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Original Article

# Compliance with endocrine therapy among breast cancer survivors

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## ABSTRACT

**INTRODUCTION.** Most postmenopausal women with early-stage oestrogen receptor-positive breast cancer are allocated to five years of endocrine therapy. This treatment is not without adverse effects, which may lead to treatment discontinuation. This study aimed to assess compliance with endocrine therapy among postmenopausal women with early-stage oestrogen receptor-positive breast cancer and examine its association with disease-free survival.

**METHODS.** This study retrospectively identified a cohort of 360 postmenopausal women diagnosed in the period from 1 January 2015 to 31 December 2017 at Rigshospitalet, Copenhagen, Denmark, with early-stage oestrogen receptor-positive breast cancer in the clinical database of the Danish Breast Cancer Group. Kaplan-Meier was used to estimate compliance and disease-free survival.

**RESULTS.** A total of 346 patients receiving endocrine therapy were included, 240 were compliant, and 106 were non-compliant. The median follow-up was 6.5 years (95% confidence interval (CI): 6.4-6.7 years). The compliance at 4.5 years was 68.8% (95% CI: 64.1-74.0%). Disease-free survival was significantly higher for the compliant group (adjusted HR = 2.29; 95% CI: 1.34-3.91).

**CONCLUSIONS.** We found a low compliance at 4.5 years and most discontinuations were due to adverse effects. The study provides evidence that low compliance with endocrine therapy had a negative impact on disease-free survival.

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**TRIAL REGISTRATION.** The study was approved by the research overview of the Capital of Denmark and the Center for Health.

In Denmark, a Prognostic Standard Mortality Rate Index has been used nationwide to guide adjuvant treatment for postmenopausal women with oestrogen receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative early-stage breast cancer. The Prognostic Standard Mortality Rate Index assigns patients to one of four risk groups according to a multivariate algorithm, where each group has a higher excess mortality than the previous group [1]. A survival comparable to the age-matched general female population is achieved with locoregional treatment and adjuvant endocrine therapy by postmenopausal women in the Prognostic Standard Mortality Rate Index Low group or in the two lowest groups if the females are of the luminal A subtype by the PAM50 gene test [2]. However, the outcome may deteriorate following discontinuation of endocrine therapy, typically caused by adverse effects [3, 4]. The most common adverse effects related to endocrine therapy are arthralgia, vaginal dryness, thinning of hair, hot flashes and sweating [5].

In previous studies, endocrine therapy discontinuation rates have ranged from 16% to 31% [1, 3]. The wide range of results challenges the application of current evidence to clinical practice.

This study aimed to examine compliance, changes in treatment and disease-free survival (DFS) among postmenopausal women diagnosed with early-stage oestrogen receptor-positive breast cancer and treated with endocrine therapy. The secondary endpoint was to investigate overall survival (OS).

## Methods

### Study design

This was a retrospective, observational cohort study based on real-world data from the national Danish Breast Cancer Group database. The study is presented following the STROBE reporting guidelines [6].

### Patient selection

We included all postmenopausal women from Rigshospitalet, Copenhagen, Denmark, who were diagnosed with early-stage breast cancer and allocated to adjuvant endocrine therapy with no chemotherapy according to either the Prognostic Standard Mortality Rate Index Low group or second lowest if of the luminal A subtype, between 1 January 2015 and 31 December 2017. Patients were eligible for analyses if they were diagnosed with early-stage breast cancer and were postmenopausal at the time their treatment was initiated. Furthermore, tumours had to be oestrogen receptor-positive, defined as oestrogen receptor-positive ≥ 10% and HER2 normal.

Data on follow-up visits during treatment were obtained through the Danish Breast Cancer Group database, which was cross-referenced with hospital patient files. For most patients, follow-up visits consisted of physical examination, administration of endocrine therapy and biennial mammography. Data were collected on 1 March 2023.

### Compliance and change in treatment

The cohort was divided into a compliant and a non-compliant group. Compliance was defined as no less than 4.5 years of endocrine therapy, allowing a single pause of up to six months or treatment continued up until an event including death for any reason, recurrent disease or other malignant disease. The reasons for discontinuation and changes in treatment were obtained from the patient files and categorised by the authors. A change in medication was defined as a switch from one generic drug to another, irrespective of brand name, including changes between aromatase inhibitors. Patients with changes in medication, indicating sequential therapy, were also considered compliant if endocrine therapy was consistently maintained throughout the treatment period.

