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Predictors for discontinuation of adjuvant hormone therapy in breast cancer patients

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Running head: Predictors of adjuvant hormone therapy discontinuation

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Abstract

PURPOSE

To identify predictors for discontinuation of adjuvant hormone therapy in breast cancer patients.

PATIENTS AND METHODS

We conducted a record-linkage study based on data from Stockholm-Gotland Breast Cancer Register, Swedish Prescribed Drug Register, and self-reported questionnaire. Women diagnosed with breast cancer between 2005 and 2008 in Stockholm, Sweden, were prospectively followed for five years until 2013, starting from their first prescription of tamoxifen or aromatase inhibitors (N=3 395).

RESULTS

Family history of ovarian cancer (HR, 1.55; 95% CI: 1.19-2.02), younger (<40 years; HR, 1.39; 95% CI: 1.08-1.78) and older (≥65 years; HR, 1.15; 95% CI: 1.03-1.28) age, higher Charlson comorbidity index (≥2 *vs* 0; HR, 1.35; 95% CI: 1.03-1.76), use of analgesics (HR, 1.33; 95% CI: 1.16-1.52), hypnotics/sedatives (HR, 1.24; 95% CI: 1.07-1.43), gastrointestinal drugs (HR, 1.25; 95% CI: 1.08-1.43), and hormone replacement therapy (HR, 1.27; 95% CI: 1.08-1.49), were identified as baseline predictors for hormonal treatment discontinuation. Use of analgesics (HR, 1.22; 95% CI: 1.08-1.37), hypnotics/sedatives (HR, 1.21; 95% CI: 1.07-1.37), antidepressants (HR, 1.22; 95% CI: 1.06-1.40), or gastrointestinal drugs (HR, 1.27; 95% CI: 1.13-1.43), and switching therapy between tamoxifen and aromatase inhibitors (HR, 1.50; 95% CI: 1.23-1.83), during the first year of hormonal treatment were associated with increased risk of discontinuation during the following four years.

CONCLUSION

Predictors identified in our study can be used in developing targeted intervention to prevent adjuvant hormone therapy discontinuation and subsequently to improve breast cancer outcomes.

INTRODUCTION

Adjuvant hormone therapy, such as tamoxifen and aromatase inhibitors (AIs), lowers the risk of breast cancer recurrence by 41% and cancer-specific mortality by 31%.[1] However, despite the survival benefit of adjuvant hormone therapy,[2] a substantial proportion of breast cancer patients – ranging from 31 to 73% – discontinue their treatment[3-6] and therefore diminished therapeutic effects.[4,7-10]

Treatment-related side effects, including pain, depression, sleep disorders, and gastrointestinal reaction such as nausea and vomiting, are known as the major reason for discontinuing adjuvant hormone therapy.[6,11,12] Clinicians do their best to support patients by prescribing symptom-relieving drugs. However, whether a prescription of a symptom-relieving drug is still associated with future discontinuation remains unknown.

Apart from treatment-related side effects, several factors have been suggested to be associated with discontinuation of adjuvant hormone therapy, including younger and older age, higher prescription co-payment, higher Charlson comorbidity index, and switching therapy between tamoxifen and AIs.[3,6,13,14] However, previous studies usually suffer from small sample size, short follow-up time, and selected study population (such as using hospital based samples or including only low income women); and contradictory results for some predictors have also been reported.[5,12-21]

By linking data from several Swedish registers and a large population-based cohort, the present study was conducted to identify predictors for discontinuation of adjuvant hormone therapy in breast cancer patients. Our first aim was to identify baseline predictors for discontinuation, including use of hormone replacement therapy (HRT), use of symptom-relieving drugs prior to diagnosis, lifestyle factors, reproductive factors, socio-economic status, family history of breast or ovarian cancer, comorbidities and tumor characteristics. Our second aim was to identify early-treatment-stage predictors for long-term discontinuation by

investigating whether use of symptom-relieving drugs and switching therapy between tamoxifen and AIs, within the first year of treatment could be used to predict the discontinuation of adjuvant hormone therapy in the following four years.

PATIENTS AND METHODS

Data sources and patients

Swedish Registers

The Stockholm-Gotland Breast Cancer Register contains detailed information on all patients diagnosed with breast cancer in Stockholm-Gotland region of Sweden since 1976, including data on pre-surgical diagnostics, tumor characteristics, therapy of the breast cancer, and post-treatment follow-up.[22]

The Swedish Prescribed Drug Register contains information on all prescribed medicines dispensed by Swedish pharmacies since July 1, 2005, including dates of prescription and dispense, number of defined daily dose, and classification of drugs according to the Anatomical Therapeutic Chemical (ATC) Classification System. This register is reported to be nationwide complete, with <0.3% of data entries with missing Personal Identification Numbers.[23]

Using the individually unique Personal Identification Numbers,[24] we linked the Stockholm-Gotland Breast Cancer Register to the Swedish Prescribed Drug Register. Through this linkage, we identified 3 470 patients diagnosed with breast cancer between 2005 and 2008 in Stockholm, Sweden, who initiated adjuvant hormone therapy with at least one prescription of tamoxifen (ATC codes L02BA01) or AIs (ATC codes L02BG). Furthermore, we excluded 45 patients with distant metastasis at diagnosis and 30 patients with ER-negative breast cancer, leaving a total of 3 395 breast cancer patients for the final analysis. (Figure 1)

Self-reported Questionnaire Survey

During 2009-2010, 1 997 (59 %) of the 3 395 breast cancer patients answered a structured questionnaire in order to identify prognostic factors for breast cancer.[25,26] All subjects participated in the questionnaire survey provided written informed consent.

