Adjuvant Hormone Therapy–Related Hot Flashes Predict Treatment Discontinuation and Worse Breast Cancer Prognosis

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ABSTRACT

Background: Clinical trials have shown that adjuvant hormone therapy (AHT)–related hot flashes can predict better breast cancer outcomes. This population-based cohort study investigated whether this result can be generalized to a real-world setting. **Patients and Methods:** By linking the National Quality Registry for Breast Cancer, Prescribed Drug Register, and Cause-of-Death Register, we identified 7,152 chemotherapy-free patients with breast cancer who initiated AHT in Stockholm from 2006 through 2019, and followed them until 2020. Hot flashes were defined as new use of drugs for hot flashes within 6 months after initiating AHT. We used Cox models to compare disease-free survival and treatment discontinuation among patients with and without hot flashes. **Results:** Patients who newly used drugs for hot flashes shortly after AHT initiation had worse disease-free survival (adjusted hazard ratio [HR], 1.67; 95% CI, 1.11–2.52) and a higher treatment discontinuation rate (adjusted HR, 1.47; 95% CI, 1.21–1.78). The association between drugs for hot flashes and discontinuation of AHT differed by patient characteristics, with stronger associations among low-income patients (HR, 1.91; 95% CI, 1.41–2.59) and those without first-degree relatives who had cancer (HR, 1.81; 95% CI, 1.39–2.35) or died from cancer (HR, 1.71; 95% CI, 1.37–2.12). **Conclusions:** AHT-related hot flashes predict worse, rather than better, breast cancer outcomes among patients in clinical routine practice. The identification of adverse effects by the initiation of hot flash medications may identify a subset of patients with more severe hot flashes who are more likely to discontinue AHT and need more support for treatment adherence.

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Background

Breast cancer is the most common female cancer worldwide, with approximately 2.1 million incident cases in 2018.[1] Among them, 70% to 80% are estrogen receptor–positive breast cancers.[2,3] Adjuvant hormone therapy (AHT), including tamoxifen and/or aromatase inhibitors (AIs), have been proven to reduce breast cancer mortality by approximately 30% for tamoxifen and 40% for AIs for estrogen receptor–positive patients in randomized clinical trials.[4–6]

However, despite the established efficacy, AHT brings adverse effects. Hot flashes are one of the most common adverse effects caused by estrogen deprivation, which could compromise patients' quality of life.[7] Several studies have explored the relationship between hot flashes during AHT and breast cancer outcomes. However, conflicting results have been reported and all previous studies were conducted within the confines of clinical trials examining other aims.[8–12] Whether these results can be generalized to patients treated in clinical routine practice remains unknown. The discontinuation rate of AHT ranges from 31% to 73% in real-world settings, which is considerably higher than 8% to 28% reported in the clinical trials.[13,14]

By linking several Swedish registries, this population-based cohort study aims to examine the association of hot flashes shortly after AHT initiation with disease-free survival (DFS) and treatment discontinuation in a real-world setting.

Patients and Methods

Data Source and Study Population

The National Quality Registry for Breast Cancer (the Stockholm-Gotland Breast Cancer Registry, 1976–2007, and the National Breast Cancer Register, 2008 onwards) covers all patients with breast cancer diagnosed in the Stockholm-Gotland region of Sweden, collecting detailed information on tumor characteristics and treatments.[15,16] The Swedish Prescribed Drug Register (SPDR) is a nationwide database that records all dispensed prescription

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drugs in pharmacies since July 2005, with <0.3% of data missing.[17] The SPDR includes data on drugs' dispensation date, defined daily doses, days of supply, and medication's classification code based on Anatomical Therapeutic Chemical (ATC) Classification System, but does not include indications for prescriptions.[17] The Swedish Cause-of-Death Register collects data on all deaths in Sweden since 1952, including date and cause of death.[18]

Using unique personal identification numbers,[19] we linked the National Quality Registry for Breast Cancer to the SPDR. Through this linkage, we identified 15,197 women who were diagnosed with breast cancer between 2006 and 2019 in the Stockholm-Gotland region, who initiated AHT with ≥1 prescription of tamoxifen (ATC code L02BA01) or AIs (ATC code L02BG) after breast cancer diagnosis. We further excluded 267 patients with distant metastases at diagnosis, 232 patients with estrogen receptor–negative breast cancer, 215 patients who initiated AHT 1 year after breast cancer diagnosis, and 149 patients who emigrated or died after diagnosis and within the first year of AHT. To exclude patients in whom hot flashes were caused by AHT, we further excluded 131 patients who had any breast cancer event (local recurrence, distant metastasis, contralateral breast cancers, or death from breast cancer) before the end of the first year of AHT, 6,159 patients treated with chemotherapy or unknown, and 892 patients who used drugs for hot flashes within 1 year before AHT initiation, leaving 7,152 patients in the final cohort (supplemental eFigure 1, available with this article at JNCCN.org).

