Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: a population-based analysis

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EPIDEMIOLOGY

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Abstract Observational studies on long-term endocrine treatment among breast cancer patients have presented discontinuation rates on tamoxifen, but lack information on the continuance of any endocrine treatment [both tamoxifen and aromatase inhibitors (AIs)] within the same cohort. In this study we determined switching rates from tamoxifen to AIs, discontinuation rates of tamoxifen only, discontinuation rates of any endocrine treatment and determinants of first treatment switch and treatment discontinuation. Patients with early stage breast cancer (stage I–IIIa) starting on tamoxifen were selected from the linked Eindhoven Cancer Registry-PHARMO RLS cohort in the period 1998–2006. Continuous use (allowing a 60 days gap between refills) of tamoxifen only and any endocrine treatment were determined after various follow-up periods: 1, 2, 3, 4, and 5 years. Time to first switch from tamoxifen to an AI was assessed. Cox regression was used to identify determinants of first treatment switch, discontinuation of tamoxifen, and discontinuation of any endocrine treatment. A total of 1,451 new early stage breast cancer patients started on tamoxifen. Of those, 380 had a treatment switch to an AI during follow-up. Of the patients followed for 5 years, 40% continuously used tamoxifen, which was 49% for any endocrine treatment. Older age (older than 70 versus 50–69 years) was independently associated with increased discontinuation of tamoxifen and any endocrine therapy. Patients with two or more concomitant diseases (versus no comorbidity) showed an increased likelihood to stop any endocrine treatment or switch treatment from tamoxifen to an AI. In conclusion, up to half of the breast cancer patients starting tamoxifen continued 5 years of endocrine treatment. Identification of patients at risk of discontinuation will assist in the development of interventions to improve treatment continuation comparable to that of patients included in clinical trials.

Keywords Adjuvant endocrine therapy · Aromatase inhibitors · Discontinuation · Early stage breast cancer · Recurrence · Switching · Tamoxifen

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Introduction

Adjuvant endocrine treatment in women with early stage breast cancer significantly prolongs disease free and overall survival time [1, 2]. For nearly 20 years the antiestrogen tamoxifen was the standard endocrine adjuvant treatment used for postmenopausal women with hormone receptor-positive early stage breast cancer [1]. In the late nineties of the previous century, aromatase inhibitors (AIs) became available for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer. Since about 5 years AIs also have been approved for the adjuvant treatment of women with hormone receptor positive, early stage breast cancer [2].

Discontinuation with endocrine therapy among early stage breast cancer patients in daily practice has become a widespread concern. While breast cancer patients are likely to be highly motivated to continue endocrine treatment [3], many studies using pharmacy, medical, and health insurance records have reported high rates of discontinuation of tamoxifen ranging from 35 to 51% in study periods of 3.5–5 years [4–6].

The question remains whether these patients actually stop endocrine treatment or whether they switch from tamoxifen to an AI. Recently, a study using health insurance records, reported rates of treatment discontinuation of all types of endocrine treatment together (tamoxifen, anastrozole, letrozole, or exemestane): 20% of the women discontinued endocrine treatment after 1 year of follow-up [7]. Moreover, one recent chart review reported next to treatment discontinuation, results on switching from first-line endocrine therapy [8]. However, to our knowledge there are no published studies with 5 years of follow-up, in which discontinuation rates on both tamoxifen only and any endocrine treatment have been studied.

Among early stage breast cancer patients we determined the following during the first 5 years after start of tamoxifen: switching rates from tamoxifen to AIs, discontinuation rates of tamoxifen only, discontinuation rates of any endocrine treatment and determinants of first treatment switch and treatment discontinuation. For a subcohort of patients, the date of first breast cancer recurrence was studied in relation to the date of discontinuation of tamoxifen or switch from tamoxifen to an AI.

