11.7)	
50-59	8,944	(51.6)	10,254	(59.1)	
60-69	3,932	(22.7)	3,797	(21.9)	
≥70	1,676	(9.7)	1,159	(6.7)	
Insurance based income					
1st (lowest)	4,565	(26.3)	4,425	(25.5)	-0.02
2nd	3,296	(19.0)	3,242	(18.7)	
3rd	3,972	(22.9)	3,988	(23.0)	
4rd (highest)	5,503	(31.7)	5,681	(32.8)	
Region of residence					
Metropolitan	8,894	(51.3)	8,898	(51.3)	<0.01
Urban	3,281	(18.9)	3,394	(19.6)	
Rural	5,128	(29.6)	5,012	(28.9)	
Histological type					
Invasive	17,236	(99.4)	17,233	(99.4)	<0.01
In situ	100	(0.6)	103	(0.6)	
Surgery					
No	2,493	(14.4)	2,205	(12.7)	0.05
Yes	14,843	(85.6)	15,131	(87.3)	
Chemotherapy					
No	4,430	(25.6)	4,529	(26.1)	-0.01
Yes	12,906	(74.4)	12,807	(73.9)	
Radiotherapy					
No	6,387	(36.8)	5,955	(34.4)	0.05
Yes	10,949	(63.2)	11,381	(65.6)	
Trastuzumab					
No	1,485	(8.6)	15,152	(87.4)	-0.06
Yes	2,531	(14.6)	2,184	(12.6)	
Hypertension					
No	13,768	(79.4)	13,584	(78.4)	0.03
Yes	3,568	(20.6)	3,752	(21.6)	
Dyslipidemia					
No	14,973	(86.4)	14,899	(85.9)	0.01
Yes	2,363	(13.6)	2,437	(14.1)	
Osteoporosis					
No	15,355	(88.6)	15,396	(88.8)	-0.01
Yes	1,981	(11.4)	1,940	(11.2)	

PSM, propensity score matching; AIs, aromatase inhibitors; SMD, standardized mean difference. If SMD >0.1, the covariate has the poor balance.

Table S20. Baseline characteristics of study population after PSM; AIs vs. SERMs

	SERMs (N=11,209, 50.0%)		AIs (N=11,209, 50.0%)		SMD
Age at diagnosis (mean, SD)	55.2	(8.9)	55.2	(8.4)	0.01
<40	105	(0.9)	90	(0.8)	
40-49	2,406	(21.5)	2,046	(18.3)	
50-59	6,052	(54.0)	6,519	(58.2)	
60-69	1,588	(14.2)	1,633	(14.6)	
≥70	1,058	(9.4)	921	(8.2)	
Insurance based income					
1st (lowest)	2,914	(26.0)	2,888	(25.8)	-0.01
2nd	2,223	(19.8)	2,103	(18.8)	
3rd	2,462	(22.0)	2,422	(21.6)	
4rd (highest)	3,610	(32.2)	3,796	(33.9)	
Region of residence					
Metropolitan	5,468	(48.8)	5,493	(49.0)	<0.01
Urban	2,356	(21.0)	2,388	(21.3)	
Rural	3,358	(30.0)	3,303	(29.5)	
Histological type					
Invasive	11,072	(98.8)	11,108	(99.1)	0.03
In situ	137	(1.2)	101	(0.9)	
Surgery					
No	1,551	(13.8)	1,451	(12.9)	0.03
Yes	9,658	(86.2)	9,758	(87.1)	
Chemotherapy					
No	3,808	(34.0)	4,120	(36.8)	-0.06
Yes	7,401	(66.0)	7,089	(63.2)	
Radiotherapy					
No	3,795	(33.9)	3,964	(35.4)	-0.03
Yes	7,414	(66.1)	7,245	(64.6)	
Trastuzumab					
No	10,148	(90.5)	10,248	(91.4)	-0.03
Yes	1,061	(9.5)	961	(8.6)	
Hypertension					
No	9,126	(81.4)	9,075	(81.0)	0.01
Yes	2,083	(18.6)	2,134	(19.0)	
Dyslipidemia					
No	9,807	(87.5)	9,946	(88.7)	-0.04
Yes	1,402	(12.5)	1,263	(11.3)	
Osteoporosis					
No	10,062	(89.8)	10,112	(90.2)	-0.01
Yes	1,147	(10.2)	1,097	(9.8)	

PSM, propensity score matching; SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors; SMD, standardized mean difference. If SMD >0.1, the covariate has the poor balance.