AHT-Related Hot Flashes

New use of drugs for hot flashes (ATC codes N06AB selective serotonin reuptake inhibitors, N06AX16 venlafaxine, and N03AX12 gabapentin) was used as an indicator for AHT-related hot flashes.[20,21] We did not use clonidine because it is only available as an injection in Sweden, which is unlikely to be used for treating hot flashes. New use of drugs for hot flashes was defined as having at least one prescription of corresponding drugs within 6 months after initiating AHT but not having any such prescription in the preceding 12 months. Information on the use of drugs was retrieved from the SPDR.

Covariates Definition

Information on age, menopausal status, tumor size, lymph nodes status, tumor grade, and progesterone receptor status at diagnosis were retrieved from the National Quality Registry for Breast Cancer. Use of hormone replacement therapy was defined as systematic use of estrogen/progesterone (ATC codes G03C, G03D, G03F) within 1 year before breast cancer diagnosis, excluding patch and vaginal cream, which was retrieved from the SPDR.[22] Charlson comorbidity score at breast cancer diagnosis was calculated using main diagnosis retrieved from the Swedish Patient Register.[23]

Socioeconomic factors, including education, employment, and income, were obtained from longitudinal integration database for health insurance and labor market studies. Average income 5 years before breast cancer diagnosis was categorized into low-, middle-, and high-income groups using tertiles. Data on family history of cancer and death from cancer among first-degree relatives were retrieved through the linkage between the Multi-Generation Register to the Swedish Cancer Register and the Cause-of-Death Register.[24]

Outcome Definition

Disease-Free Survival

Breast cancer events were defined as local recurrence, distant metastasis, contralateral breast cancer (>3 months after the primary breast cancer diagnosis), or death from breast cancer. Patients were followed until breast cancer events, death from causes other than breast cancer, emigration, or end of the study period (September 17, 2020), whichever came first, in order to define DFS. Information on local recurrence, distant metastasis, and contralateral breast cancer was obtained from the National Quality Registry for Breast Cancer. Deaths due to breast cancer were identified through the ICD-10 code C50 as main underlying cause of death, which was retrieved from the Swedish Cause-of-Death Register.

Discontinuation of AHT

Patients were followed from 6 months after initiation of AHT until treatment discontinuation, local recurrence, distant metastasis, contralateral breast cancer, death, emigration, endometrial cancer, venous thromboembolism, completion of 5 years of treatment, or end of the study period (September 17, 2020), whichever came first. Information on venous thromboembolism (ICD-10: I260, I269, I801, I808, I822, I828) was retrieved from the Swedish Patient Register. Information on endometrial cancer (ICD-10: C541) was retrieved from the Swedish Cancer Register. Discontinuation of AHT was defined as having intervals between any refills for tamoxifen or AIs exceeding 6 months during the follow-up.[25] Six months was used because Swedish pharmacies can only prescribe medications for a maximum of 3 months. Thus, lack of any dispensation of tamoxifen or AIs for a continuous period of 6 months suggests ≥2 dispensations have been missed, resulting in a shortage of the drug.[26] Information on dispensations of tamoxifen and AIs was retrieved from the SPDR.

Statistical Analysis

A chi-square test was used to compare baseline characteristics by use of drugs for hot flashes. The life table

approach was used to calculate 5- and 10-year DFS, and 3- and 5-year rate of AHT discontinuation. We conducted 2 analyses to examine the associations between AHT-related hot flashes and DFS, and between AHT-related hot flashes and treatment discontinuation. Cox regression models were used and adjusted for age at diagnosis, baseline type of AHT, menopausal status, use of hormone replacement therapy, Charlson comorbidity score, primary tumor size, lymph node status, tumor grade, and progesterone receptor status. All analyses were stratified by baseline type of AHT. We further performed stratified analyses to investigate whether the association between AHT-related hot flashes and treatment discontinuation differed by socioeconomic factors and family history information. All covariates were adjusted according to the categories presented in Table 1.

