The Breast 44 (2019) 52–58

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Adherence to adjuvant endocrine therapy in postmenopausal breast cancer patients: A 5-year prospective study

Kari Britt Hagen [a, b, *], Turid Aas [a], Jan Terje Kvaløy [c, d], Håvard Søiland [e, f], Ragna Lind [b, g]

[a] Department of Breast and Endocrine Surgery, Haukeland University Hospital, Bergen, Norway
[b] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[c] Research Department, Stavanger University Hospital, Stavanger, Norway
[d] Department of Mathematics and Physics, University of Stavanger, Stavanger, Norway
[e] Department for Breast and Endocrine Surgery, Stavanger University Hospital, Stavanger, Norway
[f] Department of Clinical Science, University of Bergen, Bergen, Norway
[g] Department of Medicine, Haukeland University Hospital, Bergen, Norway

ARTICLE INFO

Article history:
Received 24 October 2018
Received in revised form
20 December 2018
Accepted 7 January 2019
Available online 8 January 2019

Keywords:
Breast cancer
Adjuvant endocrine therapy
Adherence
Self-reported health complaints
Body mass index

ABSTRACT

Purpose: Adjuvant endocrine therapy (ET) in breast cancer reduces recurrence risk and increases overall survival. The aim of the study was to quantify non-adherence and discontinuation to ET in postmenopausal women with breast cancer, and identify possible clinical or social risk factors.
Methods: Women with hormone-receptor positive breast cancer (N = 138), mean age 58 (SD 9.3) years, filled in 4 questionnaires within 1–12, 24, 36 and 48–60 months after surgery; Subjective Health Complaints Inventory (SHC), Functional Assessment of Cancer Therapy-Social Support Subscale (FACT-ES), and Quality of Patient Information Questionnaire (QPI). Adherence to Tamoxifen (Tam) or Aromatase Inhibitors (AI) was examined using the self-reported Morisky Medication Adherence Scale (MMAS-8) and data from the Norwegian Prescription Database (NorPD). Kaplan-Meier curves and Cox proportional hazards regression models estimated adherence to ET.
Results: The estimate of discontinued ET within 60 months was 38%. Self-reported discontinuation was 7% compared with 25% from the NorPD. Being overweight or obese were significantly time dependent factors predictive for discontinuing ET, $p = 0.025$.
Conclusion: Closer follow-ups, tailor-made information about the proven benefits of ET, and keeping a normal body mass index (BMI) may improve adherence to ET in postmenopausal women with breast cancer.

© 2019 Elsevier Ltd. All rights reserved.

1. Introduction

Approximately 75% of all breast cancers are classified as luminal subtypes [1], which express one or both of two hormone receptors; the estrogen receptor (ER) and or the progesterone receptor (PR) in the primary tumor. Therefore, a rather large proportion of breast cancer patients receive adjuvant endocrine therapy (ET) i.e. anti-estrogen therapy by means of the ER blocking drug tamoxifen (Tam) or inhibition of the estrogen production by aromatase inhibitors (AI) [2]. Guidelines for ET include 5–10 years on Tam in premenopausal women, and five years with an AI alone, or AI for two years followed by Tam for three years in postmenopausal women [3,4]. Importantly, late recurrences and death due to breast cancer occur even after 5–20 years of ET use [5]. Thus, the intrinsic biology of luminal breast cancers calls for persistent attention in the clinical management and follow-up of these patients [5].

Being overweight, body mass index (BMI) of 25.0–29.9 kg/m^2 and obesity (BMI ≥ 30 kg/m^2) are increasing problems in postmenopausal women [6]. Obesity contributes to increasing levels of circulating sex hormones, including estrogen, and an inflammatory cytokines production [7].The condition is associated with higher risk of developing ER + breast cancers [8], and side effects from ET [9]. Furthermore, clinical trials have showed that obesity may reduce the effectiveness of AI treatment for ER + breast cancers [6].

* Corresponding author. Department of Breast and Endocrine Surgery, Haukeland University Hospital, Bergen, N- 5021 Bergen, Norway.
E-mail addresses: kari.britt.hagen@helse-bergen.no (K.B. Hagen), turid.aas@helse-bergen.no (T. Aas), jan.t.kvaloy@uis.no (J.T. Kvaløy), hsoiland@gmail.com (H. Søiland), ragna.lind@helse-bergen.no (R. Lind).

https://doi.org/10.1016/j.breast.2019.01.003
0960-9776/© 2019 Elsevier Ltd. All rights reserved.