Table S21. The comparison of results between before and after PSM (SERMs vs. non-users)

	Before PSM (Main findings)						After PSM					
	No. of total	No. of events	(%)	1,000 PY	HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	HR (95% CI)†	
Composite of CVD												
Non-users	36,699	1,339	(3.65)	190.0	1.00	(Reference)	31,022	965	(3.11)	164.0	1.00	(Reference)
SERMs	61,195	1,526	(2.49)	318.0	1.13	(1.05-1.21)	31,022	1,009	(3.25)	164.7	1.02	(0.91-1.15)
Stroke												
Non-users	36,699	335	(0.91)	190.0	1.00	(Reference)	31,022	216	(0.70)	164.0	1.00	(Reference)
SERMs	61,195	356	(0.58)	318.0	1.20	(1.04-1.40)	31,022	265	(0.85)	164.7	1.15	(0.91-1.46)
CHD												
Non-users	36,699	414	(1.13)	190.0	1.00	(Reference)	31,022	315	(1.02)	164.0	1.00	(Reference)
SERMs	61,195	465	(0.76)	318.0	1.03	(0.90-1.18)	31,022	303	(0.98)	164.7	0.98	(0.78-1.23)
VTE												
Non-users	36,699	96	(0.26)	190.0	1.00	(Reference)	31,022	68	(0.22)	164.0	1.00	(Reference)
SERMs	61,195	154	(0.25)	318.0	1.47	(1.13-1.90)	31,022	86	(0.28)	164.7	1.60	(1.05-2.44)
HF												
Non-users	36,699	231	(0.63)	190.0	1.00	(Reference)	31,022	162	(0.52)	164.0	1.00	(Reference)
SERMs	61,195	206	(0.34)	318.0	0.98	(0.81-1.18)	31,022	153	(0.49)	164.7	0.87	(0.66-1.14)
Arrhythmia												
Non-users	36,699	263	(0.72)	190.0	1.00	(Reference)	31,022	204	(0.66)	164.0	1.00	(Reference)
SERMs	61,195	346	(0.57)	318.0	1.14	(0.97-1.34)	31,022	203	(0.65)	164.7	0.93	(0.71-1.22)
T2DM												
Non-users	36,699	1,581	(4.31)	190.0	1.00	(Reference)	31,022	1,216	(3.92)	164.0	1.00	(Reference)
SERMs	61,195	2,136	(3.49)	318.0	1.22	(1.14-1.30)	31,022	1,397	(4.50)	164.7	1.25	(1.13-1.39)

PSM, propensity score matching; PY, person-years; SERMs, selective estrogen receptor modulators; CVD, cardiovascular diseases; CHD, coronary heart diseases; VTE, venous thromboembolism; HF, heart failure; T2DM, type 2 diabetes mellitus; *Adjusted for age, insurance based income, region of residence, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (of CVDs). †Non-users and SERMs users were matched as the 1:1 ratio according to age, insurance based income, region of residence, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, and osteoporosis using the PSM, and T2DM (or CVDs) was added in the adjusted model

Table S22. The comparison of results between before and after PSM (AIs vs. non-users)

	Before PSM (Main findings)						After PSM					
	No. of total	No. of events	(%)	1,000 PY	HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	HR (95% CI)†	
Composite of CVD												
Non-users	36,699	1,339	(3.65)	190.0	1.00	(Reference)	17,336	870	(5.02)	87.2	1.00	(Reference)
AIs	24,633	1,159	(4.71)	120.2	1.14	(1.05-1.23)	17,336	762	(4.40)	87.0	0.92	(0.81-1.04)
Stroke												
Non-users	36,699	335	(0.91)	190.0	1.00	(Reference)	17,336	256	(1.48)	87.2	1.00	(Reference)
AIs	24,633	337	(1.37)	120.2	1.16	(0.99-1.35)	17,336	209	(1.21)	87.0	0.79	(0.61-1.01)
CHD												
Non-users	36,699	414	(1.13)	190.0	1.00	(Reference)	17,336	269	(1.55)	87.2	1.00	(Reference)
AIs	24,633	389	(1.58)	120.2	1.22	(1.06-1.41)	17,336	262	(1.51)	87.0	1.00	(0.80-1.24)
VTE												
Non-users	36,699	96	(0.26)	190.0	1.00	(Reference)	17,336	61	(0.35)	87.2	1.00	(Reference)
AIs	24,633	74	(0.30)	120.2	1.17	(0.86-1.58)	17,336	49	(0.28)	87.0	0.96	(0.58-1.59)
HF												
Non-users	36,699	231	(0.63)	190.0	1.00	(Reference)	17,336	126	(0.73)	87.2	1.00	(Reference)
AIs	24,633	156	(0.63)	120.2	1.05	(0.85-1.29)	17,336	110	(0.63)	87.0	0.90	(0.66-1.24)
Arrhythmia												
Non-users	36,699	263	(0.72)	190.0	1.00	(Reference)	17,336	158	(0.91)	87.2	1.00	(Reference)
AIs	24,633	205	(0.83)	120.2	1.08	(0.90-1.30)	17,336	133	(0.77)	87.0	1.05	(0.77-1.42)
T2DM												
Non-users	36,699	1,581	(4.31)	190.0	1.00	(Reference)	17,336	1,015	(5.85)	87.2	1.00	(Reference)
AIs	24,633	1,490	(6.05)	120.2	1.22	(1.14-1.31)	17,336	1,021	(5.89)	87.0	1.03	(0.92-1.16)

