

ORIGINAL ARTICLE



Good adherence to adjuvant endocrine therapy in early breast cancer – a population-based study based on the Swedish Prescribed Drug Register

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ABSTRACT

Introduction: Adjuvant endocrine therapy improves recurrence-free and overall survival in primary breast cancer. However, not all patients complete their planned treatment, mostly because of side-effects. The aim of this study was to examine the adherence to adjuvant endocrine therapy in a cohort of primary breast cancer patients in Region Jönköping County, Sweden, after 3 and 5 years.

Material and methods: The Swedish Breast Cancer Register was used to identify patients diagnosed with hormone receptor positive breast cancer in Region Jönköping County between 2009 and 2012. Adherence was evaluated based on data from the Swedish Prescribed Drug Register, and Medication Possession Ratio (MPR), defined as the days' supply of medication during the period from the first dispensing till the last dispensing in the time period (3 and 5 years), divided by number of days. Adherence was defined as $MPR \geq 80\%$. Regression analyses were used to identify subgroups associated with adherence; age, type of endocrine treatment, additional adjuvant therapy, and hospital responsible for the follow-up (Eksjö, Jönköping, and Värnamo).

Results: We identified 634 patients who were recommended adjuvant endocrine therapy and to be able to estimate adherence after 3 and 5 years, 488 patients were included in the analysis. After 3 years of treatment, 91.2% of the patients (95% confidence interval (CI) 88.7–93.6; $n = 445$), were found to be adherent. The corresponding figure for the 271 patients who had completed 5 years of treatment was 91.5% (95% CI 88.2–94.8; $n = 248$). No subgroups (age, endocrine therapy, radio/chemotherapy, or hospital) were significantly associated with adherence in the multiple logistic regression analysis.

Discussion: This study shows substantially higher adherence to adjuvant endocrine therapy than previously reported. Reasons for this could be differences in routines for therapy information and follow-up, but this needs to be further investigated.

ARTICLE HISTORY

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Introduction

Approximately 85% of all primary breast cancers express estrogen receptors (ER) and these patients are generally recommended adjuvant endocrine therapy, such as tamoxifen or an aromatase inhibitor (AI) [1,2]. Tamoxifen inhibits ER-positive breast cancer by competitively binding to ER and is effective irrespective of menopausal status. AIs inhibit the aromatase enzyme thereby reducing estrogen levels in the blood. To be effective in premenopausal women, AIs have to be combined with ovarian suppression to inhibit the positive feedback system regulated by the hypothalamus and the pituitary gland [3,4].

Five years of tamoxifen reduces the recurrence rate by 39% at 15 years in patients with ER-positive breast cancer, compared with no endocrine therapy, and the corresponding figure regarding breast cancer mortality is 30% [5]. AI is significantly more effective compared with tamoxifen in postmenopausal women [6]. Nowadays, extended treatment is

often recommended to patients with a higher risk of recurrence [7–10]. A recent meta-analysis has shown a risk of recurrence and breast cancer mortality up to 20 years, in patients treated with 5 years of adjuvant tamoxifen therapy, strongly correlated to tumor size and nodal status [11].

Despite the positive effects of endocrine treatment, many patients stop taking their prescribed medicine, mostly because of side-effects. Tamoxifen and AIs have side effects similar to those often seen in menopause, such as hot flashes and vaginal dryness. Musculoskeletal symptoms may be associated with both drugs, but are more frequently reported during treatment with AIs [12]. Moreover, AIs increase the risk of osteoporosis and bone fractures and the risk of these events increases with longer treatment [6]. Tamoxifen is associated with an increased incidence of venous thromboembolism as well as proliferative endometrial abnormalities with increased risk of endometrial cancer [13,14].

Previous studies investigating the adherence to endocrine therapy in breast cancer differ in their methods

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and definitions. They may be based on pharmacy databases, medical record reviews, patient self-reports, interviews, prospective trials, or assessments of drug concentrations. Studies based on register/databases report a wide range of adherence [15–17].