Abbreviations

AI	Aromatase Inhibitor
BMI	Body Mass Index
CI	Confidence Interval
ET	Endocrine Therapy
FEC	Flourouracil + Epirubicin + Cyclophosfamide
FACT-ES	Functional Assessment of Cancer Therapy-Endocrine Subscale
HR	Hazard Ratio
MIM	Medication Interest Model
MMAS-8	Morisky Medication Adherence Scale
NorPD	Norwegian Prescription Database
QPI	Quality of Patient Information
SD	Standard Deviation
SHC	Subjective Health Complaints
Tam	Tamoxifen

Non-adherence to ET is defined as not taking the medication for periods, or to stop taking the medication all together before 5 years has passed [10]. Women who adhere to ET less than fully (i.e. < 80% of the duration) show reduced survival compared to women who follow the recommended regime [11,12]. Despite the patient benefits associated with ET and, conversely, negative outcomes associated with their absence, previous studies have shown that adherence to ET remains far less than optimal [13,14]. The discontinuation rate for ET falls on average 14% in the first year of ET, and 48% within the fifth year [14,15]. Age below 40 and over 70, lack of social support, side effects and information from health providers, as well as being employed are associated with higher risks of discontinuing ET [14,16]. Information given may play an important role to improve adherence to ET [17]. The Medication Interest Model (MIM) defines how to talk with patients about their medications [18], and grew directly from the fields of psychiatry, primary care medicine, and nursing [19]. The MIM replaces negative or neutral terms such as compliance, adherence, or persistency with the positive and empowering concept of "medication interest" [18]. When the provider expresses respect for the patients' right to make their own choice, it may lead to a patient's increased respect for the clinician's medical recommendation [18].

For assessment of adherence, pharmacy refill data is often considered a superior approach [20]. Although self-reported data is easier and cheaper to collect, their accuracy remains questionable [20]. In a previous review article on adherence to ET, only 6 out of 21 studies used validated questionnaires [15]. The main objective in this study was to evaluate 60 months adherence to ET prospectively in postmenopausal patients with breast cancer. The specific study aims were to explore whether clinical data, information, social support, self-reported health complaints or being employed were predictors for discontinuing ET.

2. Material and method

2.1. Study participants

Postmenopausal women with breast cancer, recruited from June 2012 to June 2013, and for further yearly follow-ups to December 2016, were included in this study. Median follow-up was 48 months. Patients were consecutive ethnic Norwegian women attending an outpatient's clinic at two university hospitals, aged 18 years or older and receiving curative breast cancer treatment (surgery, chemotherapy, radiation, and/or hormonal therapy). Within 1–12 months after surgery, the women received information about the study. Those who agreed to participate were mailed a packet of questionnaires, a consent form, and a stamped envelope for return mail. During the inclusion period, 229 patients returned the completed questionnaires whereof 20 patients dropped out due to travel distance (N = 7), fatigue (N = 5), metastasis (N = 5), and unknown reasons (N = 3). Among the remaining 209 patients, 138 received ET and were included in the present study (Fig. 1). The Regional Committee for Medical Research Ethics (REK–Nord no. 2011/2161), and The Norwegian Social Science Data Services (2012/5293) approved the study and written consents were obtained.

2.2. Questionnaires

2.2.1. Morisky Medication Adherence Scale (MMAS-8)

The self-reported scale, Cronbach's alpha reliability of 0.83 [21,22], consists of seven items answered with a "yes" or "no", and one on a 5-point Likert scale ("never" to "always"). Each question measures specific medication behaviour [21]. Total MMAS-8 scores range from 0 to 8. Following the methodology used in previous literature [21], high adherence is a MMAS-8 score of eight, medium is six or seven, and < six is low adherence. A license fee was paid before using a validated Norwegian version of MMAS-8. After permission from Professor Donald E. Morisky, the items were modified to make the scale appropriate for breast cancer patients (personal communication). Cronbach's alpha for the modified version was 0.72.