Discontinuation of adjuvant hormone therapy

Information on prescription and dispense of tamoxifen and AIs was obtained from the Swedish Prescribed Drug Register. We defined discontinuation of adjuvant hormone therapy as having any interval between two consecutive dispenses exceeding 180 days during the follow-up. Since a maximum of 3-month supply of prescription drugs can be dispensed in Sweden, a gap of 180 days indicates that at least two dispenses have been missed, thus resulting in a shortage of the drug.[27]

Patients were followed from the first prescription of tamoxifen or AIs, until treatment discontinuation, death, local recurrence, distant metastasis, contralateral cancer, endometrial cancer, venous thromboembolism, end of study period (31 August 2013), or completion of five-year treatment, whichever occurred first (Appendix Table A1, online only). Time to discontinuation was defined as the time interval between the first and last prescriptions plus the days of supply from the last prescription. Information on death, local recurrence, distant metastasis, and contralateral cancer was retrieved from the Stockholm-Gotland Breast Cancer Register. Information on endometrial cancer (ICD-10: C541) were retrieved from Swedish Cancer Register[28] and information on venous thromboembolism (ICD-10: I260, I269, I801-3, I808-9, I822-3, I828-9) was retrieved from the Swedish Inpatient Register.[29]

Baseline predictors of discontinuation

Information on baseline use of symptom relieving drugs and HRT was retrieved from the Swedish Prescribed Drug Register. Baseline use of symptom-relieving drugs, including analgesics (ATC codes N02), hypnotics/sedatives (ATC codes N05C), antidepressants (ATC codes N06A), and gastrointestinal drugs (ATC codes A02, A03, A04, A06, A07), was defined as filling at least one prescription of corresponding drugs one year before diagnosis of breast cancer (Appendix Table A2, online only). Pre-diagnosis HRT was defined as filling at least one prescription of estrogen/progesterone (ATC codes G03C, G03D, G03F) for systematic

use one year before breast cancer diagnosis, excluding local use such as patch and vaginal cream.

Information on age at diagnosis, menopausal status at diagnosis, primary tumor size, lymph node metastases, progesterone receptor status, radiotherapy, and chemotherapy was retrieved from the Stockholm-Gotland Breast Cancer Register.

Information on comorbidities used to calculate the Charlson Comorbidity Index was retrieved from Swedish Inpatient Register, including all main diagnoses for hospital admissions since 1987 but before breast cancer diagnosis.[30]

Information on education, cigarette smoking, self-reported HRT at diagnosis, body mass index (BMI), and family history of breast or ovarian cancer was retrieved from the self-reported questionnaire.

Early-treatment-stage predictors of discontinuation

Early-treatment-stage use of symptom-relieving drugs was defined as filling at least one prescription of the symptom-relieving drugs during the first year of adjuvant hormone therapy. Switching therapy was defined as switching from tamoxifen to AIs or vice versa during the first year of adjuvant hormone therapy.

Data analysis

Cox regression analysis was used to identify baseline predictors for discontinuation of adjuvant hormone therapy. The Schoenfeld residual test was used to check the proportionality assumption of the Cox regression. A violation of the assumption was suggested for pre-diagnosis HRT. The time-dependent hazard ratios (HRs) for pre-diagnosis HRT were therefore estimated using flexible parametric survival models.[31]

To identify early-treatment-stage predictors for long-term discontinuation, we used Cox regressions analysis to investigate whether use of analgesics, hypnotics/sedatives, antidepressants, and gastrointestinal drugs, as well as switching therapy between tamoxifen

and AIs, within the first year of treatment could be used to predict the discontinuation of adjuvant hormone therapy in the coming four years. Patients discontinued or censored already during the first year of follow-up were excluded in these analyses. Specifically, we used Kaplan-Meier failure time plot to illustrate the cumulative probability of treatment discontinuation during the following four years according to the number (0, 1-2, 3-4) of early-treatment-stage symptom-relieving drugs.

Sensitivity analyses were conducted to assess the robustness of our findings: we restricted our analyses to women without any prescription of symptom-relieving drugs during the year prior to breast cancer diagnosis; we redefined the use of symptom-relieving drugs as filling at least two corresponding drugs; we re-analyzed our data using competing risk regression;[32] and we stratified our analysis by type of adjuvant hormone therapy.

All analyses were conducted using SAS software (version 9.4; SAS Institute Inc, Cary, NC, USA) or Stata software (version 13.0; Stata corporation, college station, TX), at a two-tailed alpha level of 0.05. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

RESULTS

Subject characteristics

Table 1 presents baseline characteristics of breast cancer patients. Most patients were aged 40-64 years at the time of diagnosis, with 35% aged ≥65 years, and only 4% aged <40 years.

Discontinuation of adjuvant hormone therapy

Discontinuation of adjuvant hormone therapy increased in a linear fashion during the follow-up: by the end of year one, 14% of the patients discontinued the treatment; by the end of year three, 36%; by the end of year five, which was the recommended duration of adjuvant hormone therapy at the time of the study, the rate of discontinuation approached 54%.