### Statistical methods

All analyses were conducted in RStudio version 4.2.2. Categorical variables were described as numbers and proportions. Age was further described by median and interquartile range (IQR). The $\chi^2$ test or the Wilcoxon rank sum test evaluated relations between clinical characteristics of the compliant and non-compliant group. Compliance with treatment was estimated from the beginning of endocrine therapy to the end of treatment, censoring patients on treatment experiencing a recurrence, another malignancy or death. Compliance with treatment was estimated using the Kaplan-Meier method. DFS was estimated from the operation date to the date of recurrent disease, other malignant diseases or death, whichever occurred first. OS was estimated from the operation date to death or the last follow-up date (March 2023). DFS and OS were evaluated using the Kaplan-Meier method and the Cox proportional hazard regression model, and between-group difference was examined using the log-rank test. The regression models included age at diagnosis (≤ 70 years, > 70 years) and compliance as a time-dependent covariate. Reverse Kaplan-Meier was used to estimate potential median follow-up time. Estimates were given with 95% confidence intervals (CI). All p values are two-sided with a 5% significance level.

*Trial registration:* The research overview of the Capital Region of Denmark and the Center for Health approved

the study.

## Results

### Study population

A total of 360 patients were identified from the database, meeting the inclusion criteria as postmenopausal women with early-stage oestrogen receptor-positive, HER2-normal breast cancer from 1 January 2015 to 31 December 2017 and treated at Rigshospitalet, Copenhagen, Denmark. A total of 14 patients did not initiate endocrine therapy treatment and were excluded. A total of 346 patients were analysed; one patient emigrated, leaving 345 with complete follow-up. Among the 346 patients included, 240 were classified as compliant and 106 as non-compliant. **Table 1** shows the baseline characteristics of the included patients. Median age at the time of surgery was 69 years for compliant and 71 years for non-compliant women ($p < 0.001$). Patients were treated with an aromatase inhibitor (82.4%, n = 285), tamoxifen (2.9%, n = 10) or as sequential treatment (14.7%, n = 51). In the compliant group, 34 events were recorded, including 14 deaths (5.8%), 11 patients with another malignancy (4.6%) and nine with recurrence (3.8%). In the non-compliant group, 26 events were registered, comprising 18 deaths (17%), four cases of other malignancies (3.8%) and four instances of breast cancer recurrence (3.8%). Radiotherapy was administered to 83.9% of compliant patients and 85.2% of non-compliant patients with positive lymph nodes.

**TABLE 1** Baseline characteristics of the patients included overall and by compliance.

| | Compliant ($N_{com}$ = 240) | Non-compliant ($N_{non}$ = 106) | Overall ($N_{tot}$ = 346) | p value[a] |
|---|---|---|---|---|
| Age, median (IQR), yrs | 69 (63-73) | 71 (66-79) | 69 (64-76) | < 0.001 |
| *Age at surgery, n (%)* | | | | 0.004 |
| < 59 yrs | 27 (11) | 4 (3.8) | 31 (9.0) | |
| 60-69 yrs | 116 (48) | 42 (40) | 158 (46) | |
| 70-79 yrs | 77 (32) | 40 (38) | 117 (34) | |
| ≥ 80 yrs | 20 (8.3) | 20 (19) | 40 (12) | |
| *Positive lymph nodes, n (%)* | | | | 0.9 |
| 0 | 184 (77) | 79 (75) | 263 (76) | |
| 1 | 41 (17) | 19 (18) | 60 (17) | |
| 2-3 | 15 (6.3) | 8 (7.5) | 23 (6.6) | |
| *Tumour size, n (%)* | | | | 0.3 |
| ≤ 10 mm | 31 (13) | 19 (18) | 50 (14) | |
| 11-20 mm | 158 (66) | 61 (58) | 219 (63) | |
| > 20 mm | 51 (21) | 26 (25) | 77 (22) | |
| *Histologic type, n (%)* | | | | 0.6 |
| Invasive ductal | 195 (81) | 91 (86) | 286 (83) | |
| Invasive lobular | 32 (13) | 11 (10) | 43 (12) | |
| Other | 13 (5.4) | 4 (3.8) | 17 (4.9) | |
| *Malignancy grade, n (%)* | | | | 0.7 |
| Grade 1 | 104 (43) | 44 (42) | 148 (43) | |
| Grade 2 | 125 (52) | 55 (52) | 180 (52) | |
| Grade 3 | 11 (4.6) | 7 (6.6) | 18 (5.2) | |
| *Oestrogen receptor status, n (%)* | | | | 0.8 |
| 100% positive | 232 (97) | 102 (96) | 334 (97) | |
| < 100% positive[b] | 8 (3.3) | 4 (3.8) | 12 (3.5) | |
| *Loco-regional therapy, n (%)* | | | | 0.016 |
| Mastectomy: | | | | |
| Without radiotherapy | 33 (14) | 21 (20) | 56 (16) | |
| With radiotherapy | 9 (3.8) | 6 (5.7) | 15 (4.3) | |
| Breast-conserving surgery: | | | | |
| Without radiotherapy | 6 (2.5) | 9 (8.5) | 15 (4.3) | |
| With radiotherapy | 192 (80) | 70 (66) | 262 (76) | |