2.2.2. Subjective Health Complaints Inventory (SHC)

The scale measures 29 subjective, somatic and psychological complaints experienced during the last month, and has a satisfactory validity and reliability [23]. Severity of each complaint is rated on a 4-point Likert scale; 0 = "no complaints" to 3 = "severe complaints", range 0–87. SHC evaluates five domains; *musculoskeletal pain* (headache, neck pain, upper back pain, low back pain, arm pain, shoulder pain, migraine, and leg pain, range 0–24), "*pseudo-neurology*" (tiredness, sleep problems, anxiety, sadness/depression, extra heartbeats, heath flushes, and dizziness, range 0–21), *gastrointestinal problems* (gas discomfort, stomach discomfort, diarrhea, constipation, gastritis/ulcer, heartburn, and stomach pain, range 0–21), *allergy* (allergies, breathing difficulties, eczema, and asthma, range 0–15), and *flu* (cold/flu and coughing, range 0–6)

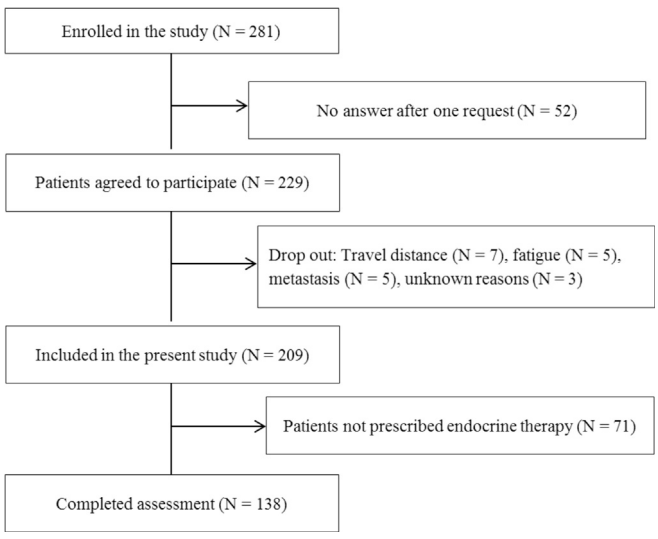

Fig. 1. Consort diagram of patients' enrollment.

[23].

2.2.3. Functional Assessment of Cancer Therapy-Social Support Subscale (FACT-ES)

The FACT-ES version 4 is a validated and widely used 46-item questionnaire that measures fatigue and physical, social, emotional, and functional aspects of quality of life [24]. "Self-reported social support" (seven statements), rated on a 5-point scale from 0 = "not at all" to 4 = "very much" are the primary outcomes in this study [24]. A license was obtained before using the FACT-ES (http://www.facit.org/).

2.2.4. Quality of Patient Information Questionnaire (QPI)

Assessment of the quality of patient information [25] is previously validated in Norwegian breast cancer patients with a Cronbach alpha of 0.81 [26]. QPI is based on four questions about the content of the information and four about the patients' experience regarding the information given [26].

2.3. Data collection and assessment of adherence to ET

Trained oncologic nurses collected data during consultations in the hospitals at 4 different time points; 1–12, 24, 36 and 48–60 months after surgery. Medical records confirmed demographic and cancer-related data. MMAS-8 and information from the Norwegian Prescription Database (NorPD), between January 2012 and October 2016, estimated adherence to ET. The NorPD records all drugs ordered and prescribed from pharmacies in Norway [27], and the database is considered as valid and reliable [28]. During a 60 months follow-up period, the patients received a prescription refill of tablets (Tam or AI) for a 100 day interval, which is the maximum that can be provided from Norwegian pharmacies [28]. The number of pills for each prescription was estimated from the date of the pharmacy's first fill and last refill, plus 100 days divided by the total number of days in the time period [11]. Patients had discontinued ET if 180 days elapsed from prior prescription without a refill prior to the completion of 54 months of therapy [11]. According to the Medication Possession Ratio (MPR) [29], adherent to therapy is taking prescribed medication equal to- or more than 80% [11].

2.4. Statistical analysis

Descriptive statistics presented data: numbers (n) and percentages (%) for categorical variables and mean and standard deviations (SD) for continuous variables. Survival probabilities of time to discontinuation of ET were estimated using the Kaplan- Meier method, and differences between groups with regard to discontinuing ET were tested by the log-rank test [30]. Univariable and multivariable regression analyses were performed using a Cox proportional hazards regression model [31], which included sociodemographic and clinical variables as covariate. Because values of employment, BMI, self-reported health complaints, social support, and quality of information given could change over time, they were entered as time dependent covariates, controlling for age, hypothyroidism and heart disease. All tests were two-sided, and tests with p value < 0.05 were considered as statistically significant. Data was analyzed using SPSS 23.0 for Windows (Armonk, NY: IBM Corp.).