Baseline predictors for discontinuation

Use of analgesics, hypnotics/sedatives, antidepressants, or gastrointestinal drugs one year before breast cancer diagnosis was all associated with higher discontinuation of adjuvant hormone therapy in the univariable models. In the multivariable model, use of analgesics (HR, 1.33; 95% CI, 1.16 to 1.52), hypnotics/sedatives (HR, 1.24; 95% CI, 1.07 to 1.43), and gastrointestinal drugs (HR, 1.25; 95% CI, 1.08 to 1.43) remained statistically significant (Table 1).

Use of HRT one year before diagnosis of breast cancer was associated with higher discontinuation of adjuvant hormone therapy during the first year but not afterwards (Figure 2). Similar associations were also observed for self-reported HRT, with significantly higher HRs for the first year of follow-up (current users: HR=1.78 [95% CI, 1.14 to 2.76]; past users: HR=1.31 [95% CI, 0.95 to 1.82]) but not afterwards.

Other baseline predictors for discontinuation of adjuvant hormone therapy included younger and older age at cancer diagnosis, higher Charlson comorbidity index, and family history of ovarian cancer (Table 1).

Early-treatment-stage (first-year) predictors for long-term discontinuation

Use of symptom-relieving drugs within the first year of follow-up was associated with higher discontinuation of adjuvant hormone therapy in the following four years (Table 2). Furthermore, the rate of discontinuation of adjuvant hormone therapy in the following four years increased significantly with the increasing number of symptom-relieving drugs used during the first year of treatment. The discontinuation rate was 37%, 50%, and 62% for patients who used 0, 1-2, and 3-4 drugs, respectively (Figure 3). Patients who switched therapy from tamoxifen to AIs or vice versa during the first year of follow-up were also at increased risk of discontinuation in the following four years (HR, 1.50; 95% CI, 1.23 to 1.83).

Sensitivity analyses

Restricting the analysis to women without any prescription of symptom-relieving drugs during the year before breast cancer diagnosis (Appendix Table A3, online only), redefining the use of symptom-relieving drugs as filling at least two corresponding drugs (Appendix Table A4 and Table A5, online only), and re-analyzing our data using competing risk regression (Appendix Table A6 and Table A7, online only) provided similar results as in the main analysis. Stratified analyses by type of adjuvant hormone therapy also yielded comparable results, with higher HRs for pre-diagnosis HRT during the first year of follow-up (Tamoxifen alone: HR=2.10 [95% CI, 1.40 to 3.14]; AIs alone: HR=1.96 [95% CI, 1.14 to 3.37]) but not the following years. Higher HRs were also found for symptom-relieving drugs in the stratified analyses (Appendix Table A8, online only).

DISCUSSION

In this population-based cohort of 3 395 breast cancer patients, over half of the patients discontinued adjuvant hormone therapy during the 5-year follow-up. Use of medications for pain, sleep disorders, depression, and gastrointestinal disorders both before diagnosis and during the first year of treatment was identified as predictors for discontinuation of adjuvant hormone therapy. Pre-diagnosis HRT was found to be associated with discontinuation of adjuvant hormone therapy in the first year of treatment, but not afterwards. Other predictors for discontinuation included younger and older age at cancer diagnosis, positive family history of ovarian cancer, higher comorbidities, and switching therapy between tamoxifen and AIs during the first year of treatment.

Women on adjuvant hormone therapy for breast cancer are generally expected to be highly motivated since they are facing a life-threating disease, the adjuvant therapy is effective, easy to use, and generally well tolerated. However, in our unselected population, over half of the breast cancer patients discontinued their treatment during a 5-year period. This rate corroborates with previous studies that have reported a 5-year discontinuation rate of 31 to 73%.[3] Discontinuation of adjuvant hormone therapy is likely to result in significantly worse outcomes for breast cancer patients,[4] thus represents an important issue that needs to be addressed.

A further problem is that women who experienced treatment-related side effects may be the ones that benefit adjuvant therapy since side effects could be a proxy for therapy response.[33] Although still somewhat controversial,[34] patients who experiencing more pronounced treatment-related symptoms have been shown to have a lower rate of breast cancer recurrence than those not reporting symptoms.[33,35] Unfortunately, higher discontinuation was found among users of symptom-relieving drugs in our study, suggesting

that patients who were potentially more likely to benefit from the treatment were more often discontinuing the adjuvant hormone therapy.

Of the patients discontinuing their therapy, most women (74%) stopped taking the drug after the first year of treatment. This gives the responsible clinician an opportunity to identify patients at higher risk of stop taking the prescribed medication. Consequently, the first year of treatment may serve as a good opportunity for potential interventions. Furthermore, it seems for instance obvious that the symptom-relieving drugs used in the current population did not stop the majority of patients from discontinuation, indicating that a therapy shift or a dose adjustment of the symptom–relieving drugs is warranted.