IQR = interquartile range.
a) Wilcoxon rank sum test; Pearson's χ2 test; Fisher's exact test.
b) ≥ 10%.

### Treatment compliance

Compliance with endocrine therapy is summarised in **Figure 1**. At 2.5 years, compliance was 78.3% (95% CI: 74.0-82.8%), declining to 68.8% (95% CI: 64.1-74.0%) at 4.5 years. After 2.5 years, only 28 (26%) of the 106 non-compliant patients were still receiving treatment. Adverse effects were the most frequent cause of discontinuation (82.1%) and comorbidities the second most frequent reason (9.4%). Overall, 103 patients (29.8%) experienced alterations in medication during their treatment, all primarily due to adverse effects, regardless of patient compliance. Notably, 42.7% underwent their initial medication change within the first six months (**Figure 2**). Among the 103 with treatment alterations, 60.2% completed their treatment.

**FIGURE 1** Compliance with endocrine therapy. Kaplan-Meier estimates at years 1, 2.5 and 4.5. The grey curve denotes a 95% confidence interval (CI). Below is a table summarising treatment discontinuation.

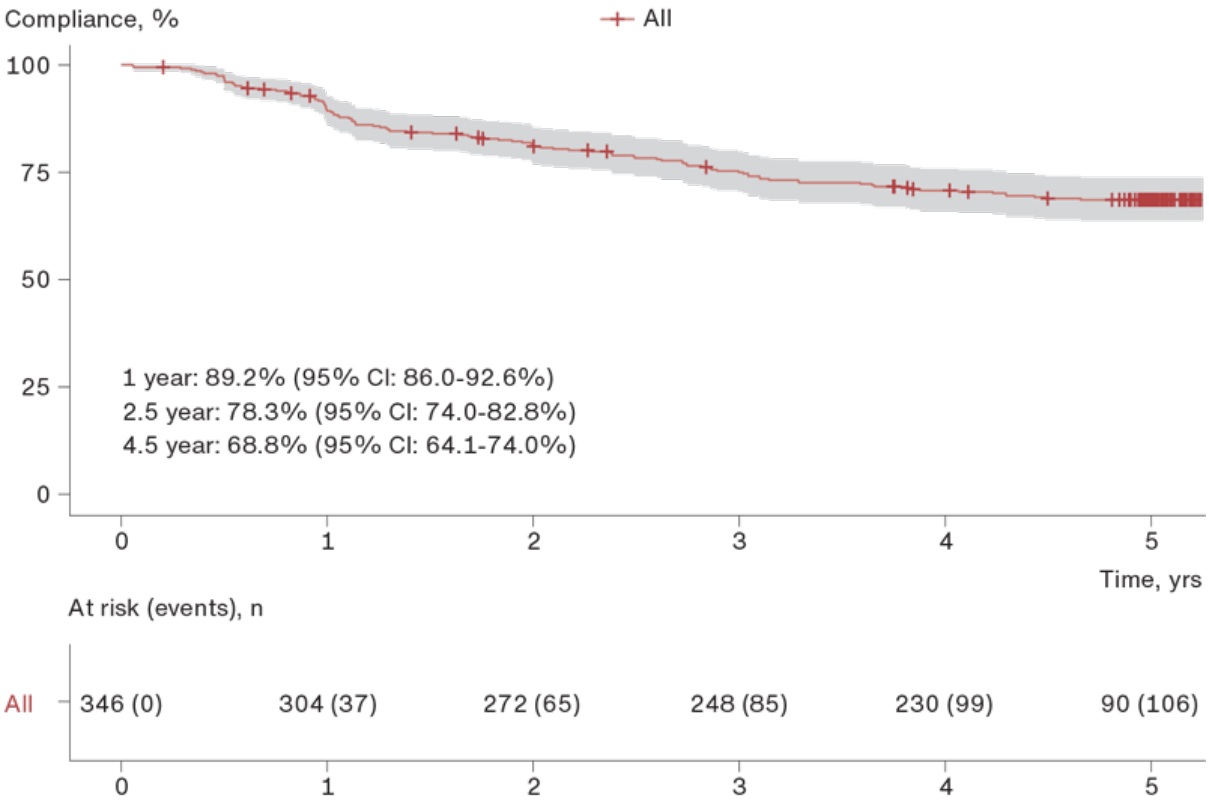