3. Results

3.1. Patient characteristics

Table 1 shows the demographics and medical characteristics of the patients (N = 138). Mean age was 58 years, ranged from 49 to 67 years. At surgery, 53 (39%) patients were overweight (BMI > 25 kg/m^2), and 22 (16%) obese (BMI ≥ 30 kg/m^2). Within 48–60 months, the parameters were 52 (38%) and 25 (18%), respectively. Furthermore, at surgery, 95 (69%) were in paid employment and 43 (31%) were retired or on disability insurance. Within 48–60 months, the parameters were 77 (56%) and 61(44%), respectively.

3.2. Discontinuation of ET

All patients picked up at least one prescription for either Tam or AI within 12 months after their breast cancer diagnosis; 43 (31%) women received Tam, 64 (46%) an AI, and 31 (23%) both types of hormones at least once during the study period. Ten (7%) patients self-reported discontinuation of ET. Data from the NorPD showed that two patients (2%) were non-adherent (MPR < 80%), and 34 (25%) had discontinued ET. Nine patients received neo-adjuvant therapy, whereof two patients discontinued ET within 7 and 41 months, respectively. The estimated proportion of patients who

Table 1
Baseline characteristics; mean (SD) for continuous data and n (%) for categorical data in postmenopausal women with breast cancer (n = 138).

	Patients
Age at diagnosis (years)	58.0 (SD 9.3)
[a]**BMI** (kg/m^2) **at surgery**	26.2 (SD 4.3)
BMI (kg/m^2) 48–60 months **after surgery**	26.2 (SD 4.4)
Marital status	
Living with a partner	103 (75)
Education	
Primary school (10 years)	74 (53)
Secondary school (11–14 years)	53 (39)
College/university	11 (8)
Employment	
At surgery	95 (69)
Within 60 months after surgery	77 (56)
Initial therapy	
Tamoxifen	54 (39)
Aromatase Inhibitor	84 (61)
Use of ET (months)	44 (SD 11.5)
Tumor size	
>2 cm	50 (36)
1–2 cm	70 (51)
<1 cm	18 (13)
Tumor grade	
1	34 (25)
2	78 (56)
3	26 (19)
Lymph node involvement	
Node-positive	46 (33)
Type of surgery	
Mastectomy	85 (62)
Lumpectomy	47 (34)
Treatment	
[b]FEC ± Taxan	95 (69)
Radiation therapy	85 (62)
[c]**Pre-existing comorbidities**	
Depression	5 (4)
Hypothyroidism	23 (17)
Diabetes Mellitus	4 (3)
[d]Cardiovascular disease	48 (35)
[e]Gastrointestinal disease	8 (6)
Rheumatological disease	5 (4)
Musculoskeletal pain	26 (19)
[f]Respiratory disease	13 (10)
No comorbidities	53 (38)

[a] Body Mass Index (BMI).
[b] Flourouracil + Epirubicin + Cyclophosfamide.
[c] Information was collected from medical records and self-reported by the patient before surgery.
[d] Hypertension, hypercholesterolemia, heart failure.
[e] Ulcerous Colitis, Mb Crohn.
[f] Chronic Obstructive Pulmonary Diseases.

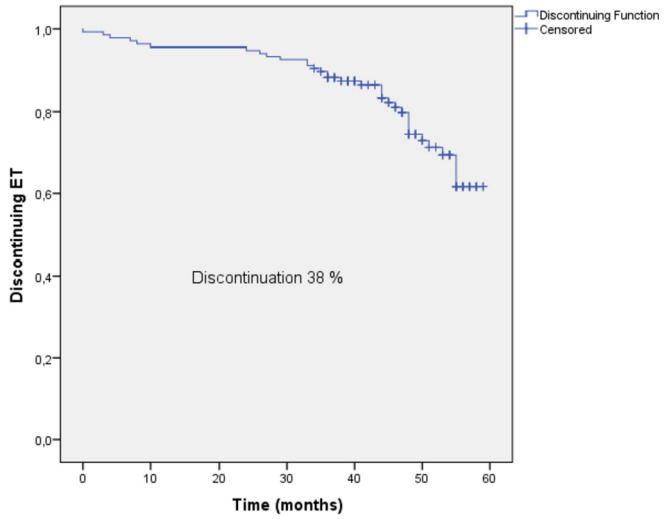

Fig. 2. Kaplan-Meier curve for discontinuation of endocrine therapy among 138 women with breast cancer within 60 months.

discontinued ET within 60 months was 38% (Fig. 2).