In addition to post-diagnosis drugs, pre-diagnosis symptom-relieving drugs were also found to be associated with early discontinuation of adjuvant hormone therapy in our study. This result is expected given that psychological problems have been cited as an important determinant for treatment compliance in oncology patients.[36] Another study by Barron et al. reported a significant association between pre-diagnosis antidepressants and discontinuation of tamoxifen treatment, but not Benzodiazepine and antipsychotic drugs.[19] That study, however, over-sampled the elderly and the socioeconomically disadvantaged groups, and used only data from a pharmacy register.

Pre-diagnosis HRT was associated with early discontinuation of adjuvant hormone therapy, which may be due to the intolerable menopause-like symptoms caused by both stopping HRT and initiation of adjuvant hormone therapy. Importantly, the impact of HRT appears to be specific for early discontinuation as the hazard ratios declined clearly over time, suggesting that early and late discontinuation of adjuvant hormone therapy may have different underlying causes. Therefore, different strategy should be considered to prevent early and late discontinuation of adjuvant hormone therapy.

In line with previous studies, discontinuation rates were higher among the younger (<40 years) and older (≥65 years) patients.[37] That younger patients are particularly likely to stop taking their medications is of concern as younger women have a worse prognosis,[38] particularly so if they discontinue treatment.[39] Furthermore, consistent with previous studies,[27] higher discontinuation of adjuvant hormone therapy was found among patients who switched therapy during the first year of treatment, potentially as an indicator of greater side effects associated with the original therapy.[40]

Our results on family history of ovarian cancer may be due to chance alone, although it is possible that having experienced another lethal cancer (e.g., ovarian cancer) in the family might have made the breast cancer patients less confident in cancer treatment in general.

The major strength of our study is that we pooled individual data from several different sources, namely the Stockholm-Gotland Breast Cancer Register, the Swedish Prescribed Drug Register, and the self-reported questionnaire data. In contrast, previous studies were either purely register-based[13,18,27] or questionnaire-based.[12,17] The similar findings of HRT, either with data obtained from the Prescribed Drug Register or from self-reported questionnaire, further stress the robustness of the different sources of information used in the present study. Furthermore, the Prescribed Drug Register provides accurate and objective estimates of medication use in the entire population of Sweden since July 2005 and has been widely used to measure medication compliance in other studies.[27] Other strengths of the present study include the population-based design and large sample size.

A few limitations should be addressed. First, prescription refill does not necessarily guarantee a patient actually consumes the prescribed medication. Hence, our study might have underestimated the prevalence of treatment discontinuation. Second, because only dispensed medications are recorded in the Prescribed Drug Register,[23] our study lack information on patients who were prescribed with tamoxifen or AIs but never withdraw them from the

pharmacies. Third, potential misclassification of the use of analgesics and gastrointestinal drugs is possible because the Swedish Prescribed Drug Register does not contain information on purchases of over-the-counter drugs.[23] However, given the fact that majority of the studied symptom-relieving drugs are prescribed medications, and small dose, long term use of analgesics is also prescribed, we believe this misclassification is likely to be small. Fourth, only 59% of the study participants responded to the questionnaire survey, which might have led to some uncertainty in the representativeness of the questionnaire-based information (e.g. family history of ovarian cancer). Fifth, given that we tested multiple predictors in the present study, false positive finding due to multiple testing to some extent remains possible. Finally, in addition to adjuvant hormone therapy, the use of symptom-relieving drugs may also be due to reasons other than the side effect of hormonal treatment, including for example severe psychological distress experienced after receiving breast cancer diagnosis. However, regardless of the underlying reasons for the use of these drugs, our conclusion that the use of symptom-relieving drugs in the first year can be used to predict the discontinuation of adjuvant hormone therapy in the following four years still holds.

In summary, during the first five years following treatment initiation more than 50% of the breast cancer patients discontinued their adjuvant hormone therapy in this population-based Swedish cohort. Predictors of discontinuation included family history of ovarian cancer, age at diagnosis, higher comorbidities, switching therapy between tamoxifen and aromatase inhibitors, use of analgesics, hypnotics/sedatives, antidepressants, and gastrointestinal drugs. Interestingly, pre-diagnosis HRT is associated with early discontinuation, but not later discontinuation of adjuvant hormone therapy. It thus seems possible for the treating physician to identify factors that indicates which patients will stop using adjuvant therapy. Future interventions, including side effect management, patient education, and frequent monitoring

of symptom-relieving drugs, may help to improve treatment continuation and subsequently improve breast cancer outcomes.

ACKNOWLEDGEMENTS

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Figure legend

Fig 1. Flow chart of study participants.

Fig 2. Time-dependent hazard ratios (HRs) for discontinuation of adjuvant hormone therapy. HRs estimated from flexible parametric survival models, adjusting for age at diagnosis, family history of ovarian cancer, Charlson comorbidity index, pre-diagnosis use of analgesics, hypnotics/sedatives, and gastrointestinal drugs. Curves cut off at 90 days from initiation of adjuvant hormone therapy because of sparse data. Pre-diagnosis hormone replacement therapy is defined as filling at least one prescription of estrogen/progesterone for systematic use one year before diagnosis of breast cancer. Premenopausal women (N=863) and women diagnosed before July 2006 (N=725) were excluded from this analysis.

Fig 3. Discontinuation of adjuvant hormone therapy according to number of post-diagnosis symptom-relieving drugs used in the first year of follow-up.