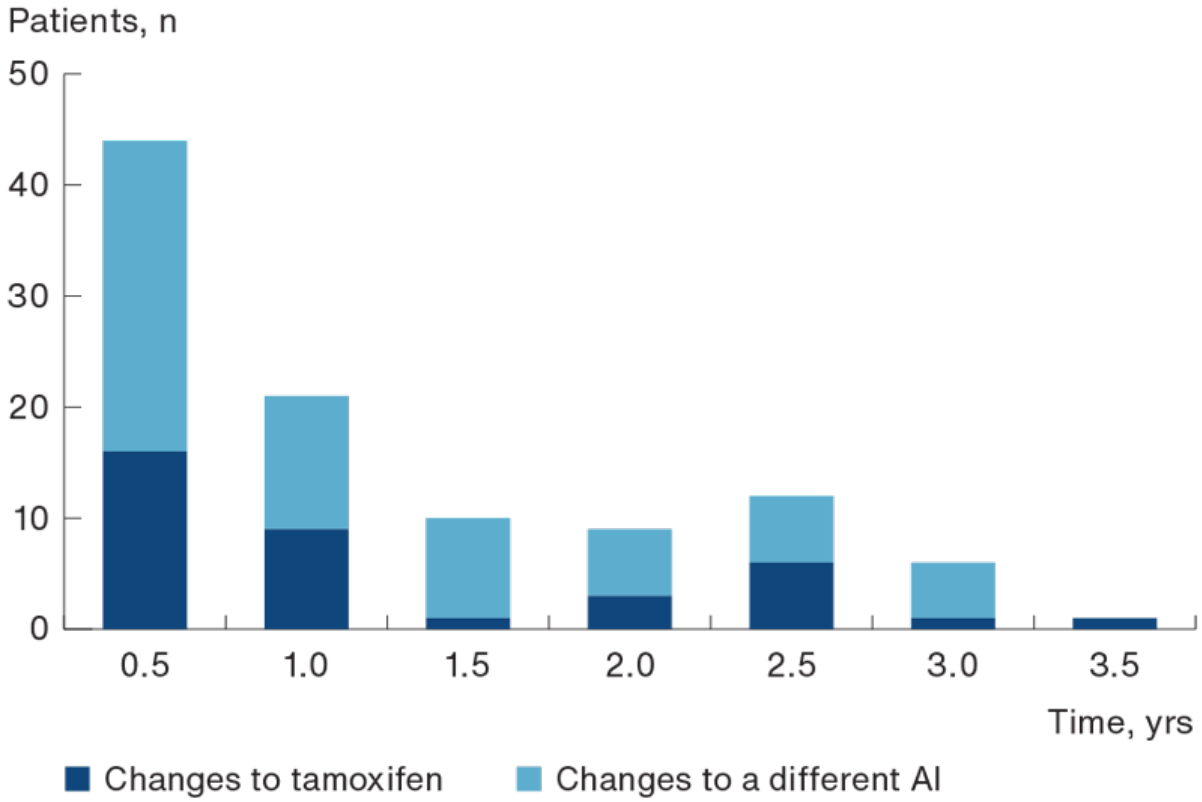


**FIGURE 2** Time of initial change to a different endocrine therapy treatment for patients in the five years.




AI = aromatase inhibitor.

**Disease-free survival**

The estimated median potential follow-up was 6.5 years (95% CI: 6.4-6.7 years), with 60 events occurring during follow-up. The five-year DFS rate was 91.6% (95% CI: 88.3-95.0%) for compliant patients and 75.7% (95% CI: 66.5-84.8%) for non-compliant patients (unadjusted HR = 2.73; 95% CI: 1.61-4.63). A univariate analysis by age showed a statistically significantly higher DFS, unadjusted HR = 0.28 (95% CI: 0.16-0.49) for patients ≤ 70 years versus > 70 years. In a multivariable model adjusted for age, we found a statistically significantly poorer DFS for the non-compliant than the compliant group, adjusted HR = 2.29 (95% CI: 1.34-3.91). As a secondary endpoint, OS was investigated. The five-year OS rate was 95.2% (95% CI: 92.6-97.8%) for compliant and 82.1% (95% CI: 74.4-90.6%) for non-compliant patients, with a statistically significant HR of 3.21 (95% CI: 1.75-5.87, unadjusted).