Table 1. Baseline Patient Characteristics

Characteristic	Use of Drugs n (%)	No Use of Drugs n (%)	*P* Value
Total, N	250	6,902	
Age at diagnosis			<.001
<40 y	59 (23.60)	837 (12.13)	
40–64 y	105 (42.00)	2,481 (35.95)	
≥65 y	86 (34.40)	3,584 (51.93)	
Adjuvant hormone therapy type			.132
Aromatase inhibitors	81 (32.40)	2,559 (37.08)	
Tamoxifen	169 (67.60)	4,343 (62.92)	
Menopause status			<.001
Premenopause	66 (27.73)	1,126 (16.92)	
Postmenopause	172 (72.27)	5,529 (83.08)	
Unknown	12	247	
HRT use 1 year before diagnosis[a]			<.001
No	122 (73.05)	4,773 (87.97)	
Yes	45 (26.95)	653 (12.03)	
Unknown	6	136	
Tumor size			.427
≤20 mm	194 (77.91)	5,311 (76.98)	
21–50 mm	53 (21.29)	1,453 (21.06)	
>50 mm	2 (0.80)	135 (1.96)	
Unknown	1	3	
Elston-Ellis tumor grade			.241
1	63 (26.25)	2,092 (31.33)	
2	157 (65.42)	4,040 (60.50)	
3	20 (8.33)	546 (8.18)	
Unknown	10	224	
Progesterone receptor status			.370
Positive	217 (87.50)	5,835 (85.46)	
Negative	31 (12.50)	993 (14.54)	
Unknown	2	74	
Charlson comorbidity score			.404
0	199 (79.60)	5,304 (76.85)	
1	31 (12.40)	865 (12.53)	
≥2	20 (8.00)	733 (10.62)	

Abbreviation: HRT, hormone replacement therapy.
[a]Analysis was restricted to postmenopausal women.

Missing values of covariates were grouped into an extra category and added into the multivariable-adjusted model.

Additional analysis was conducted to examine the association between discontinuation of AHT and DFS. All analyses were performed using SAS 9.4 (SAS Institute Inc) or STATA, version 15.1 (StataCorp LLC), at a 2-tailed alpha level of 0.05. The Regional Ethical Review Board in Stockholm, Sweden, approved the study.

Results

Patient Characteristics

Table 1 lists the baseline characteristics of chemotherapy-free patients with breast cancer by use of drugs for hot flashes. A total of 250 patients (3.5%) started to use drugs for hot flashes within the first 6 months after initiating AHT. Users of drugs for hot flashes were more likely to be younger, premenopausal, and taking hormone replacement therapy before their breast cancer diagnosis. There was no significant difference in tumor characteristics and comorbidity between users and nonusers of drugs for hot flashes.

AHT-Related Hot Flashes and DFS

The median follow-up for DFS was 6.8 years (interquartile range range, 3.9 to 10.0 years), and the 5-year and 10-year DFS was 95.8% and 91.0%, respectively. Patients who started to use drugs for hot flashes shortly after AHT initiation had significantly shorter DFS, with a multivariable-adjusted HR of 1.67 (95% CI, 1.11–2.52) (Table 2). Similar associations were observed for AI and tamoxifen users, although the association with DFS among the AI users did not reach statistical significance (Table 2).

AHT-Related Hot Flashes and Treatment Discontinuation

The median follow-up for discontinuation of AHT was 3.5 years (25%–75% interquartile range, 1.7 to 5.0 years), and the 5-year treatment discontinuation rate was 48.9%. Patients who started to use drugs for hot flashes shortly after AHT initiation were more likely to discontinue their treatment, with an adjusted HR of 1.47 (95% CI, 1.21–1.78) (Table 3). Similar associations were observed for AI and tamoxifen users (Table 3).

AHT-Related Hot Flashes and Treatment Discontinuation by Patient Characteristics

Figure 1 shows stratified analyses by patient characteristics. In most subgroups, use of drugs for hot flashes was associated with a higher risk of AHT discontinuation. Interaction analyses show that the associations were stronger among women with low income, those with no family history of cancer among first-degree relatives, and those with no first-degree relatives who died of cancer.

Additional Analyses

Additional analysis showed that patients who discontinued AHT were more likely to have shorter DFS, with a multivariable-adjusted HR of 1.46 (95% CI, 1.18–1.80) (supplemental eFigure 2).