Tables

Table 1. Baseline characteristics and their relation with discontinuation of adjuvant hormone therapy among 3 395 breast cancer patients in Stockholm, Sweden, 2005-2013.

Characteristics	No. of patients		Time to 25% Discontinuation, years (95%CI) *	Hazard ratios (95% CI)	
	Total	Discontinuers(%)		Univariable	Multivariable†
Register data					
Age at diagnosis, yrs					
<40	129	76(58.9)	1.6(1.4-2.2)	1.30(1.03-1.64)	1.39(1.08-1.78)
40-64	2083	1029(49.4)	2.1(1.9-2.2)	1.00(reference)	1.00(reference)
≥65	1183	638(53.9)	1.5(1.4-1.8)	1.21(1.10-1.34)	1.15(1.03-1.28)
Menopausal status					
Pre-menopause	863	426(49.4)	2.0(1.6-2.2)	1.00(reference)	1.00
Post-menopause	2378	1250(52.6)	1.8(1.6-1.9)	1.12(1.00-1.25)	1.05(0.86-1.30)
Unknown	154	67(43.5)	3.1(2.1-3.8)	—	—
Charlson comorbidity index					
0	3096	1589(51.3)	1.9(1.8-2.1)	1.00(reference)	1.00(reference)
1	195	96(49.2)	1.7(1.1-2.2)	1.03(0.84-1.27)	0.89(0.72-1.10)
≥2	104	58(55.8)	0.9(0.5-1.5)	1.47(1.13-1.91)	1.35(1.03-1.76)
Primary tumor					
Not palpable tumor	730	376(51.5)	1.7(1.5-2.0)	1.01(0.89-1.14)	—
Tumor<20 mm	1498	793(52.9)	2.1(1.9-2.2)	1.00(reference)	—
Tumor 21-50 mm	958	469(49.0)	1.8(1.5-2.1)	0.97(0.87-1.09)	—
Tumor>50 mm	195	99(50.8)	1.3(1.1-1.9)	1.14(0.92-1.40)	—
Unknown	14	6(42.9)	1.7(0.6-.)	—	—
Lymph node metastases					
No	2961	1523(51.4)	1.9(1.7-2.0)	1.00(reference)	—
Yes	422	214(50.7)	1.7(1.5-2.1)	1.08(0.93-1.24)	—
Unknown	12	6(50.0)	1.0(0.3-2.7)	—	—
Progesterone receptor status					
Positive	2592	1323(51.0)	1.9(1.8-2.1)	1.00(reference)	—
Negative	707	367(51.9)	1.9(1.7-2.1)	1.05(0.94-1.18)	—
Unknown	96	53(55.2)	0.9(0.5-1.1)	—	—
Radiotherapy					
No	667	333(49.9)	2.0(1.7-2.2)	1.00(reference)	—
Yes	2653	1367(51.5)	1.9(1.7-2.1)	1.02(0.91-1.15)	—
Unknown	75	43(57.3)	0.7(0.5-1.3)	—	—
Chemotherapy					
No	2346	1223(52.1)	1.8(1.6-2.0)	1.00(reference)	—
Yes	957	469(49.0)	2.0(1.8-2.3)	0.92(0.83-1.02)	—
Unknown	92	51(55.4)	1.1(0.5-1.5)	—	—
Pre-diagnosis symptom-relieving drugs‡					
Analgesics					
No	1914	908(47.4)	2.1(2.0-2.3)	1.00(reference)	1.00(reference)
Yes	519	312(60.1)	1.5(1.3-1.6)	1.51(1.33-1.72)	1.33(1.16-1.52)
Unknown	962	523(54.4)	1.7(1.4-2.0)	—	—