PSM, propensity score matching; PY, person-years; AIs, aromatase inhibitors; CVD, cardiovascular diseases; CHD, coronary heart diseases; VTE, venous thromboembolism; HF, heart failure; T2DM, type 2 diabetes mellitus; *Adjusted for age, insurance based income, region of residence, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). †Non-users and AIs users were matched as the 1:1 ratio according to age, insurance based income, region of residence, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, and osteoporosis using the PSM, and T2DM (or CVDs) was added in the adjusted model

Table S23. The comparison of results between before and after PSM (AIs vs. SERMs)

	Before PSM (Main findings)						After PSM					
	No. of total	No. of events	(%)	1,000 PY	HR (95% CI)*		No. of total	No. of events	(%)	1,000 PY	HR (95% CI)†	
Composite of CVD												
SERMs	61,195	1,526	(2.49)	318.0	1.00	(Reference)	11,209	564	(5.03)	55.7	1.00	(Reference)
AIs	24,633	1,159	(4.71)	120.2	1.01	(0.93-1.09)	11,209	462	(4.12)	58.1	0.94	(0.80-1.10)
Stroke												
SERMs	61,195	356	(0.58)	318.0	1.00	(Reference)	11,209	176	(1.57)	55.7	1.00	(Reference)
AIs	24,633	337	(1.37)	120.2	0.96	(0.83-1.12)	11,209	125	(1.12)	58.1	0.77	(0.56-1.06)
CHD												
SERMs	61,195	465	(0.76)	318.0	1.00	(Reference)	11,209	176	(1.57)	55.7	1.00	(Reference)
AIs	24,633	389	(1.58)	120.2	1.19	(1.03-1.37)	11,209	164	(1.46)	58.1	1.18	(0.88-1.59)
VTE												
SERMs	61,195	154	(0.25)	318.0	1.00	(Reference)	11,209	44	(0.39)	55.7	1.00	(Reference)
AIs	24,633	74	(0.30)	120.2	0.80	(0.60-1.06)	11,209	29	(0.26)	58.1	0.74	(0.42-1.28)
HF												
SERMs	61,195	206	(0.34)	318.0	1.00	(Reference)	11,209	70	(0.62)	55.7	1.00	(Reference)
AIs	24,633	156	(0.63)	120.2	1.07	(0.87-1.33)	11,209	61	(0.54)	58.1	0.95	(0.62-1.47)
Arrhythmia												
SERMs	61,195	346	(0.57)	318.0	1.00	(Reference)	11,209	99	(0.88)	55.7	1.00	(Reference)
AIs	24,633	205	(0.83)	120.2	0.95	(0.79-1.14)	11,209	84	(0.75)	58.1	0.96	(0.65-1.43)
T2DM												
SERMs	61,195	2,136	(3.49)	318.0	1.00	(Reference)	11,209	765	(6.82)	55.7	1.00	(Reference)
AIs	24,633	1,490	(6.05)	120.2	1.00	(0.94-1.08)	11,209	618	(5.51)	58.1	0.80	(0.70-0.93)

PSM, propensity score matching; PY, person-years; AIs, aromatase inhibitors; SERMs, selective estrogen receptor modulators; CVD, cardiovascular diseases; CHD, coronary heart diseases; VTE, venous thromboembolism; HF, heart failure; T2DM, type 2 diabetes mellitus; *Adjusted for age, insurance based income, region of residence, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and T2DM (or CVDs). †SERMs and AIs users were matched as the 1:1 ratio according to age, insurance based income, region of residence, histological type, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, and osteoporosis using the PSM, and T2DM (or CVDs) was added in the adjusted model