Discussion

In contrast to previous findings from clinical trials, our population-based study found shorter DFS among patients who started to use drugs for hot flashes during the first 6 months after initiation of AHT. Further analysis showed that those patients with new use of drugs for hot flashes had a 14.2% higher 5-year discontinuation rate,

Table 2. Use of Drugs for Hot Flashes Shortly After Initiating AHT and Their Relationships With DFS

Strata	Drugs for Hot Flashes	Total n	Breast Cancer Event n	DFS (%)		HR (95% CI)	
				5-Year	10-Year	Age-Adjusted	Multivariable[a]
Full cohort	Nonuser	6,902	434	95.9	91.0	Ref	Ref
	User	250	25	92.3	87.0	1.70 (1.13–2.55)	1.67 (1.11–2.52)
Therapy type at baseline							
Aromatase inhibitors	Nonuser	2,559	175	94.1	89.0	Ref	Ref
	User	81	7	91.9	88.1	1.24 (0.58–2.67)	1.46 (0.67–3.20)
Tamoxifen	Nonuser	4,343	259	96.8	92.0	Ref	Ref
	User	169	18	93.5	86.8	1.91 (1.18–3.08)	1.82 (1.12–2.96)

Use of drugs for hot flashes shortly after initiating AHT was defined as having at least one prescription of drugs for hot flash within 6 months after initiating AHT but not having any corresponding prescription in the preceding 12 months. Patients who used drugs for hot flash within 1 year prior to AHT initiation were excluded.

Abbreviations: AHT, adjuvant hormone therapy; DFS, disease-free survival; HR, hazard ratio.

[a]Multivariable model adjusted for age at diagnosis, baseline type of AHT, menopause status, use of hormone replacement therapy, Charlson comorbidity score, tumor size, lymph node status, grade, and progesterone receptor status.

Table 3. Use of Drugs for Hot Flashes Shortly After Initiating AHT and Their Relationships With Treatment Discontinuation

Strata	Drugs for Hot Flashes	Total n	Discontinued Treatment n	Discontinuation Rate (%)		HR (95% CI)	
				3-Year	5-Year	Age-Adjusted	Multivariable[a]
Full cohort	Nonuser	6,443	2,397	27.2	43.3	Ref	Ref
	User	229	109	34.6	57.5	1.46 (1.21–1.77)	1.47 (1.21–1.78)
Therapy type at baseline							
Aromatase inhibitors	Nonuser	2,430	863	28.3	45.7	Ref	Ref
	User	76	36	33.1	59.1	1.40 (1.00–1.96)	1.45 (1.03–2.04)
Tamoxifen	Nonuser	4,013	1,534	26.6	42.2	Ref	Ref
	User	153	73	35.3	56.5	1.48 (1.17–1.87)	1.47 (1.16–1.87)

Use of drugs for hot flashes shortly after initiating AHT was defined as having at least one prescription of drugs for hot flashes within 6 months after initiating AHT but not having any corresponding prescription in the preceding 12 months. Patients who initiated and then discontinued AHT or had severe adverse effects (venous thromboembolism or endometrial cancer) within 6 months and patients who used drugs for hot flashes within 1 year prior to AHT initiation were excluded.

Abbreviations: AHT, adjuvant hormone therapy; HR, hazard ratio.

[a]Multivariable model adjusted for age at diagnosis, baseline type of AHT, menopause status, use of hormone replacement therapy, Charlson comorbidity score, tumor size, lymph node status, tumor grade, and progesterone receptor status.

which may subsequently lead to shorter DFS. In addition, we found that the association between use of drugs for hot flashes and treatment discontinuation differed by income and family history of having first-degree relatives with cancer or who died from cancer.

Treatment-emergent adverse effects have been hypothesized to be a useful marker for treatment efficacy of AHT. This hypothesis has been supported by data from several clinical trials.[8–10] For example, the Women's Healthy Eating and Living (WHEL) trial observed that women who reported hot flashes were less likely to develop breast cancer recurrence compared with those not reporting these symptoms,[9] suggesting that the occurrence of hot flashes can predict the likelihood of treatment success in the WHEL trial.