Characteristics	No. of patients		Time to 25% Discontinuation, years (95%CI) *	Hazard ratios (95% CI)	
	Total	Discontinuers(%)		Univariable	Multivariable†
Hypnotics and sedatives					
No	1966	942(47.9)	2.1(1.9-2.2)	1.00(reference)	1.00(reference)
Yes	467	278(59.5)	1.4(1.1-1.6)	1.44(1.26-1.65)	1.24(1.07-1.43)
Unknown	962	523(54.4)	1.7(1.4-2.0)	—	—
Antidepressants					
No	2112	1034(49.0)	2.0(1.8-2.1)	1.00(reference)	1.00(reference)
Yes	321	186(57.9)	1.7(1.4-2.1)	1.29(1.11-1.51)	1.09(0.92-1.28)
Unknown	962	523(54.4)	1.7(1.4-2.0)	—	—
Gastrointestinal drugs					
No	1930	920(47.7)	2.1(1.9-2.2)	1.00(reference)	1.00(reference)
Yes	503	300(59.6)	1.6(1.3-1.8)	1.43(1.26-1.63)	1.25(1.08-1.43)
Unknown	962	523(54.4)	1.7(1.4-2.0)	—	—
Pre-diagnosis HRT‡					
No	1479	729(49.3)	2.0(1.8-2.2)	1.00(reference)	1.00(reference)
Yes	328	192(58.5)	1.4(1.0-1.7)	1.27(1.09-1.49)	1.27(1.08-1.49)
Unknown	1588	822(51.8)	1.9(1.6-2.1)	—	—
Questionnaire data					
Education, years					
>12	818	385(47.1)	2.3(2.0-2.7)	1.00(reference)	—
9-12	443	212(47.9)	2.1(1.8-2.4)	1.04(0.88-1.23)	—
≤9	266	141(53.0)	2.1(1.6-2.6)	1.17(0.96-1.41)	—
Other	376	206(54.8)	1.9(1.5-2.2)	1.23(1.04-1.46)	—
Unknown	1492	799(53.6)	1.6(1.4-1.7)	—	—
Cigarette smoking					
Never	815	388(47.6)	2.2(2.1-2.5)	1.00(reference)	—
Ever	1099	557(50.7)	2.0(1.8-2.2)	1.08(0.95-1.23)	—
Unknown	1481	798(53.9)	1.5(1.4-1.7)	—	—
Body mass index (BMI)					
BMI<25 kg/m^2	986	483(49.0)	2.1(1.9-2.3)	1.00(reference)	—
25≤BMI<30 kg/m^2	691	346(50.1)	2.0(1.7-2.3)	1.02(0.89-1.18)	—
BMI≥30 kg/m^2	286	142(49.7)	2.2(1.7-2.7)	1.00(0.83-1.21)	—
Unknown	1432	772(53.9)	1.5(1.4-1.7)	—	—
Self-reported HRT					
Never user	692	329(47.5)	2.2(1.9-2.7)	1.00(reference)	—
Past user	670	353(52.7)	2.0(1.7-2.2)	1.17(1.01-1.36)	—
Current user	179	91(50.8)	1.8(1.3-2.4)	1.09(0.86-1.37)	—
Unknown	1854	970(52.3)	1.7(1.5-1.9)	—	—
Family history of ovarian cancer					
No	1112	557(50.1)	2.1(1.8-2.2)	1.00(reference)	1.00(reference)
Yes	94	62(66.0)	1.3(1.0-1.7)	1.56(1.20-2.02)	1.55(1.19-2.02)
Unknown	2189	1124(51.3)	1.8(1.6-2.0)	—	—
Family history of breast cancer					
No	1551	766(49.4)	2.1(1.9-2.3)	1.00(reference)	—
Yes	382	187(49.0)	2.1(1.8-2.5)	0.99(0.84-1.16)	—
Unknown	1462	790(54.0)	1.5(1.4-1.7)	—	—

Abbreviation: BMI, body mass index; HRT, hormone replacement therapy.

* Time to 25% discontinuation is the time at which 25% of the women discontinued their adjuvant hormone therapy.

† Variables were not included in the multivariable model if they were not significantly associated with discontinuation of adjuvant hormone therapy in the univariable models.

‡ Pre-diagnosis symptom-relieving drugs and hormone replacement therapy were defined as filling at least one prescription of corresponding drugs one year before diagnosis of breast cancer.

Table 2. Early-treatment-stage (first-year) predictors for discontinuation of adjuvant hormone therapy in the following four years among 2 865 breast cancer patients.

	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	P
Therapy type						
Tamoxifen only	1.00	Reference		1.00	Reference	
Aromatase inhibitor only	1.18	1.05 to 1.33	0.005	1.12	0.99 to 1.26	0.066*
Switching therapy	1.62	1.33 to 1.98	<.001	1.50	1.23 to 1.83	<.001*
Symptom-relieving drugs						
Analgesics						
No	1.00	Reference		1.00	Reference	
Yes	1.42	1.27 to 1.58	<.001	1.22	1.08 to 1.37	0.001*
Hypnotics and sedatives						
No	1.00	Reference		1.00	Reference	
Yes	1.43	1.27 to 1.61	<.001	1.21	1.07 to 1.37	0.003*
Antidepressant						
No	1.00	Reference		1.00	Reference	
Yes	1.42	1.24 to 1.62	<.001	1.22	1.06 to 1.40	0.007*
Gastrointestinal drugs						
No	1.00	Reference		1.00	Reference	
Yes	1.44	1.29 to 1.62	<.001	1.27	1.13 to 1.43	<.001*
Number of symptom-relieving drugs						
0	1.00	Reference		1.00	Reference	
1	1.44	1.25 to 1.66	<.001	1.41	1.22 to 1.62	<.001†
2	1.57	1.34 to 1.83	<.001	1.54	1.31 to 1.80	<.001†
3	1.99	1.66 to 2.39	<.001	1.89	1.57 to 2.27	<.001†
4	2.55	1.96 to 3.31	<.001	2.41	1.85 to 3.14	<.001†

Note: Patients discontinued or censored already during the first year of follow-up were excluded in these analyses.

* Adjusting for age at diagnoses, Charlson comorbidity index, family history of ovarian cancer, and all variables listed in this table except for number of symptom-relieving drugs.

† Adjusting for age at diagnoses, Charlson comorbidity index, family history of ovarian cancer, and therapy type.

Fig 1.