Region Jönköping County has a population of approximately 340,000 and about 300 patients are diagnosed with primary breast cancer each year, including DCIS (ductal carcinoma *in situ*). As a result of centralization of breast cancer care in the region, the Department of Oncology, County Hospital Ryhov, Jönköping, has been responsible for the follow-up of all patients with invasive breast cancer since 2016. However, before that the responsibility for follow-up was shared between all three hospitals in the region; the Department of Oncology, County Hospital Ryhov, Jönköping, the Department of Surgery, Highland Hospital, Eksjö, and the Department of Surgery, Värnamo Hospital, Värnamo.

The aim of this study was to examine the adherence to adjuvant endocrine treatment in Region Jönköping County, Sweden, after 3 and 5 years, in patients diagnosed with primary breast cancer between 2009 and 2012. A secondary aim was to investigate the adherence in different subgroups.

Material and methods

Definition of adherence

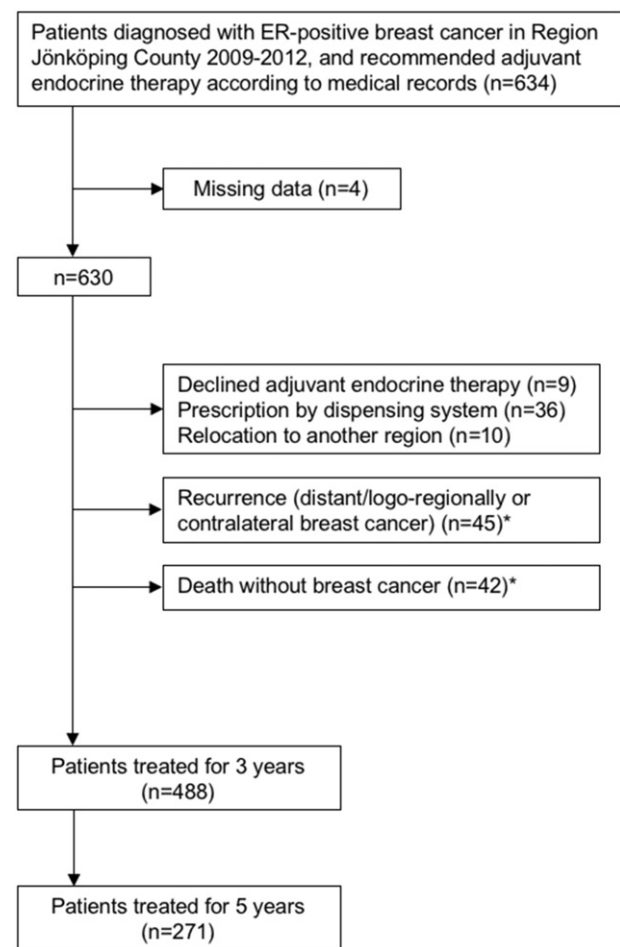
Different terms are used for specifying how well patients follow prescription recommendations. Adherence, compliance, and persistence are terms often used in studies for this purpose. The word adherence will be used in this article, indicating the extent to which patients follow the recommendation of endocrine treatment for a specific time period. MPR (Medication Possession Ratio) is a common definition in adherence analyses and implies the ratio of total days' supply to the number of days in the observation period. The lower limit of $\geq 80\%$ is often used to define if the patient is adherent [18]. We, therefore, chose to define adherence as coverage by available medication of at least 80% of the days during the 3-year and 5-year periods.

Patients and methods

The Swedish Breast Cancer Register contains information of patient and tumor characteristics, adjuvant therapy, and follow-up data [19]. Patients who were diagnosed with ER-positive breast cancer in Region Jönköping County between 1 January 2009 and 31 December 2012, were identified using the Swedish Breast Cancer Register ($n=802$). Review of medical records was performed to identify patients that were recommended adjuvant therapy ($n=634$). According to the former Swedish guidelines, patients were generally recommended adjuvant therapy if they had an ER-positive tumor >10 mm and/or lymph node positivity. Forty-five patients were excluded because they either declined adjuvant endocrine treatment ($n=9$) or were prescribed the treatment by a dispensing system ($n=36$). As our aim was to investigate adherence in our region after the specific time points of 3 and 5 years, and not adherence up to any event that would imply end of treatment or lost to follow-up,

patients were also excluded for the following reasons; relocation to another health care region ($n=10$), death without breast cancer during follow-up ($n=42$), and recurrence or contralateral breast cancer during the planned treatment period ($n=45$), as this was expected to alter treatment recommendations. However, as a post-hoc analysis, medical records for the excluded patients were reviewed to estimate the impact of the exclusion. Another four patients were accidentally not included in the adherent analyses for the following reasons; dispersing system initiated after 5 years of treatment, ER-negative contralateral relapse, relocation to another region although Region Jönköping County still prescribed treatment, and one was missed in the prescription data request. In total, 488 patients were included in the analyses (Figure 1).