Despite that, whether these results from clinical trials can be generalized to real-world settings remains unknown. To the best of our knowledge, our study is the first population-based study designed to investigate the long-term treatment outcome among women with treatment-related hot flashes utilizing the use of drugs for hot flashes as an objective indicator. We found that patients with breast cancer and new use of drugs for hot flashes had worse DFS, suggesting that patients with hot flashes during AHT had worse, rather than better, breast cancer outcomes.

Our findings suggest that differences in treatment discontinuation should be considered before results from clinical trials can be generalized to clinical practice. However, our results do not necessarily invalidate results from clinical trials. First, the TEAM trial indicated that 32% of patients reported vasomotor symptoms during the first year of AHT.[10] In our study, 5.6% of patients started to use drugs for hot flashes during the first year. Clinical trials may have detected low-grade hot flashes by using a patient-reported questionnaire, whereas our study may have captured more severe hot flashes by using prescribed drugs for hot flashes. Second, lower discontinuation rates of AHT were observed in clinical trials than in our study. For example, in the TEAM trial, only 1.8% of patients discontinued AHT during the first year,[10] compared with >12% observed in our study.

The association between AHT-related hot flashes and treatment discontinuation differed by subgroups in our study, suggesting that different women may respond differently when having AHT-related hot flashes. We observed that this association was most pronounced for the low-income patients. These patients may have weak health awareness of adverse effects management and suboptimal social or medical support, suggesting that more frequent reminders or telephone appointments might be impactful in treatment adherence. For instance, a Swedish study showed that the proportion of patients needing but not seeking medical care was significantly higher in a low-income group compared with a high-income group.[27] In addition, our study found that use of drugs for hot flashes was associated with treatment discontinuation among patients without first-degree relatives who had cancer or died of cancer, whereas no association was observed among patients with first-degree relatives who had cancer or died of cancer. This may be because patients with family members who had cancer or died of cancer had a stronger motivation to complete AHT, even if they experienced treatment-related adverse effects.

Strata	Total	5-Year Discontinuation Rate: Use of Drugs	5-Year Discontinuation Rate: No Use of Drugs	Multivariable aHR (95% CI)[a]	*P* for Interaction
Socioeconomic factors					
Education					.187
≤12 y	3,769	61.2	43.3	**1.69 (1.31–2.19)**	
>12 y	2,826	53.6	42.8	1.31 (0.98–1.76)	
Employment[b]					.724
Unemployed	469	71.7	46.8	**1.85 (1.04–3.29)**	
Employed	2,765	52.8	39.4	**1.42 (1.08–1.87)**	
Average income during past 5 years					**.044**
Low	2,222	74.1	48.7	**1.91 (1.41–2.59)**	
Middle	2,223	56.9	43.1	1.33 (0.95–1.87)	
High	2,222	41.8	38.0	1.20 (0.82–1.76)	
Family history					
Family history of breast cancer among female FDRs					.470
No	5,090	58.0	43.1	**1.52 (1.23–1.88)**	
Yes	968	48.6	37.7	1.32 (0.71–2.43)	
Death from breast cancer among female FDRs					.828
No	5,816	56.3	42.4	**1.49 (1.22–1.83)**	
Yes	242	73.2	39.7	1.35 (0.45–4.02)	
Family history of cancer among FDRs					**.048**
No	2,834	64.8	44.0	**1.81 (1.39–2.35)**	
Yes	3,514	50.9	41.3	1.24 (0.92–1.66)	
Death from cancer among FDRs					**.031**
No	4,357	63.0	43.2	**1.71 (1.37–2.12)**	
Yes	1,991	42.4	41.1	1.01 (0.64–1.60)	

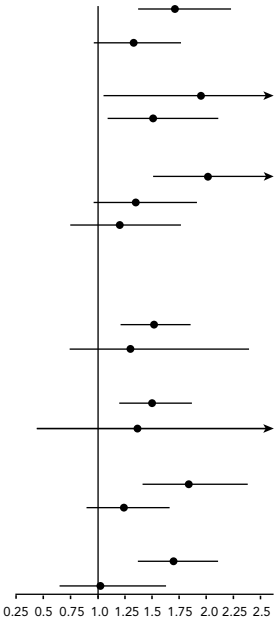

Figure 1. Association between use of drugs for hot flashes shortly after initiating adjuvant hormone therapy and treatment discontinuation by socioeconomic factors and family history information.
Bold indicates a statistically significant interaction with a *P* value <.05.
Abbreviations: aHR, adjusted hazard ratio; FDR, first-degree relative.
[a]Multivariable model adjusted for age at diagnosis, baseline type of adjuvant hormone therapy, menopause status, use of hormone replacement therapy, Charlson comorbidity score, tumor size, lymph node status, grade, and progesterone receptor status.
[b]Stratified analyses by employment were conducted among patients who were diagnosed before 65 years of age.