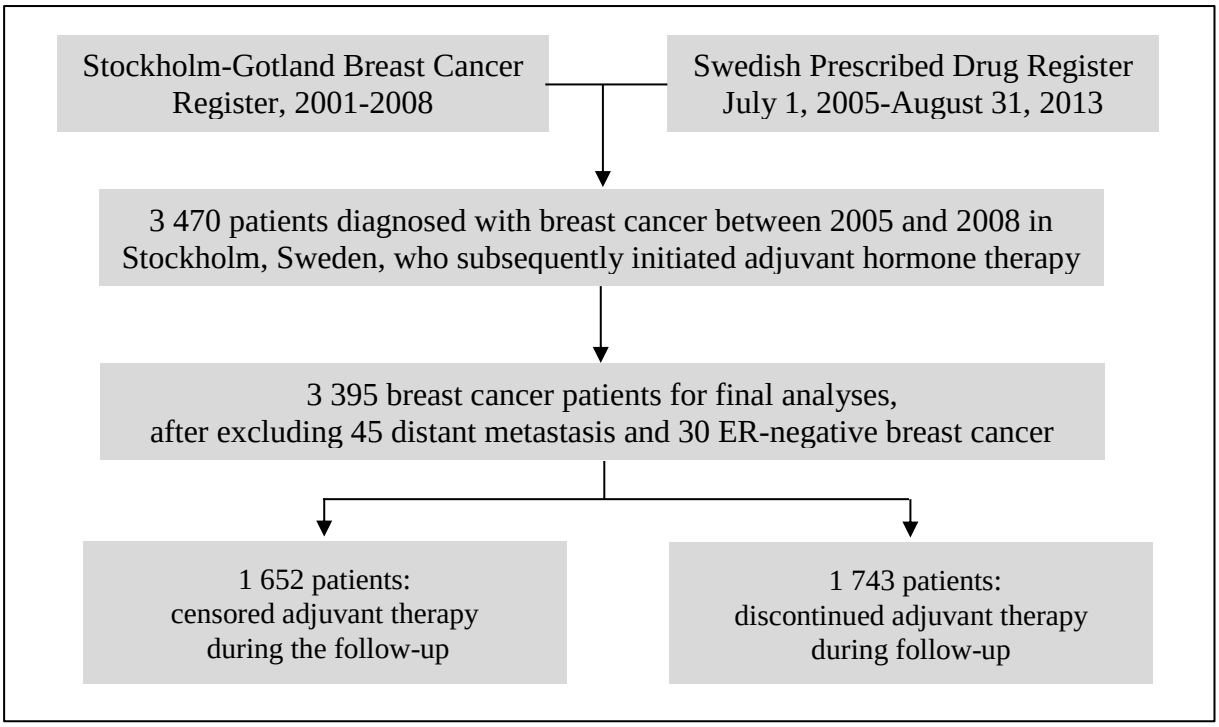

Stockholm-Gotland Breast Cancer Register, 2001-2008
Swedish Prescribed Drug Register July 1, 2005-August 31, 2013
3 470 patients diagnosed with breast cancer between 2005 and 2008 in Stockholm, Sweden, who subsequently initiated adjuvant hormone therapy
3 395 breast cancer patients for final analyses, after excluding 45 distant metastasis and 30 ER-negative breast cancer
1 652 patients: censored adjuvant therapy during the follow-up
1 743 patients: discontinued adjuvant therapy during follow-up