3.3. Predictors for discontinuation ET at baseline

Tam and AI did not significantly influence discontinuation of ET within 60 months when stratifying on the baseline variables, (log rank, p = 0.785) (Fig. 3).

3.4. Subjective health complaints (SHC)

SHC score < 20 is considered as normal self-reported health complaints during a month [32,33]. The estimate of discontinued therapy within 60 months showed no significance when stratifying on the patients' baseline SHC; SHC< 20 and SHC ≥20 respectively (log rank, p = 0 0.723) (Fig. 4).

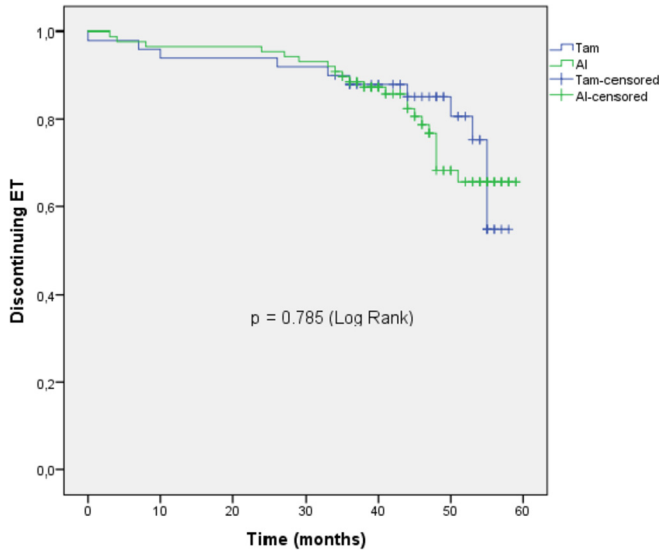

Fig. 3. Kaplan-Meier curve for discontinuation of endocrine therapy according to tamoxifen and aromatase inhibitors among 138 women with breast cancer within 60 months.

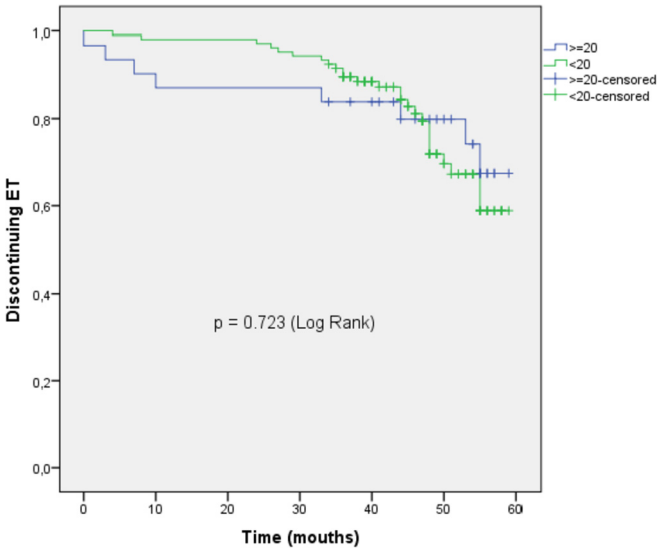

Fig. 4. Kaplan-Meier curve of discontinuing endocrine therapy comparing patients with self-reported healt complaints sum score, SHC >20 and SHC <20 among 138 women with breast cancer within 60 months.

3.5. Cox regression analysis

Univariable Cox regression examined the association between ET discontinuation with baseline characteristics. Baseline BMI (HR

Table 2
Baseline, univariable Cox regression analysis for characteristics for discontinued endocrine therapy in postmenopausal women with breast cancer (n = 138).