Methods

Data source

Data were obtained from the Eindhoven Cancer Registry (ECR) linked on a patient level to the PHARMO Record Linkage System (PHARMO RLS) covering a demographic region in the southeastern part of the Netherlands of approximately 1 million inhabitants. The construct, validity, and contents of the PHARMO-ECR cohort are described elsewhere [9].

Study population

The source population included all women registered in the PHARMO-ECR cohort in the period 1998–2006 diagnosed with early stage breast cancer (stage I–IIIa). Of these, it was determined whether they started endocrine treatment (cohort entry date) in the first year after diagnosis. Patients were followed from the cohort entry date onwards and were censored at time of hospitalization for cancer other than breast cancer (ICD-9-CM codes 140-230 excl. 174, 196, 197, 198, or 199), death, loss to follow-up in the PHARMO RLS, or end of study period (December 31, 2007), whichever occurred first.

Endocrine treatment of early stage breast cancer

In our study period, 5 years of tamoxifen only, 5 years of AIs (anastrozole, letrozole, and exemestane) or sequential therapy of 2–3 years of tamoxifen followed by 3–2 years of AIs were advised in the Dutch guidelines. Treatment choice was dependent on the patient characteristics such as menopausal status and tumor characteristics such as Her2/neu status. Patients intolerant of one type of endocrine therapy were advised 5 years of treatment with the other [10, 11]. As starting on AI was advised in the guidelines from 2004 onwards, patients starting on AI were excluded from further analyses as they did not have 5 years of follow-up time.

Treatment discontinuation and switching

Treatment continuation is defined as the percentage of patients who used the drug during a specific period of time without failure to continue renewals [12, 13]. In this study, treatment continuation was assessed using episodes of endocrine treatment based on the method published by Catalan and LeLorier [14]. To assemble endocrine treatment episodes, the duration of use of each dispensing was calculated by dividing the number of units dispensed by the number of units to be used per day, as defined in the pharmacies. In case of an interruption between two dispensings, the episode was considered uninterrupted if the duration of this gap was less than the permissible gap of 60 days [6]. We additionally performed sensitivity

analyses allowing a gap of 90 days [7] and 180 days [4, 5]. The treatment episode was measured as the time span between the start of the first dispensing until the end of the final dispensing. The latter was set at half the duration of time after the last date that the drug was dispensed, with the assumption that patients stopped their medication somewhere in time after filling their last prescription. Treatment continuation with tamoxifen was defined as the number of days from start of therapy (cohort entry date) to the date of first failure to continue renewals of tamoxifen (end date of the first treatment episode) or the start date of an AI (switch), whichever occurred first. In addition, we assessed treatment continuation with any endocrine therapy (irrespective of type of treatment; tamoxifen or AIs), i.e., the number of days of continuous use of any endocrine therapy from cohort entry date onwards. Treatment episodes of continuous use of tamoxifen (initial treatment) and any endocrine therapy were defined up to 5 years, following the guidelines [10, 11].

Determinants of treatment discontinuation

The following potential determinants of discontinuation of tamoxifen, first treatment switch, and discontinuation of any endocrine treatment were considered, based on available information in the PHARMO-ECR cohort, clinical knowledge and recently published studies [4, 6, 15–17]: age, hormone receptor status, tumor size, lymph node status, histologic tumor grade, treatments other than endocrine treatment (surgery, chemotherapy, and radiation therapy), comorbidity at diagnosis according to a slightly modified version of the Charlson classification [18], drug treatment in the year before cohort entry, the number of different drug classes used (anatomical classes ATC level 1, excluding use of endocrine treatment) and socioeconomic status.

Breast cancer recurrence

Since 1989, the Eindhoven Cancer Registry has recorded follow-up information for a subcohort of breast cancer patients diagnosed in the eastern part of the region. Follow-up information included the date and site of local, regional, and distant recurrence. In contrast to the actively performed data collection on diagnosis and treatment of the primary tumor, this follow-up information is a passive registration. Histologic or cytologic confirmed breast cancer recurrences are provided by the pathology departments and assumed to be complete. However, information on breast cancer recurrences without a cytologic or histologic confirmation had to be provided by surgeons, radiotherapists, and oncologist and was not actively collected. This means that there was an unknown amount of underreporting. No breast cancer recurrence can mean that a woman was indeed disease free or that the data is missing. For the patients included in our study population, date of the first reported breast cancer recurrence was defined when recorded before loss to follow-up in the PHARMO RLS, or end of study period (December 31, 2007).