Fig 2

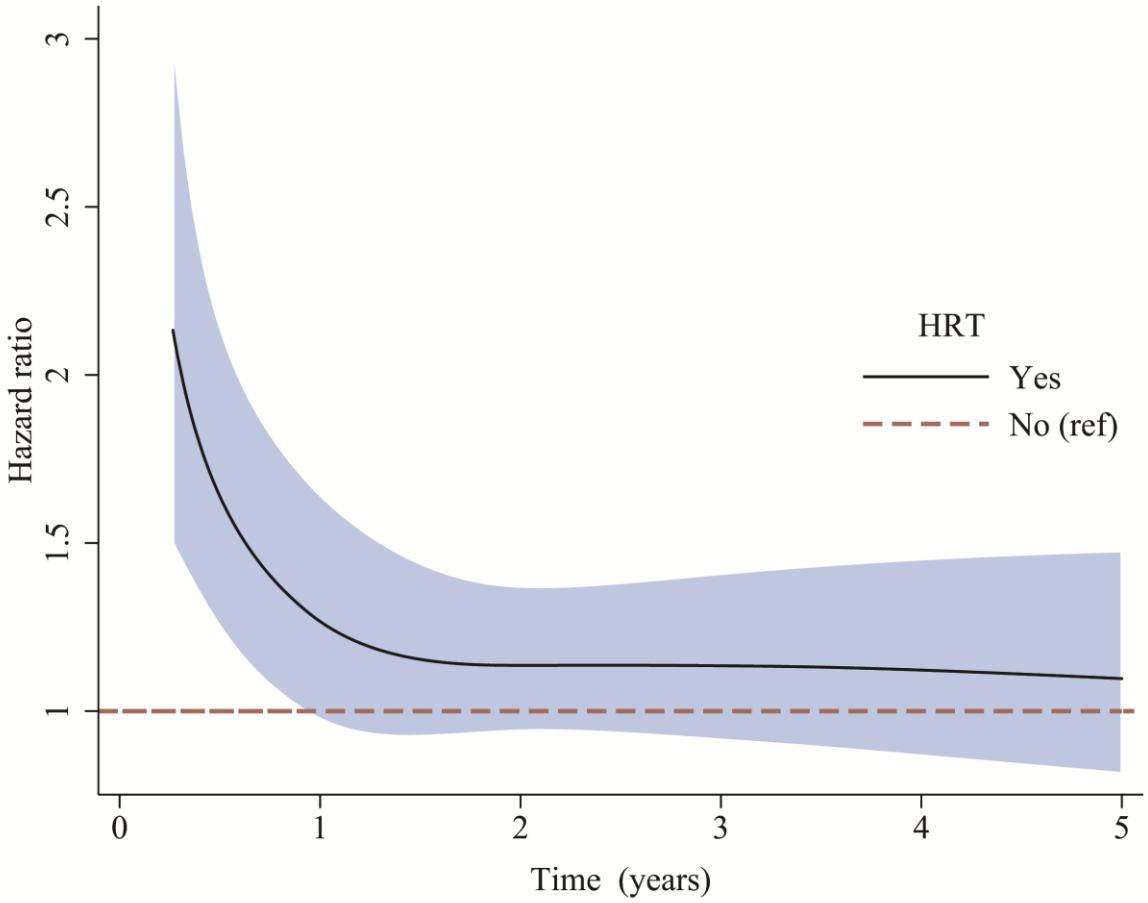
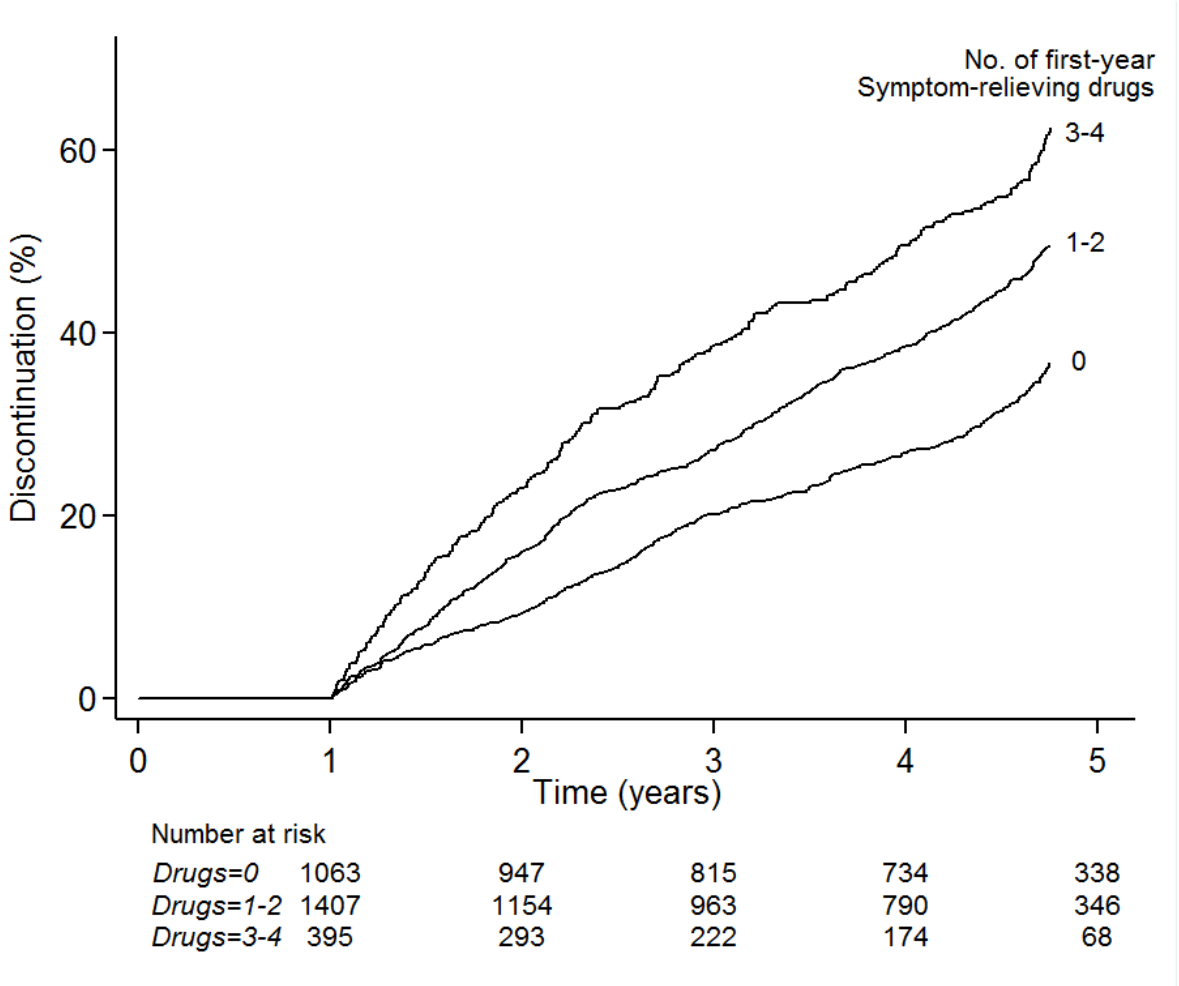


Fig 3


No. of first-year
Symptom-relieving drugs
3-4
1-2
0
Discontinuation (%)
60
40
20
0
0
1
2
3
4
5
Time (years)
Number at risk
Drugs=0 1063 947 815 734 338
Drugs=1-2 1407 1154 963 790 346
Drugs=3-4 395 293 222 174 68