	HR (95% CI)	p-Value
Age at diagnosis (years)	1.04 (1.00–1.08)	0.050
[a]**BMI** (kg/m^2) at surgery	1.10 (1.02–1.18)	**0.008**
Living with a partner		
No	1.00 (Ref)	
Yes	0.72 (0.31–1.66)	0.442
Education		
Primary school, 10 years	1.00 (Ref)	
Secondary school, 11–14years	0.38 (0.09–1.63)	0.344
College/university	0.71 (0.35–1.5)	0.191
Endocrine therapy		
Tamoxifen	1.00 (Ref)	
Aromatase Inhibitor	1.10 (0.54–2.23)	0.786
Tumor size		
<1 cm	1.00 (Ref)	
1–2 cm	2.30 (0.53–9.94)	0.266
>2 cm	2.67 (0.61–11.66)	0.193
Tumor grade		
1	1.00 (Ref)	
2	0.78 (0.37–1.67)	0.526
3	0.53 (0.17–1.70)	0.288
Lymph node involvement		
Node-negative	1.00 (Ref)	
Node-positive	0.42 (0.18–0.97)	**0.043**
Mastectomy		
No	1.00 (Ref)	
Yes	0.88 (0.44–1.79)	0.732
Lymphectomy		
No	1.00 (Ref)	
Yes	0.57 (0.27–1.23)	0.152
[b]**FEC ± Taxan**		
No	1.00 (Ref)	
Yes	0.59 (0.30–1.17)	0.129
Radiation therapy		
No	1.00 (Ref)	
Yes	0.77 (0.39–1.52)	0.448

[a] Body Mass Index.
[b] Flourouracil + Epirubicin + Cyclophosfamide.

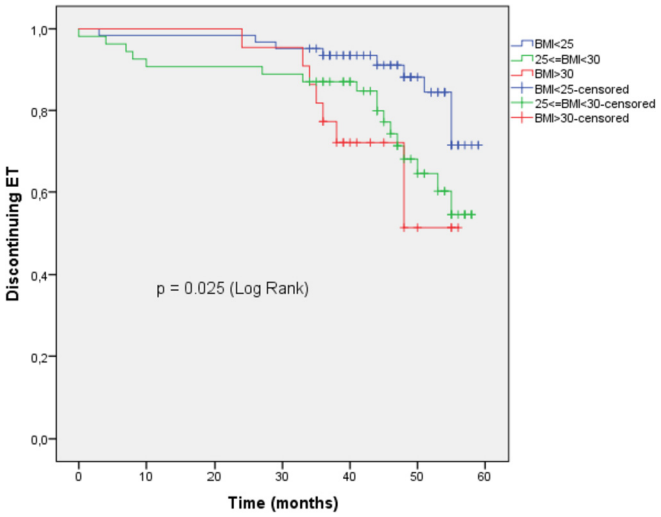

Fig. 5. Kaplan-Meier curve for discontinuation of endocrine therapy according to BMI <25, 25–30 and >30 kg/m^2 among 138 women with breast cancer within 60 months.

1.10, 95% CI 1.02–1.18) was a significant independent predictor of discontinuation ET, while a positive lymph node significantly reduced the risk of discontinuation ET (HR 0.42, 95% CI 0.18–0.97) (Table 2). None of the pre-existing comorbidities were significant predictors for discontinuation ET.

3.6. Body mass index (BMI)

Thirty-one of the patients in the present study changed their diet two years after diagnosis [34], whereof six discontinued ET. Those 25 who continued ET had a mean BMI 27.5 (SD 3.6) kg/m$_2$ compared to 28.3 (SD 6.6) kg/m$_2$ in those who discontinued. To examine the influence of BMI on ET discontinuation, we found a log-linear relationship between baseline BMI and the 60-month ET-discontinuation (HR 1.1, 95% CI 1.02–1.18), indicating a 10% increase in hazard for discontinued ET for each unit increase in BMI. We further explored the difference between various clinically used BMI groups; < 25 kg/m^2, 25–30 kg/m^2 and >30 kg/m^2, and observed an estimated 60 months discontinuation of 28%, 45% and 48%, respectively (log rank, p = 0.025) (Fig. 5).

3.7. Time dependent factors predictive for discontinuing ET

Uni- and multivariable Cox regression analyzed the association between discontinuation of ET and time dependent factors like social support, SHC, BMI, QPI, and paid employment. When only baseline values were considered, social support was associated with discontinuation of ET, (HR 0.91, 95% CI 0.86–0.98, p = 0.008), but not when considered as a time dependent covariate (HR 0.99 (0.92–1.06, p = 0.830)). Employment was a significant time dependent predictor when adjusted for hypothyroidism and cardiovascular disease (p = 0.040), but not when BMI was included in the model (p = 0.259). BMI was a significant predictor as a time dependent covariate in both the univariable and multivariable analysis (Table 3).