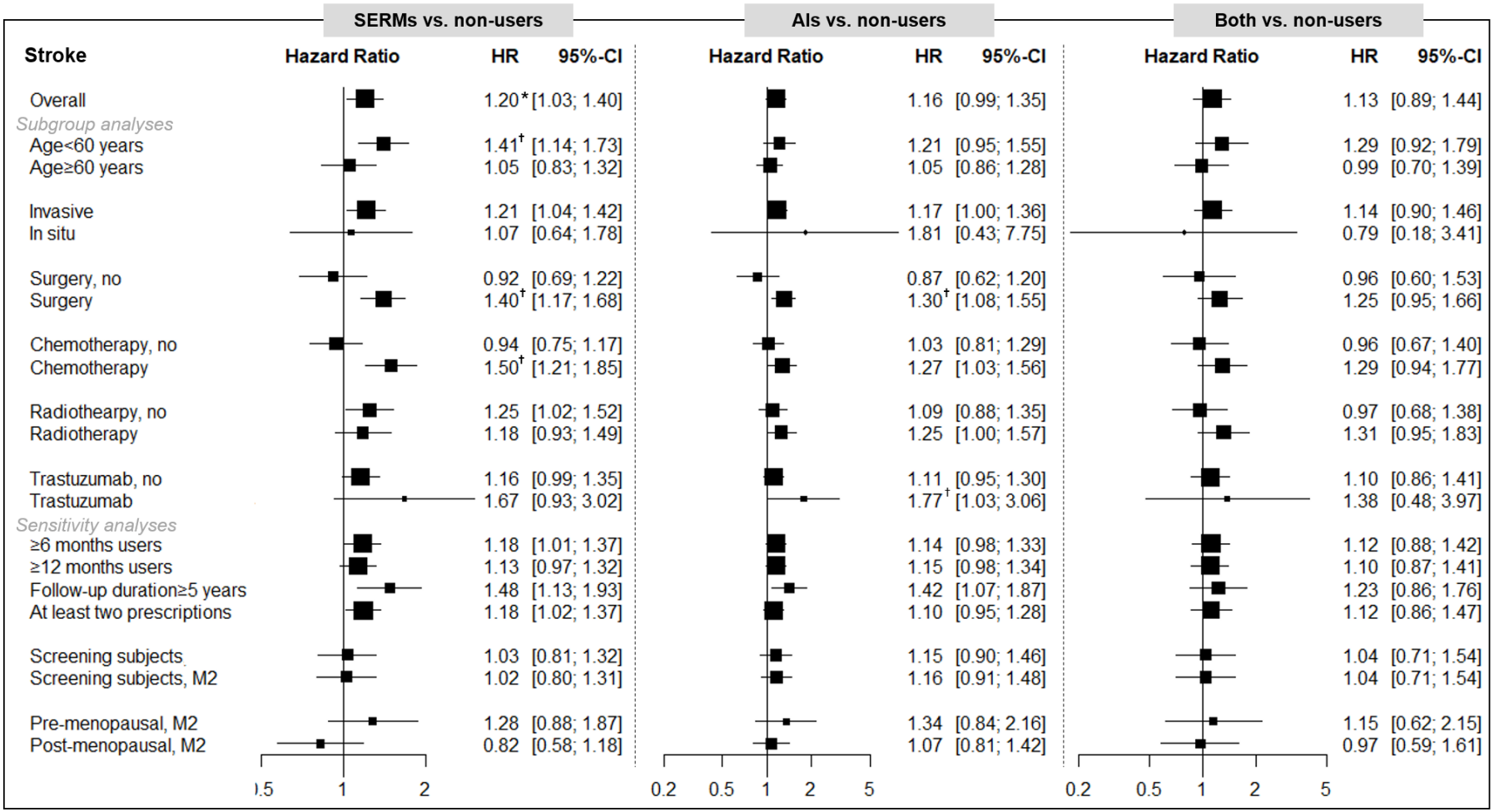

Figure S1. Summary of results for stroke (comparison with non-users)

SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors. The multivariable adjusted model included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes; however, model 2 (M2) additionally include body, mass index, lifestyle factors, and menopausal status. The * mark indicates the significance after multiple-testing by a false discovery rate (FDR; P for FDR<0.05) in Table 2. The † mark indicates the results of heterogeneity (P-value <0.1 or I^2>50%) by the stratified factor in supplementary materials.