The routines for follow-up differed slightly among the different hospitals. Generally, at the start of treatment the patients were carefully informed about the endocrine therapy effects and side effects. Written information was handed out, and the patients were encouraged to contact the clinical department for discussion of treatment issues. After 1 year, there was a follow-up visit to a doctor, and a yearly



* Twenty-three of these could have been included in the 3-year analysis. Post-hoc analysis has been done to further investigate the effect of this exclusion.

Figure 1. Flow chart of the inclusion and exclusion of patients.

mammography was performed. At the Department of Surgery, Eksjö, a nurse contacted the patient after 3 months and yearly to give the mammography results and at the same time follow up on the endocrine treatment and make sure a new prescription was available. At the Department of Surgery, Värnamo, the doctor yearly wrote a letter to inform the patient about the mammography results and that a new prescription of the endocrine drug had been prescribed. At the Department of Oncology, Jönköping, a nurse initially called patients once a year for support, but this follow up was ended in 2013. According to our new local guidelines, patients are encouraged to call the clinic for support and if they have any questions as well as for new prescriptions, and they are asked not to stop therapy without discussing it with their oncology nurse or treating physician.

The Swedish prescribed drug register

The Swedish Prescribed Drug Register has been in use since 1 July 2005 and contains data about a patient's prescribed drugs, such as costs, dates of prescription and dispensing, Anatomical Therapeutic Chemical Classification (ATC)-codes, active substances, number of packages and Defined Daily Doses (DDD) [20]. Drugs are coded according to the ATC-code. DDD is the average daily dose when the drug is used according to its main indication. It is a technical measurement used in statistical analyses and is often used in combination with the ATC-system. For the present study, data regarding the following information were retrieved; dates of prescription and dispensing, number of packages, ATC-code, product name, substance name, DDD for each prescription, and DDD for each package (28 October 2016). We chose to focus on the adherence of oral endocrine treatment, and therefore, omitted to include information regarding GnRH-analogues.

Ethics

This study was approved by the Regional Ethical Review Board in Linköping, registration number 2016/61-31 (approved 24 February 2016).

Statistical analysis

Our primary endpoint was adherence after 3 and 5 years. We used the date of the first prescription to determine the treatment periods of 3 and 5 years. All collected medications from the first dispensing till the last one before the end date in the respective time periods were added and the total DDD for all endocrine drugs were summarized. The sum was divided by the days in the time period (3×365 or 5×365 d). Patients were defined as adherent if this ratio was $\geq 80\%$ for the 3-year and 5-year periods. As data cutoff from the drug register was 28 October 2016, patients who collected their first prescription after 28 October 2011 were not included in the 5-year analysis. Bootstrapping (resampling 1000 times)

was used to calculate confidence interval (CI) for adherence of the 3-year and 5-year analyses.

To estimate the degree of non-adherence, the MPR of the non-adherent population was subdivided into three different subgroups; 0–30%, 31–60%, and 61–79% and the percentage distribution was calculated.

The following subgroups were investigated; age at time for diagnosis (<40 , 40–59, 60–79, ≥ 80), adjuvant radiotherapy (yes/no), adjuvant chemotherapy (yes/no), hospital responsible for the follow-up; (Eksjö/Jönköping/Värnamo), and treatment category (AI/tamoxifen/sequenced tamoxifen and AI). In patients who had been treated for <5 years, the type of endocrine prescribed during the first 3 years was recorded in the sub-group analysis. If a patient had switched endocrine treatment at any point during the period, the patient was recorded as having sequenced therapy. To calculate predictors of adherence, binary logistic regression analyses were performed to estimate odds ratios (ORs), corresponding confidence intervals and p-values. Both univariate and multiple logistic regression analyses were performed. Microsoft Excel 2010 and 2016 and IBM® SPSS® Statistics Version 24 (SPSS, Chicago, IL, USA) were used to handle data and perform calculations.