Analyses

Baseline and treatment characteristics of early stage breast cancer patients who did not switch (tamoxifen use only) and patients who switched to an AI were compared using the Chi-square test. Survival functions describing the proportion of continuous drug users over time for (a) tamoxifen use only or (b) any endocrine treatment were computed using Kaplan–Meier survival analyses with treatment discontinuation or—in case of tamoxifen use only—switch to an AI, considered as elimination and censoring patients who were considered lost to follow-up. Rates of endocrine treatment discontinuation were determined at 1, 2, 3, 4, and 5 years after start tamoxifen treatment. Cox proportional hazards regression models were used to identify independent determinants of discontinuation of tamoxifen, switch to an AI, or discontinuation of any endocrine treatment within 5 years after start of treatment (cohort entry date). Adjusted hazard ratios (HR) and 95% confidence intervals (CI) are presented for independent variables, with variables associated with treatment change (discontinuance or switch) in the univariate analyses included in the multivariate analyses. Statistical significance was defined at an alpha level of 0.05. For a subcohort of patients with data on breast cancer recurrence, the date of first breast cancer recurrence was set out against the date of first treatment change: either stop with endocrine (tamoxifen) treatment or switch to an AI and the linear correlation between these dates was determined using the Pearson correlation test. Data were analyzed using SAS programs that are organized within SAS Enterprise Guide version 4.1 (SAS Institute Inc., Cary, NC, USA). Data management was conducted under UNIX using SAS version 9.1.

Results

The PHARMO-ECR cohort included 4,917 women diagnosed with early stage breast cancer in the period 1998–2006 of whom 1,725 (35%) started endocrine treatment in the first year after diagnosis (Fig. 1). The median duration