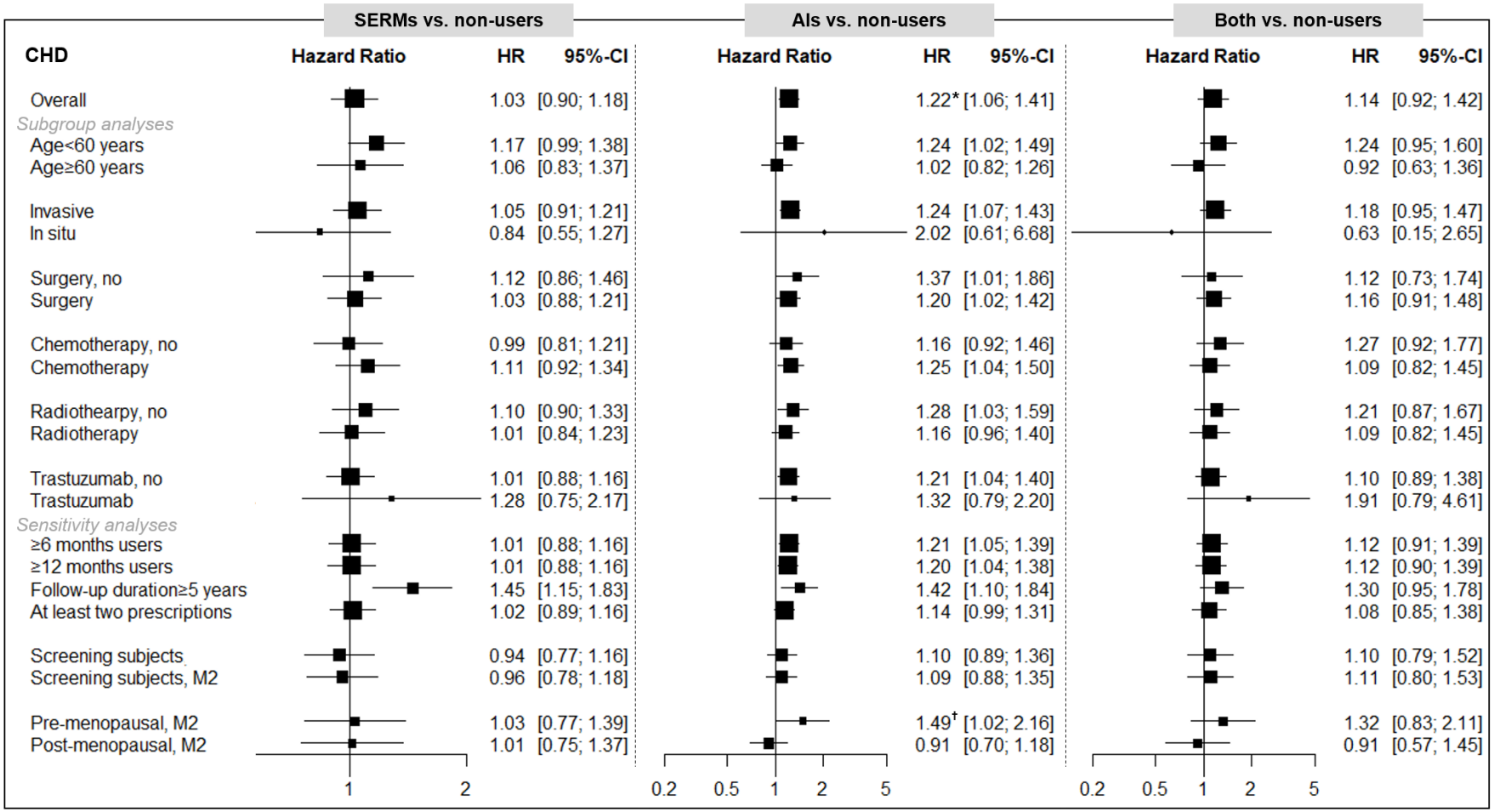

Figure S2. Summary of results for coronary heart diseases (comparison with non-users)

CHD, coronary heart diseases; SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors. The multivariable adjusted model included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes; however, model 2 (M2) additionally include body, mass index, lifestyle factors, and menopausal status. The * mark indicates the significance after multiple-testing by a false discovery rate (FDR; P for FDR<0.05) in Table 2. The † mark indicates the results of heterogeneity (P-value <0.1 or I^2>50%) by the stratified factor in supplementary materials.