Results

Of the 488 patients who had been treated for 3 years, 91.2% (95% CI 88.7–93.6; $n = 445$) were defined as adherent. Of the 271 patients who had reached a treatment period of 5 years, 91.5% (95% CI 88.2–94.8; $n = 248$) were defined as adherent for the full treatment period (Figure 2).

Radiotherapy was significantly associated with adherence in the 3-year analysis according to univariate regression (OR 1.9, 95% CI (1.0–3.6), $p = .041$). However, multiple logistic regression analyses did not find any significant association (p values $\geq .05$) with age at time of diagnosis, the type of endocrine treatment, if radio/chemotherapy was/were given or to the hospital responsible for the follow-up (Table 1(A, B)). The analysis of the degree of non-adherence is presented as descriptive data (Table 2).

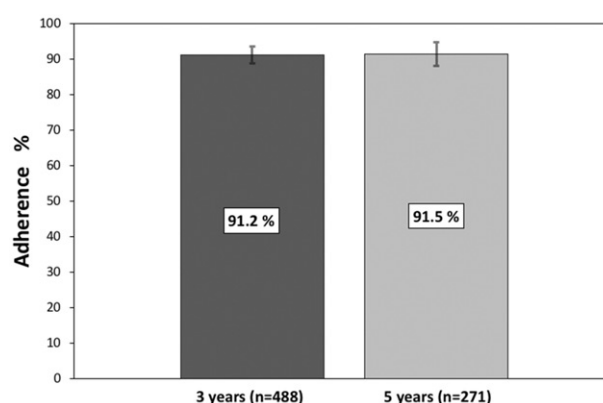


Figure 2. Percentage of patients adherent to endocrine treatment after 3 years (91.2%; 95% CI 88.7–93.6) and 5 years (91.5%; 95% CI 88.2–94.8), respectively.

Table 1(A). Predictors of adherence to adjuvant endocrine treatment after 3 years ($n = 488$) according to univariate and multiple logistic regression.

Characteristic	Adherent no. (%)	Non-adherent no. (%)	OR (95% CI) univariate	<i>p</i> Value	OR (95 % CI) multiple ^b	<i>p</i> Value
Total	445 (91.2)	43 (8.8)	(88.7–93.6)			
Hospital						
Jönköping ($n = 227$)	206 (90.7)	21 (9.3)	Ref.		Ref.	
Eksjö ($n = 173$)	159 (91.9)	14 (8.1)	1.2 (0.6–2.3)	.685	1.2 (0.5–2.4)	.701
Värnamo ($n = 88$)	80 (90.9)	8 (9.1)	1.0 (0.4–2.4)	.965	1.0 (0.4–2.4)	.977
Type of endocrine therapy						
Tamoxifen ($n = 236$)	215 (91.1)	21 (8.9)	Ref.		Ref.	
Aromatase inhibitor ($n = 96$)	90 (93.8)	6 (6.3)	1.5 (0.6–3.8)	.426	1.3 (0.5–3.8)	.570
Sequenced ^a ($n = 156$)	140 (89.7)	16 (10.3)	0.9 (0.4–1.7)	.653	0.7 (0.3–1.5)	.356
Age at time of diagnosis (years)						
<40 ($n = 18$)	15 (83.3)	3 (16.7)	0.5 (0.1–1.8)	.268	0.3 (0.1–1.3)	.113
40–59 ($n = 187$)	174 (93.0)	13 (7.0)	1.3 (0.6–2.6)	.513	1.0 (0.5–2.3)	.925
60–79 ($n = 242$)	221 (91.3)	21 (8.7)	Ref.		Ref.	
≥80 ($n = 41$)	35 (85.4)	6 (14.6)	0.6 (0.2–1.5)	.235	0.7 (0.2–2.0)	.484
Radiotherapy						
Yes ($n = 330$)	307 (93.0)	23 (7.0)	1.9 (1.0–3.6)	.041	1.6 (0.8–3.2)	.187
No ($n = 158$)	138 (87.3)	20 (12.7)	Ref.		Ref.	
Chemotherapy						
Yes ($n = 168$)	159 (94.6)	9 (5.4)	2.1 (1.0–4.5)	.056	2.0 (0.9–4.6)	.113
No ($n = 320$)	286 (89.4)	34 (10.6)	Ref.		Ref.	