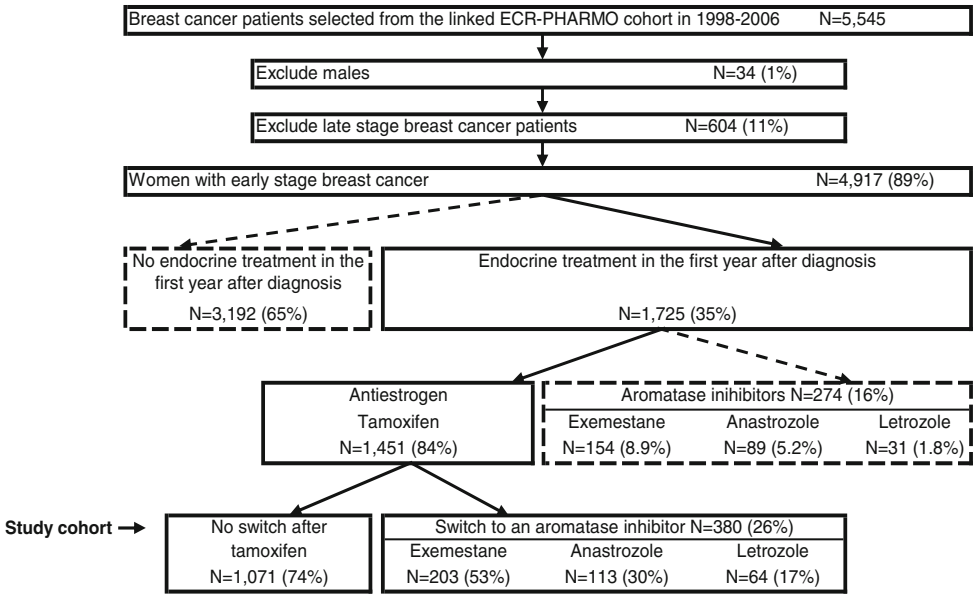

Fig. 1 Flowchart patient selection

(interquartile range) between diagnosis and start of endocrine treatment was 2 (1–5) months. Of the 1,725 patients, 1,451 (84%) started on tamoxifen and 274 (16%) started treatment with an AI. There were no patients who started on the antiestrogen fulvestrant or the AI aminoglutethimide in the first year after diagnosis. The 1,451 patients starting on tamoxifen were included in the study cohort. They had a mean follow-up of 4.1 ± 2.4 years in the PHARMO RLS. Patients were censored at time of hospitalization for cancer other than breast cancer (7%), death (15%), loss to follow-up in the PHARMO RLS (17%), or end of study period at December 31, 2007 (61%).

Of the patients who started on tamoxifen, 380 (26%) switched to an AI during follow-up (Table 1). Patients who switched to an AI were younger than patients who used tamoxifen only; mean age (±SD) of 57 (±12) years versus 62 (±15) years ($P < 0.0001$). They started treatment in the more recent years, had received more often surgery, chemotherapy and radiotherapy, had used more different classes of drugs in the year after starting on tamoxifen and had a higher socioeconomic status. When not taking into account the proportion of patients with an unknown lymph node status, there was no difference in lymph node status between patients who only used tamoxifen and patients who switched to an AI.

The percentage of continuous users of tamoxifen only ($N = 1,071$) at 1, 2, 3, 4, and 5 years was 83, 70, 55, 50, and 40%, respectively (Fig. 2a). Sensitivity analyses showed that allowing a gap of 90 or 180 days instead of 60 days increased the percentage of continuous users of tamoxifen at 5 years; 50 and 56%, respectively. Of the 380 patients who switched to an AI, the largest decrease in continuance of tamoxifen (switch to an AI) was shown in the period from 2 to 3 years: from 55 to 25%. The mean duration (±SD) of tamoxifen use until switch was 1.9 ± 1.2 years until switch to anastrozole, 2.0 ± 1.3 years until switch to exemestane and 2.1 ± 1.4 years until switch to letrozole.

The percentage of continuous users of any endocrine treatment at 1, 2, 3, 4, and 5 years was 87, 78, 69, 63, and 49%, respectively (Fig. 2b). Allowing a gap of 90 or 180 days instead of 60 days showed an increase of the percentage of continuous users of any endocrine treatment at 5 years; 59 and 66%, respectively.

Multivariate analyses in Table 2 show that patients who did not continue tamoxifen were less likely to be aged 50–69 years (vs. ≥70 years; hazard ratio (HR) = 0.74; 95% CI: 0.61–0.90). This was also seen for discontinuation of any endocrine therapy (50–69 years vs. ≥70 years; HR = 0.71; 95% CI: 0.59–0.85). Moreover, multivariate analyses showed that patients who did not continue any endocrine therapy were more likely to have two or more concomitant diseases (vs. no comorbidity; HR = 1.58; 95% CI: 1.10–2.25). Multivariate analyses of switch from tamoxifen to an AI showed that women with one or multiple comorbidities were more likely to switch from tamoxifen to an AI than patients without comorbidities at diagnosis: HR = 2.08 (95% CI: 1.01–4.31) for patients with one comorbidity and HR = 4.56 (95% CI: 1.96–10.6) for patients with two or more comorbidities.