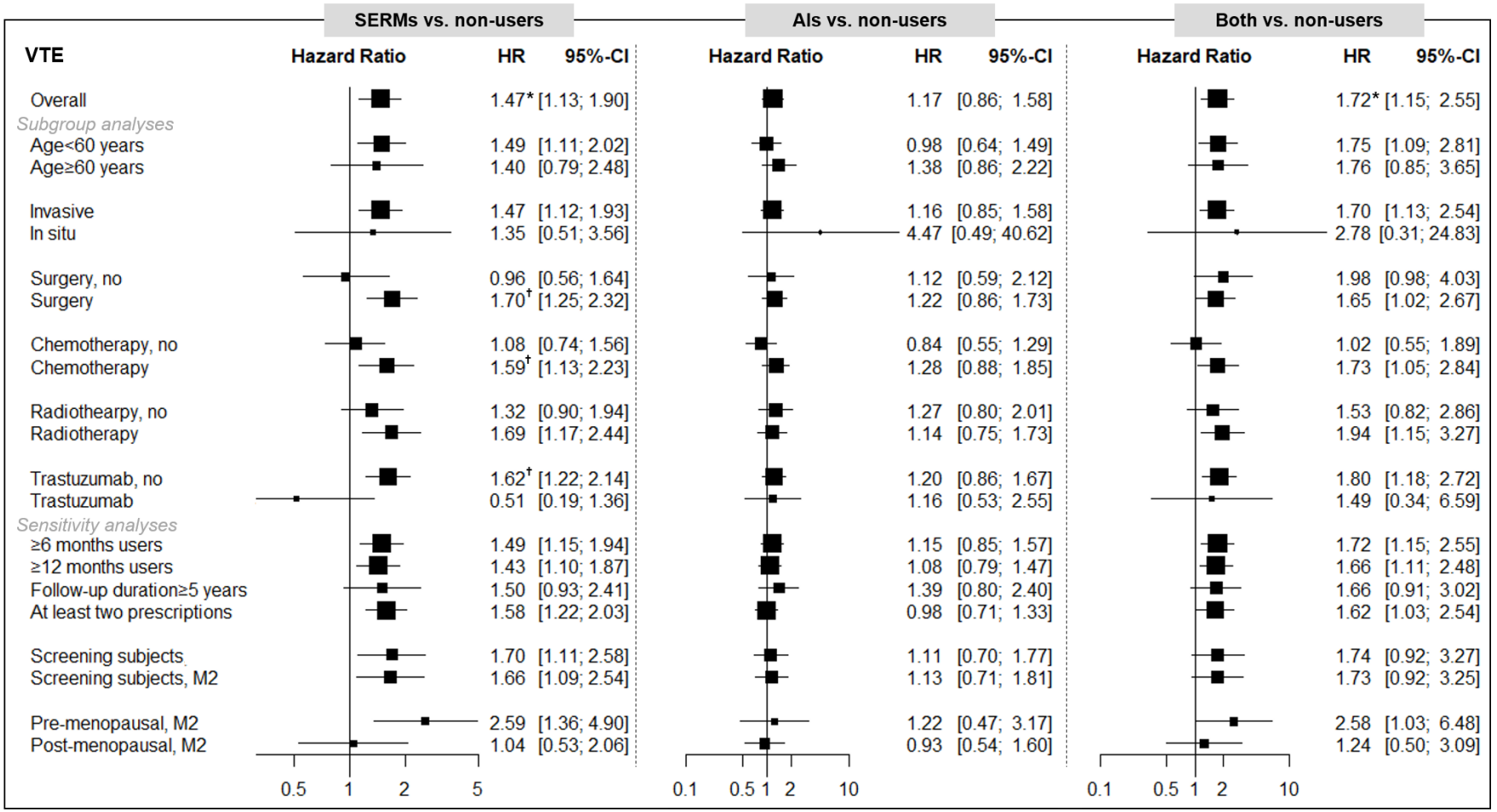

Figure S3. Summary of results for venous thromboembolism (comparison with non-users)

VTE, venous thromboembolism; SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors. The multivariable adjusted model included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes; however, model 2 (M2) additionally include body, mass index, lifestyle factors, and menopausal status. The * mark indicates the significance after multiple-testing by a false discovery rate (FDR; P for FDR<0.05) in Table 2. The † mark indicates the results of heterogeneity (P-value <0.1 or I^2>50%) by the stratified factor in supplementary materials.