^aSequenced treatment with tamoxifen and aromatase inhibitor.^bIncluding hospital, type of endocrine therapy, age at time of diagnosis, radiotherapy, and chemotherapy.**Table 1(B).** Predictors of adherence to adjuvant endocrine treatment after 5 years ($n = 271$) according to univariate and multiple logistic regression.

Characteristic	Adherent No. (%)	Non-adherent No. (%)	OR (95 % CI) univariate	<i>p</i> Value	OR (95 % CI) multiple ^b	<i>p</i> Value
Total	248 (91.5)	23 (8.5)	(88.2–94.8)			
Hospital						
Jönköping ($n = 125$)	116 (92.8)	9 (7.2)	Ref.		Ref.	
Eksjö ($n = 101$)	93 (92.1)	8 (7.9)	0.9 (0.3–2.4)	.838	0.9 (0.3–2.5)	.808
Värnamo ($n = 45$)	39 (86.7)	6 (13.3)	0.5 (0.2–1.5)	.220	0.4 (0.1–1.3)	.117
Type of endocrine therapy						
Tamoxifen ($n = 136$)	122 (89.7)	14 (10.3)	Ref.		Ref.	
Aromatase inhibitor ($n = 44$)	41 (93.2)	3 (6.8)	1.6 (0.4–5.7)	.496	2.0 (0.5–8.7)	.363
Sequenced ^a ($n = 91$)	85 (93.4)	6 (6.6)	1.6 (0.6–4.4)	.339	1.3 (0.4–4.0)	.614
Age at time of diagnosis (years)						
<40 ($n = 13$)	10 (76.9)	3 (23.1)	0.3 (0.1–1.1)	.072	0.3 (0.0–1.4)	.109
40–59 ($n = 103$)	95 (92.2)	8 (7.8)	1.0 (0.4–2.5)	.917	1.0 (0.3–2.8)	.940
60–79 ($n = 135$)	125 (92.6)	10 (7.4)	Ref.		Ref.	
≥80 ($n = 20$)	18 (90.0)	2 (10.0)	0.7 (0.1–3.6)	.687	1.0 (0.2–5.3)	.960
Radiotherapy						
Yes ($n = 178$)	166 (93.3)	12 (6.7)	1.9 (0.8–4.4)	.159	2.1 (0.8–5.6)	.150
No ($n = 93$)	82 (88.2)	11 (11.8)	Ref.		Ref.	
Chemotherapy						
Yes ($n = 83$)	76 (91.6)	7 (8.4)	1.0 (0.4–2.6)	.983	0.9 (0.3–2.6)	.795
No ($n = 188$)	172 (91.5)	16 (8.5)	Ref.		Ref.	

^aSequenced treatment with tamoxifen and aromatase inhibitor.^bIncluding hospital, type of endocrine therapy, age at time of diagnosis, radiotherapy, and chemotherapy.**Table 2.** Descriptive data of medication possession ratio (MPR) among non-adherent patients after 3 ($n = 43$) and 5 years ($n = 23$), respectively.

MPR %	3 years % (<i>n</i>)	5 years % (<i>n</i>)
0–30	37 (16)	48 (11)
31–60	30 (13)	22 (5)
61–79	33 (14)	30 (7)

Discussion

Endocrine adjuvant therapy is known to be effective in preventing relapse and reducing mortality in primary ER-positive breast cancer [5,6]. Decreased levels of adherence are associated with increased risk of death and it is therefore of utmost importance to ensure that patients actually take their prescribed therapy [21,22]. In the present study, adherence exceeded 90% after both 3 and 5 years and we hereby show

that very good adherence to adjuvant endocrine therapy in primary breast cancer can be achieved. The degree of non-adherence, according to descriptive data of the three different MPR groups, was similar among the patients after 3 years. However, after 5 years, as expected, there was a trend towards more non-adherent patients with lower MPR values.