4. Discussion

The present study evaluated prospectively non-adherence and discontinuation to ET, within 60 months after surgery, in postmenopausal women with luminal breast cancer. An estimated risk of discontinuing ET within 30 months was about 10%, which is in line with prior studies reporting discontinuance rates like 8%–24% of ET after two years [35,36]. However, after 60 months, the estimated discontinuation increased to 38%. The result was surprisingly high in light of the close monitoring during the study period and the satisfaction regarding information given at diagnosis and during follow-ups [26]. Previous studies have also reported rates of non-adherence to ET ranging from 30 to 50% [13,16]. Hershman et al. showed that among 8.769 women with breast cancer, 31.5% discontinued therapy early, and 49% fulfilled the treatment period [13]. Furthermore, estimated survival at 10 years was 81% for those who continued ET compared to 74% for those who discontinued [13]. Also, results from a large study including 6.193 postmenopausal women, showed both low adherence to AI and compliance score <90% were associated with reduced disease-free survival [12].

The present study shows, as previous findings [37], a substantial discrepancy between patients' self-reported adherence to ET compared to information from the NorPD. Patients may be reluctant to admit that they do not follow the prescribed regime in general; the question may be too intrusive to answer [38]. Also, if the patients are told in a superficial manner that they have to take ET for 5–10 years, they may not understand benefits of the medicine and the importance of following the prescribed ET [39].

A previous study in our patients showed that 76% self-reported health complaints equal to healthy postmenopausal controls [32]. Also, a recently published prospective study, up to six years after ET, did not show any effect or impairment of ET on neuropsychological performance [40]. Although one third of the patients reported high scores on several health complaints [32], these complaints were not a time dependent factor predictive for discontinuing ET. Therefore, ET-related health complaints may not play a major role in determining discontinuation of the medication [20,41].

While ET discontinuation was not associated with social support over time, the support seems to be important within the first year

Table 3
Baseline, univariable and multivariable Cox proportional regression analysis for time dependent factors predictive for discontinuing endocrine therapy in postmenopausal women with breast cancer (n = 138).

	Univariable HR (95% CI)	p-Value	*Multivariable HR (95% CI)	p-Value
FACT- ES, social support	0.99 (0.92–1.07)	0.830		
SHC Inventory, total score	1.01 (0.98–1.04)	0.740		
Pseudoneurology	0.97 (0.88–1.07)	0.555		
Musculoskeletal complaints	1.03 (0.96–1.10)	0.400		
Gastrointestinal complaints	1.03 (0.93–1.13)	0.639		
QPI	0.99 (0.92–1.07)	0.887		
***Employment**	0.48 (0.24–0.97)	**0.040**	0.56 (0.21–1,53)	0.259
***BMI**	1.08 (1.01–1.16)	**0.027**	1,08 (1.00–1.17)	**0.042**

*Notes: adjusted for age, hypothyroidism and cardiovascular disease.
Abbreviations; HR (Hazard Ratio), CI (Confidence Interval), FACT-ES (Functional Assessment of Cancer Therapy-Endocrine Subscale), SHC Inventory (Self-reported Health Complaints Inventory), QPI (Quality of Patient Information), BMI (Body Mass Index).

of treatment, and may contribute to a process of later discontinuation of ET. It is worth noting that, a positive lymph node reduced the risk of discontinuing ET. These patients may have received comprehensive information, which in turn has influenced the understanding about the advantages and disadvantages of ET [38,42]. The physicians often focus on curing the disease, and may forget to discuss perceived bothersome health complaints [42,43].

Notably, more than 50% of the patients were overweight or obese. Change in diet two years after diagnosis [34] did not affect BMI, which was stable throughout the entire study period. In the present study, it was observed that baseline BMI might be a novel risk factor to predict discontinuing ET down-stream in the breast cancer trajectory. Interestingly, others have observed a positive linear correlation between BMI and pre-treatment circulating estrogen levels, which are produced by aromatization of adrenal androgens in the peripherally adipose tissue in postmenopausal women [44]. On ET treatment, they found no difference in the circulating estrogen levels between the BMI groups, but patients with the highest BMI had the largest reduction in systemic estrogen levels on ET [44]. It is tempting to suggest that ET in patients with the highest BMI are likely to experience the largest drop in circulating estrogens, which may create a larger discomfort compared with the hormonal alterations in patients with a normal BMI. Thus, these underlying endocrine mechanisms may affect overweight or obese patients to be more prone to discontinue ET than slim patients. Therefore, high BMI may be considered a promising clinical predictor for ET-discontinuation, and may contribute to explain the increased breast cancer recurrence and mortality observed in these patients [6, 45].