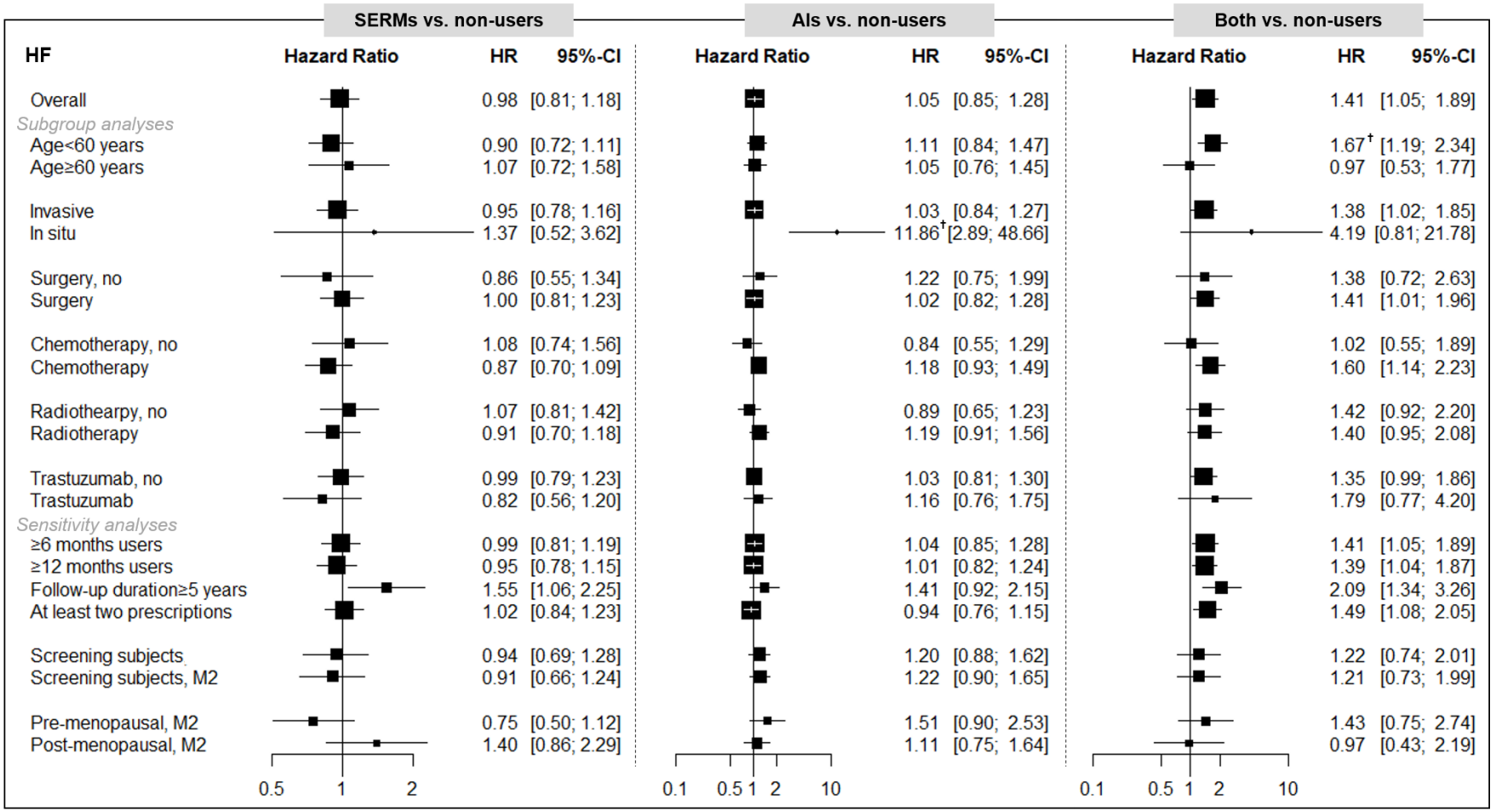

Figure S4. Summary of results for heart failure (comparison with non-users)

HF, heart failure; SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors. The multivariable adjusted model included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes; however, model 2 (M2) additionally include body, mass index, lifestyle factors, and menopausal status. The * mark indicates the significance after multiple-testing by a false discovery rate (FDR; P for FDR<0.05) in Table 2. The † mark indicates the results of heterogeneity (P-value <0.1 or I^2>50%) by the stratified factor in supplementary materials.