Treatment-related adverse effects are often not optimally measured due to infrequent clinic visits and rare clinical diagnosis.[28] A systematic review suggested that initiation of a medication can be a valid indicator for the development of a treatment-related adverse event.[29] Therefore, in the present study, we used new use of drugs for hot flashes to estimate the occurrence of hot flashes during AHT. We excluded patients who were treated with chemotherapy, used drugs for hot flashes within 1 year before therapy initiation, and had any breast cancer events during the first year of AHT, allowing us to exclude patients with hot flashes not related to AHT. In addition, sensitivity analyses performed by excluding patients who were concomitantly diagnosed with other indications for these drugs (eg, mental disorders or seizures) showed consistent results.

The following limitations of this study should be considered. First, due to lack of indications for prescriptions in the SPDR, we cannot rule out the possibility that some use of drugs for hot flashes may be due to other reasons. To minimize this possibility, we restricted our analyses to chemotherapy-free patients and excluded patients who ever used the corresponding hot flash drugs 1 year before treatment initiation. Furthermore, given the difficulty of collecting population-based, repeatedly measured, patient-reported hot flashes, the use of drugs for hot flashes is a realistic second-best approach that is currently available to answer the proposed research questions. Second, although the SPDR captures all dispensed prescriptions, a prescription refill does not necessarily mean that a patient is taking the medication. However, this misclassification would likely attenuate rather than create the observed association in our study. Third, this study was performed in a country with a unified healthcare system; thus, generalization to other countries should be made with caution.

Our findings reinforce the concept that AHT-related hot flashes may lead to treatment discontinuation and thereby affect breast cancer prognosis. Use of low-dose tamoxifen was associated with fewer adverse effects, which could potentially be an alternative to reduce treatment discontinuation and improve breast cancer outcomes in clinical practice.[30,31] Nevertheless, the effectiveness and adherence of using low-dose tamoxifen in adjuvant settings remains unclear. Personalized treatment of patients' adverse effects remain critical to optimize adherence and outcomes.

Conclusions

In contrast to results from clinical trials, our population-based study shows a worse, rather than better, DFS among patients with AHT-related hot flashes. These findings again suggest that results from clinical trials cannot be readily generalized to the real-world setting. Our findings also highlight that current approaches to managing therapy-related hot flashes by simply prescribing symptom-relieving drugs are insufficient. Other interventions on targeted risk groups are needed to reduce treatment discontinuation among women with severe AHT-related adverse effects to improve their breast cancer outcomes.

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Adjuvant Hormone Therapy–Related Hot Flashes Predict Treatment Discontinuation and Worse Breast Cancer Prognosis