## Discussion

This study, comprising 346 postmenopausal patients with early-stage oestrogen receptor-positive breast cancer assigned to five years of adjuvant endocrine therapy revealed that adverse effects were the primary cause of endocrine therapy discontinuation. Furthermore, compliance with endocrine therapy was low, with only 69% being compliant with treatment at 4.5 years, and non-compliance was associated with a shorter DFS.

A systematic review from 2023 stated that the measurement method and the definition of compliance are inconsistent across studies, making the comparison with other studies difficult [7]. Studies based on self-reported questionaries for compliance measurement have generally found higher compliance throughout, ranging from 89-93% [8, 9]. Others have found compliance rates ranging from 68% to 92% by examining the refill of prescription orders [10, 11]. Our results suggest a much lower compliance due to adverse effects than previously found in a Danish setting [1]. Self-reported questionnaires are prone to recall bias and may favour more compliant patients. Neither refills of prescription orders nor database studies can guarantee that the actual intake of the medication is measured [12, 13]. To achieve greater insight and a more accurate compliance measure, blood samples may be used to detect drug levels. However, this method is more burdensome to the patients and might result in smaller cohorts.

A Swedish study by Chamalidou et al. employed a combination of patient files and a database registry similar to ours and found compliance of 71.1% at four years [14]. Yet neither considered the influence of sociodemographic factors, which have been known to significantly impact compliance [15, 16]. Interventions to optimise compliance have suggested lowering medical costs, and results from a recent study from Denmark concluded that unemployed women had lower compliance to endocrine therapy than occupationally active women [7, 16]. Although endocrine therapy medication is free of charge in Denmark, other potential sociodemographic variables should be considered. It is worth noting that the study cohort is drawn from a single institution in one Danish region, which may result in selection bias and limit the generalisability of the results due to demographic differences. However, a forthcoming study examining a national cohort found similar results regarding compliance with endocrine therapy, indicating that these findings may be consistent across a wider population.

We also observed that more than half of the patients who experienced alterations because of adverse effects succeeded with complete treatment. This suggests that changes in medication are justified and could enhance compliance.

The present study confirmed that older age is associated with lower treatment compliance [14, 15, 17]. However, there is some variation regarding the impact of age. Thus, one study reported no correlation between age and compliance, whereas Henry et al. concluded that being under 55 years old was predictive of non-compliance [10, 17]. A reasonable explanation for these conflicting results may be the selective focus of our study on an intermediate low-risk group with good prognostic factors and high age; older patients with low-risk disease characteristics might be more reluctant to stay on the prescribed medication if adequately informed of the low excess mortality, thus avoiding adverse effects.

The DFS estimates registered herein align with those of others [14]. However, events were dominated by death as the first event due to the high age cohort. Prior studies have reported significant findings that advancing age is associated with increased comorbidities, which may, in turn, exert a considerable impact on mortality [18, 19].

The estimate was adjusted for age, but the limited sample size does not allow further differentiation.

**Strengths and limitations**

The main limitation of this study was the small study size with 346 patients included from a single Danish hospital. However, we cross-referenced the Danish Breast Cancer Group database with patient records from the hospital. Furthermore, we analysed a group of patients who were not allocated to chemotherapy, thus removing potential adverse effects caused by chemotherapy as a non-compliance factor. The inclusion period allowed us to analyse the current standard regimen for postmenopausal women, with more patients being introduced to aromatase inhibitors. We consider one of the strengths of this study to be the Danish Breast Cancer Group database, a population-based register allowing for complete follow-up.

## Conclusions

We found low compliance with endocrine therapy treatment, with 69% compliance at 4.5 years among postmenopausal women with early-stage oestrogen receptor-positive breast cancer. This was largely due to adverse effects. The study provides evidence that low compliance with endocrine therapy and age above 70 years is associated with a shorter DFS and should be addressed at consultations.

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**Conflicts of interest** Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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**Artificial intelligence** In this paper, the programme "Grammarly" was used to review and correct grammatical errors and misspellings. Additionally, ChatGPT 3.5 was used to assist the Rstudio coding process.

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