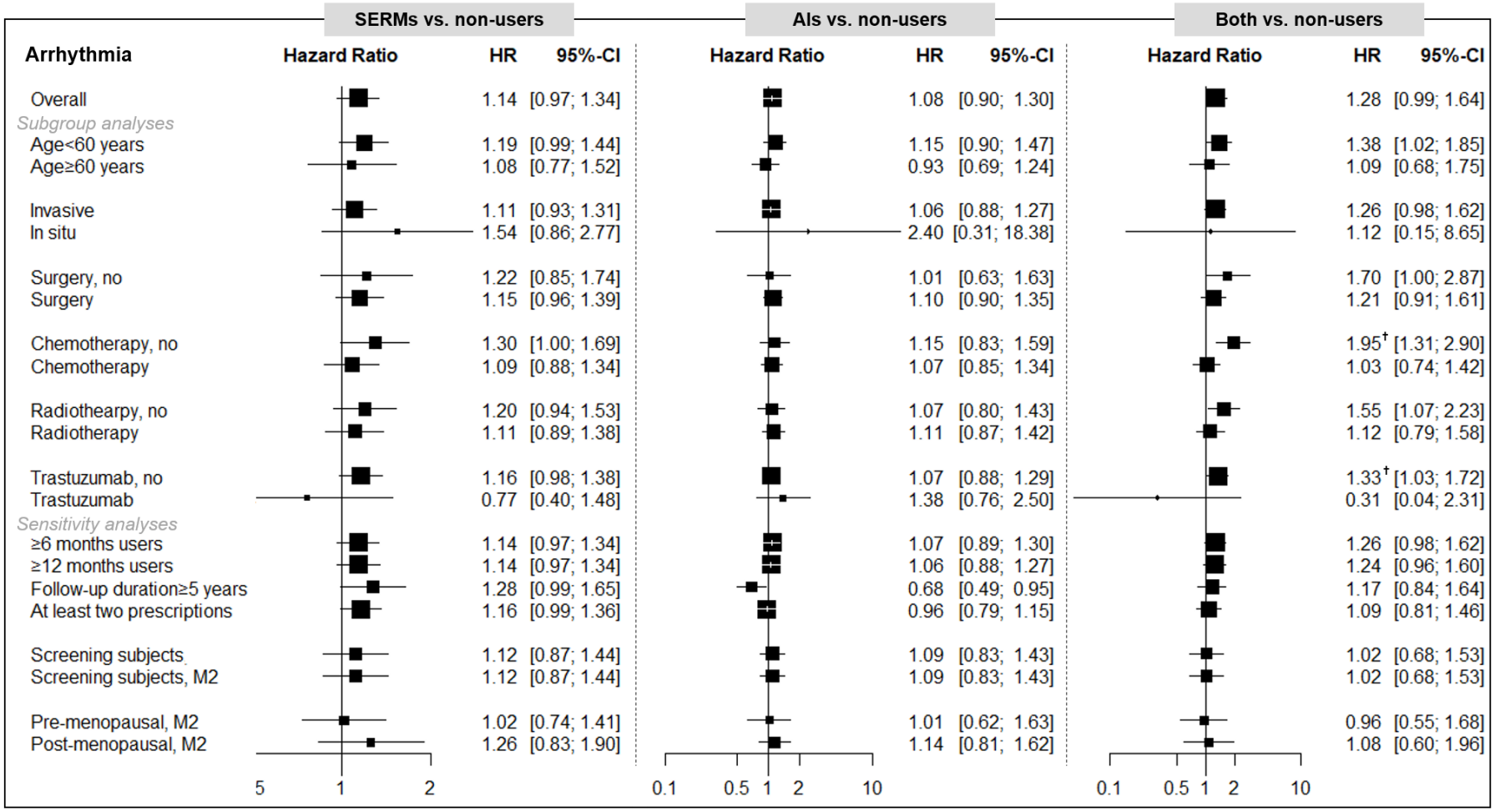

Figure S5. Summary of results for arrhythmia (comparison with non-users)

SERMs, selective estrogen receptor modulators; AIs, aromatase inhibitors. The multivariable adjusted model included age at diagnosis (continuous), insurance-based income level, region of residence, histological subtype, surgery, chemotherapy, radiotherapy, trastuzumab, hypertension, dyslipidemia, osteoporosis, and type 2 diabetes; however, model 2 (M2) additionally include body, mass index, lifestyle factors, and menopausal status. The * mark indicates the significance after multiple-testing by a false discovery rate (FDR; P for FDR<0.05) in Table 2. The † mark indicates the results of heterogeneity (P-value <0.1 or I^2>50%) by the stratified factor in supplementary materials.