Of the 1,451 patients starting on tamoxifen, 98 patients were known to have developed a breast cancer recurrence during follow-up. For these patients, the date of first treatment change (either stop or switch) was set out against

Table 1 Characteristics at diagnosis of early stage breast cancer patients, by type of endocrine treatment

Characteristics at diagnosis	Tamoxifen only and no switch ($N = 1,071$) (%)	Tamoxifen and switch to aromatase inhibitor ($N = 380$) (%)	*P*-value
Age (years)			
≤35	2	2	<0.0001
36–49	21	26	
50–59	21	31	
60–69	21	23	
≥70	35	18	
Period of diagnosis			
1998–2001	46	26	<0.0001
2002–2003	20	39	
2004–2006	34	35	
Hormone receptor status			
ER+ and/or PR+	76	81	0.187
ER− and PR−	2	1	
Unknown	22	18	
Tumor size (cm)			
≤1.0	9	7	0.503
1.1–2.0	39	40	
2.1–5.0	46	47	
>5.0	5	6	
Lymph node status			
Positive	29	27	0.001
Negative	66	72	
Unknown	6	1	
Histologic tumor grade			
Well	15	15	0.133
Moderate	32	32	
Poor	21	26	
Unknown	32	27	
Therapies other than endocrine			
Surgery (yes)	96	99	0.004
Chemotherapy (yes)	31	46	<0.0001
Radiotherapy (yes)	65	74	0.002
Number of comorbidities at diagnosis			
None	82	82	0.522
1	4	4	
≥2	4	3	
Unknown	10	11	
Most frequent comorbidities at diagnosis			
Lung disease	4	5	0.670
Cardiovascular disease (incl. hypertension)	26	20	0.094
Diabetes	8	6	0.372
Number of different drug classes used in the year after start tamoxifen			
0–1 class	8	1	<0.0001
2–3 classes	12	15	
4–5 classes	24	32	
≥6 classes	24	26	
Unknown[a]	31	27	
Socioeconomic status			
High	28	34	0.030
Intermediate	39	39	
Low	26	23	
Institutionalized (nursing homes)	6	2	
Unknown	1	1	

ER estrogen receptor, *PR* progesterone receptor

[a] Not able to define number of drug classes used in the year after cohort entry as patients were not registered for 1 year or more in the PHARMO RLS after cohort entry

the date of first breast cancer recurrence (Fig. 3a, b). The average time (±SD) from cohort entry until first breast cancer recurrence was 2.8 (±1.8) years. Of the 56 women with a breast cancer recurrence who stopped with endocrine treatment ($N = 21$ with a local/regional recurrence and $N = 35$ with a distant recurrence), the date of stop and date of recurrence were significantly correlated ($r = 0.74$, $P < 0.0001$). Of the 42 women with a breast cancer recurrence who switched from tamoxifen to an AI during follow-up ($N = 12$ with a local/regional recurrence and $N = 30$ with a distant recurrence), the date of switch and date of recurrence were even more significantly correlated ($r = 0.93$, $P < 0.0001$).

Discussion

This observational study showed that in daily practice 40–56% of patients with early stage breast cancer continuously used tamoxifen over a 5 year follow-up period, allowing a permissible gap of 60–180 days, respectively. When evaluating the use of all types of endocrine treatment together (tamoxifen, anastrozole, letrozole, or exemestane) and allowing patients to switch endocrine treatment multiple times, the percentage of patients continuously using any endocrine treatment over a 5 year follow-up period was still only 49–66%. Increasing the permissible gap from