Most previous studies have reported significantly lower figures. Kimmick and colleagues reported adherence as low as 60% after 1 year in low-income patients with primary breast cancer [23]. Another study found an adherence range of 50–68% after 3 years [24]. Retrospective studies based on databases and registers have shown adherence around 60–82% and 46–73% after 3 and 5 years, respectively [15,16]. However, as different methods and definitions are used to define adherence, it is difficult to directly compare results

from different studies. Adherence might strictly be based on MPR, calculating MPR over all time periods, or annually. In this study, MPR was calculated after 3 and 5 years.

Another Swedish study by Wigertz et al., using a similar design, included 1741 patients from two other regions (Uppsala/Örebro and Stockholm/Gotland) and showed 69% adherence after 3 years [17]. Despite the smaller size of our study, the confidence intervals are not overlapping. Since the follow-up routines were not presented in their study, we were not able to investigate if the differences in adherence were related to the follow-up routines.

A limitation in this study is the small sample size, which does not allow identification of differences among patient groups in the subgroup analyses. However, the confidence intervals for the main results after 3 and 5 years are small and even the lower limits of 88.2% and 88.7% are well beyond earlier described results. There were trends towards higher adherence among those given radio/chemotherapy and less adherence in the youngest and oldest age groups, which is consistent with earlier studies [25,26]. One reasonable explanation could be that those patients receiving additional adjuvant treatment had more established contact with specialized health care, and were engaged in more discussions about their adjuvant treatment, which could positively affect adherence. Even though the follow-up routines differed somewhat between the three departments in the region, no significant difference could be seen in adherence. Another limitation is the assumption that a patient actually takes the pills they have collected. The way MPR is defined and calculated is also associated with risks of error. Even if register data of prescription are a reliable source of information, there is a risk of overestimation of the true adherence when a patient may have had extra prescriptions during the measurement interval. Further, if patients switch endocrine drugs, there is a risk of a similar type of error due to overlap of prescribed tablets. In the definition of MPR in this study, the last prescription's surplus of days' supply exceeding the observation period, was not subtracted from the total days' supply in the time period. This could positively affect the adherence, depending on how close the last prescription was to the final date of the observational time period.

Twenty-three patients who were excluded due to recurrence or death without breast cancer could have been included in the 3-year analysis. To investigate the potential effect of the selection bias from this exclusion, medical records were reviewed for these patients. According to medical records, which include information of prescribed drugs from all health care providers in our region, 18 patients (78%) were still prescribed endocrine therapy at time for the event of recurrence or death. If these patients had been included in the 3-year analysis, it would not have significantly affected the final results.

The strengths of this study are that it is population-based and that the calculation of adherence is based on data from the Swedish Prescribed Drug Register. Data from sources such as questionnaires or interviews seem to have low concordance to register data [27], and adherence in clinical trials might be biased by factors such as monitored and motivated patients. Moreover, patient self-report and pill counts have

been found to overestimate adherence [28]. Thus, the results reported in this register study are less subjective. Another strength is the additional review of the medical records.

Even though one would aim at 100% adherence, it is not achievable nor preferable since endocrine treatment may severely impair quality of life for some patients. Patients who do not manage to complete full endocrine treatment due to side effects, should, however, be encouraged to complete at least 2 years of tamoxifen treatment, which has been shown to significantly improve survival after >25 years of follow-up [29]. There is no simple explanation for the high adherence observed in Region Jönköping County, but, based on the follow-up routines, regular doctor visits do not appear to be necessary. Instead it seems more important to provide patients with clear information regarding the reason for treatment, possible side effects and to encourage patients not to stop treatment before discussing it with their nurse or treating physician. The importance of communication about the planned treatment has also been shown by others [30]. The economic perspective may also be of importance as there seems to be an association between higher out-of-pocket costs and lower adherence [31]. In Sweden, all residents receive pharmaceutical benefits meaning reduced out-of-pocket costs for prescribed medication, which may affect the level of adherence.

Our results warrant larger future studies to more carefully study subgroups to identify predictors of adherence. Increased knowledge in this area may help to focus resources on the right patient categories and to guide us to find a better structure for breast cancer treatment organization and follow-up.

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Disclosure statement

The authors declare no conflicts of interest.

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