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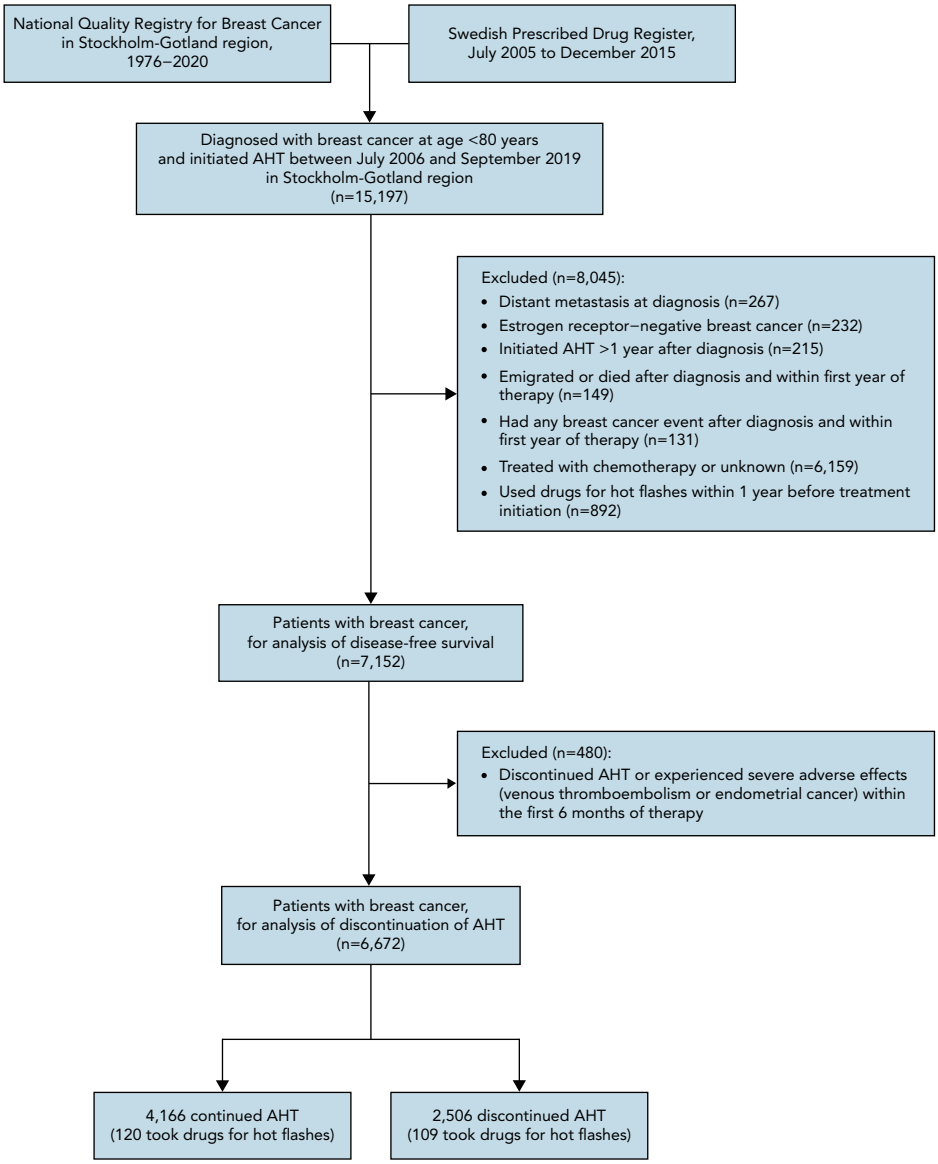
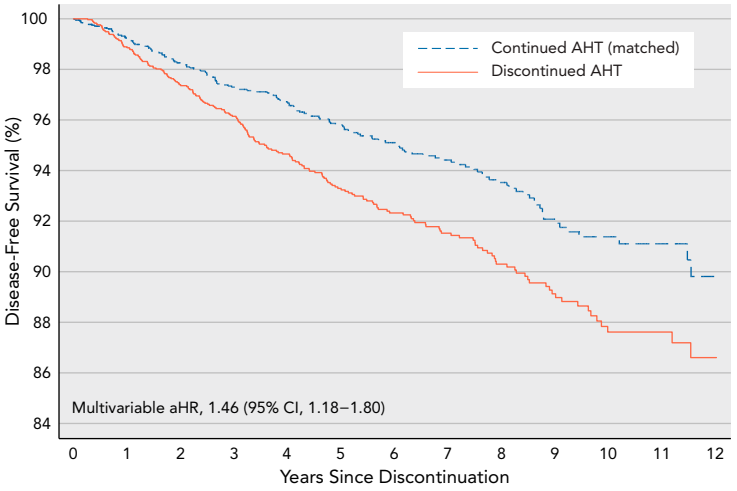


eFigure 1. Flowchart of study population.
Abbreviation: AHT, adjuvant hormone therapy.



Number at risk

Continued AHT	2,898	2,737	2,481	2,187	1,914	1,599	1,324	1,082	833	583	360	200	96
Discontinued AHT	2,979	2,793	2,453	2,178	1,861	1,581	1,291	1,034	803	598	392	229	106

eFigure 2. Disease-free survival among patients who discontinued versus continued AHT (matched).
Discontinuers of AHT were 1:1 matched to patients who continued therapy on the index date (date of treatment discontinuation) on age at diagnosis, diagnosis year (±3 years), primary tumor size, and lymph node metastasis. Patients were followed from the treatment discontinuation until death, emigration, or end of the study period (September 17, 2020), whichever came first. Multivariable model was additionally adjusted for menopause status, baseline type of AHT, use of hormone replacement therapy, Charlson comorbidity score, tumor grade, and progesterone receptor status.
Abbreviations: aHR, adjusted hazard ratio; AHT, adjuvant hormone therapy.