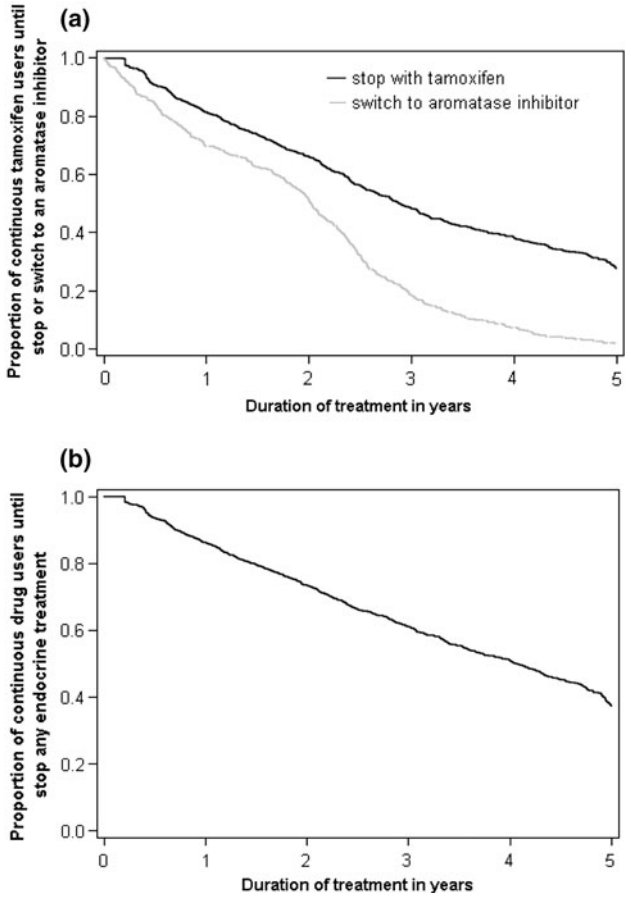

Fig. 2 Proportion of early stage breast cancer patients who start tamoxifen therapy: **a** continue tamoxifen over a 5-year follow-up period until first treatment change: stop with tamoxifen treatment ($N = 1{,}071$) or switch to an aromatase inhibitor ($N = 380$); **b** continue any endocrine treatment (irrespective of type of endocrine treatment) over a 5-year follow-up period ($N = 1{,}451$)

60 to 180 days indicates that around 15% of the patients restart treatment during 5 years of follow-up.

To date, multiple clinical trials have demonstrated that 5 year use of adjuvant endocrine treatment among patients with hormone receptor positive, early stage breast cancer improves disease free and overall survival [1, 19, 20]. However, high discontinuation rates as reported in this observational study, lower the benefit found in clinical trials. These high discontinuation rates were also found in previous studies on tamoxifen use using pharmacy, medical, and insurance records [4–6], especially when the same permissible gap and study follow-up period were taken into account.

In this study, older age (older than 70 vs. 50–69 years) was independently associated with increased discontinuation of tamoxifen. Other studies also found that extremes of age (under 45 and over 75) were associated with tamoxifen discontinuation and non-adherence [4, 6, 15–17]. For any endocrine therapy, having two or more concomitant diseases versus no comorbidity was, next to older age, also associated with an increased likelihood to discontinue any endocrine therapy. Owusu et al. [6] found that an increase in Charlson comorbidity index at 3 years from diagnosis was related with an increased likelihood to discontinue tamoxifen treatment, suggesting that patients discontinue treatment due to other life threatening diseases.

Previous studies using self-report questionnaires or telephone interviews on non-adherence or discontinuation of tamoxifen have reported that reasons for discontinuation vary, ranging from treatment related side effects, simply forgetting to take the medication, to lack of confidence in prescribed endocrine treatment [3, 15, 16, 21–25]. Psychological factors, particularly depression and anxiety also seem to contribute to treatment discontinuation. However, in our study we did not find an increased likelihood to discontinue endocrine treatment among women who received antidepressants in the year before tamoxifen initiation (10% of the women included in the study cohort).

The observational study of McCowan et al. [5] showed that decreased duration of tamoxifen use in daily practice increased the risk of all cause mortality. However, the influence of breast cancer recurrence on the decision to stop with tamoxifen could not be established, as the authors commented this to be difficult to ascertain within a community setting [5]. In our study, data on breast cancer recurrence were only available for a subcohort, due to the fact that no active follow-up had taken place of the patients documented by the Eindhoven Cancer Registry. Nevertheless, presenting the date of first breast cancer recurrence and date of stop with tamoxifen treatment showed that most patients with a breast cancer recurrence stopped tamoxifen treatment. Future observational database studies should report whether they have information on breast cancer recurrence and/or exclude these patients from further analyses, as has been done in previous interview and questionnaire studies [21, 23].

Of the patients who switched treatment from tamoxifen to an AI, most switched after 2–3 years of tamoxifen use. This is in accordance with the guidelines advising switching of treatment in this period and this is also reported in a recent performed retrospective chart review [8]. Switching to an AI within 2 years after starting on tamoxifen could be due to intolerability to tamoxifen and switching within 2 years or after 3 years of tamoxifen treatment could be due to, among other things, a breast cancer recurrence. In our study, patients having one or more concomitant diseases versus no comorbidity were more likely to switch from tamoxifen to an AI. Moreover, we found a strong correlation between date of breast cancer recurrence and date of switch. Schwartzberg and colleagues [8] performed exploratory telephone interviews to

Table 2 Determinants of discontinuation of tamoxifen due to stop of endocrine treatment or switch to an aromatase inhibitor and stop with any endocrine therapy within 5 years after start

Characteristics	Early stage breast cancer patients who start tamoxifen therapy		
	Stop with tamoxifen treatment ($N = 1{,}071$)	Switch to an aromatase inhibitor ($N = 380$)	Total, stop with any endocrine treatment ($N = 1{,}451$)
	HR adjusted[#] (95% CI)	HR adjusted[#] (95% CI)	HR adjusted[#] (95% CI)
Age at diagnosis (years)			
≤49	0.83 (0.65–1.05)	0.77 (0.46–1.30)	0.77 (0.60–1.01)
50–69	0.74 (0.61–0.90)	0.83 (0.53–1.28)	0.71 (0.59–0.85)
≥70	1	1	1
Tumor size (cm)			
≤1.0	1		1
1.1–2.0	0.98 (0.72–1.34)		0.96 (0.72–1.27)
2.1–5.0	1.12 (0.82–1.53)		1.05 (0.79–1.39)
>5.0	1.45 (0.93–2.26)		1.28 (0.86–1.91)
Number of comorbidities at diagnosis			
None	1	1	1
1	0.87 (0.55–1.39)	2.08 (1.01–4.31)	1.03 (0.70–1.53)
≥2	1.30 (0.88–1.92)	4.56 (1.96–10.6)	1.58 (1.10–2.25)
Unknown	0.83 (0.61–1.12)	1.44 (0.88–2.35)	0.93 (0.72–1.20)
Number of different drug classes used in the year after start tamoxifen			
0–1 class	1	1	1
2–3 classes	0.82 (0.62–1.07)	1.04 (0.58–1.85)	0.82 (0.64–1.05)
4–5 classes	0.89 (0.68–1.17)	1.42 (0.79–2.53)	0.96 (0.75–1.23)
≥6 classes	1.15 (0.89–1.49)	1.68 (0.95–2.98)	1.21 (0.96–1.54)
Socioeconomic status			
High			1
Intermediate			1.00 (0.83–1.21)
Low			1.11 (0.91–1.37)
Institutionalized or unknown			1.08 (0.76–1.54)

HR hazard ratio, *CI* confidence interval

[#] Adjusted for variables potentially associated with discontinuance in the crude analyses ($P < 0.05$)

determine reasons for switching and nearly all patients cited doctor recommendation or side effects as a reason for switching.

In this study, we were only able to report discontinuation rates of patients starting on tamoxifen as at the moment of the study, patients starting on AIs had too short follow-up time to be able to report 5 year discontinuation rates. While several studies have reported treatment discontinuation rates of patients starting with AIs after 1 year of follow-up [7, 26, 27], long-term observational studies are needed in the future to determine treatment continuation and switching patterns during 5 years of follow-up of patients starting on AIs.

This study reports results of observational data, however, some of the patients included in our study cohort might be included in a post-marketing multinational trial [28]. As a result, continuous use of endocrine treatment among these patients might be increased compared to the rates found in daily practice. However, in this study we still found high overall discontinuation rates of endocrine treatment.

From the results of this study we conclude that up to half of the women to whom adjuvant tamoxifen treatment was prescribed stop taking tamoxifen before the end of the recommended treatment period of 5 years. Even after increasing the permissible gap and allowing multiple switching to other endocrine therapies, the rate of patients who discontinue endocrine treatment remained high. These high discontinuation rates lower the benefit of adjuvant endocrine treatment among women with hormone receptor positive, early stage breast cancer on disease free and overall survival found in clinical trials. Identification of patients at risk of discontinuation of endocrine treatment, either or not intentionally, may help to improve treatment continuation.

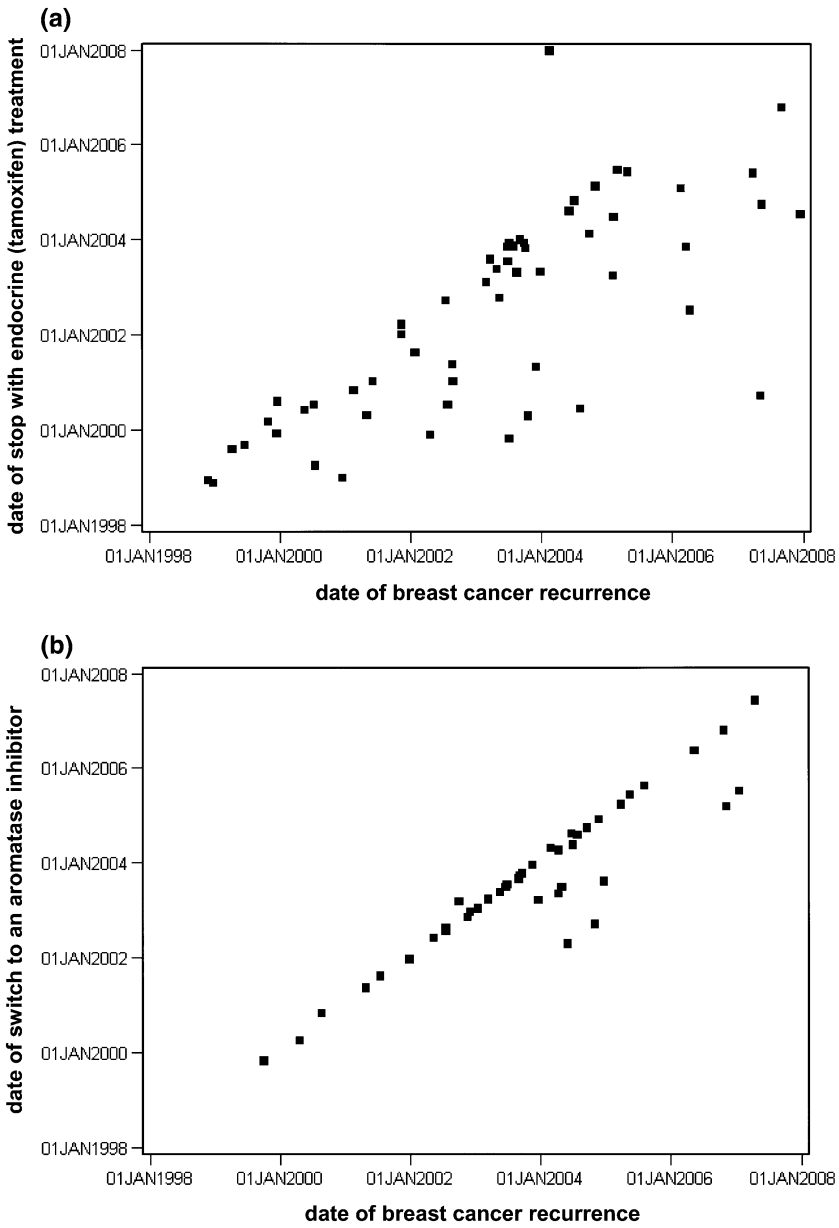

Fig. 3 Of the patients of whom a breast cancer recurrence was reported during follow-up ($N = 98$) the date of first treatment change was set out against the date of first breast cancer recurrence. With treatment change defined as **a** stop with endocrine (tamoxifen) treatment ($N = 56$) or **b** switch to an aromatase inhibitor ($N = 42$)

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