The patients should be asked more often whether they have any side effects from their medications and the benefits of taking them [20]. Our study supports the importance of establishing an “alliance” [18] between patient and provider before two years of follow-up, as most patients stop medication at that time. The health care providers must communicate with the patients in a way that makes the patients feel comfortable talking about their BMI and diet, and telling the truth about the medical adherence [39]. Educational interventions in health care providers, using the MIM, may increase the understanding of the benefits of ET and the importance of following the prescribed treatment [18].

Several strengths of the present study contribute to the legitimacy of the observations: the prospective design, and that all patients attended complete follow-ups. Both self-reported and electronic pharmacy records estimated discontinuation of ET, which strengthen the external validity of the results. The limitations that need addressing are the small sample size and that the prescription refill does not necessarily guarantee a patient actually takes the prescribed medication. Hence, discontinuation of ET may be higher than reported in this study.

5. Conclusion

The overall estimate of ET discontinuation within 60 months was 38%, and there was a discrepancy between self-reported adherence compared to prescription recorded data. Overweight and obesity were time dependent risk factors predictive for discontinuing ET, but needs verification by a larger prospective study to determine causality. Closer follow-ups, including oncology nurse consultations, and more tailor-made information following theoretical guidance models, may contribute to increased adherence to ET in breast cancer patients.

Conflict of interest statement

None declared.

Acknowledgments

Part of this work was supported by Folke Hermansen Foundation and Inge Steenslands Stiftelsen, Stavanger, Norway. The authors want to thank Sissel Vevle and Eli Bøhme for their dedicated work in the collection of patient data.

References

[1] Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci 2001;98:10869–74.
[2] Early Breast Cancer Trialists' Collaborative G. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015;386:1341–52.
[3] Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Invasive breast cancer version 1.2016, NCCN clinical practice Guidelines in oncology. J Natl Compr Canc Netw 2016;14:324–54.
[4] Norwegian Breast Cancer Group. Retrieved from, http://www.nbcg.no. [Accessed 15 January 2018].
[5] Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 2017;377:1836–46.
[6] Azrad M, Demark-Wahnefried W. The association between adiposity and breast cancer recurrence and survival: a review of the recent literature. Curr Nutr Rep 2014;3:9–15.
[7] Howe LR, Subbaramaiah K, Hudis CA, Dannenberg AJ. Molecular pathways: adipose inflammation as a mediator of obesity-associated cancer. Clin Canc Res 2013;19:6074–83.
[8] Gerard C, Brown KA. Obesity and breast cancer - role of estrogens and the molecular underpinnings of aromatase regulation in breast adipose tissue. Mol Cell Endocrinol 2017;466:15–30.
[9] Playdon MC, Bracken MB, Sanft TB, Ligibel JA, Harrigan M, Irwin ML. Weight gain after breast cancer diagnosis and all-cause mortality: systematic review and meta-analysis. J Natl Cancer Inst 2015;107:275.
[10] Sebate E. Adherence to long-term therapies: evidence for actions. Switzerland: World Health Organization; 2003.
[11] Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Canc Res Treat 2011;126:529–37.
[12] Chirgwin JH, Giobbie-Hurder A, Coates AS, Price KN, Ejlertsen B, Debled M, et al. Treatment adherence and its impact on disease-free survival in the breast international group 1-98 trial of tamoxifen and letrozole, alone and in sequence. J Clin Oncol 2016;34:2452–9.
[13] Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A, Tsai W-Y, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 2010;28:4120–8.
[14] He W, Fang F, Varnum C, Eriksson M, Hall P, Czene K. Predictors of discontinuation of adjuvant hormone therapy in patients with breast cancer. J Clin Oncol 2015;33:2262–9.
[15] Moon Z, Moss-Morris R, Hunter MS, Carlisle S, Hughes LD. Barriers and facilitators of adjuvant hormone therapy adherence and persistence in women with breast cancer: a systematic review. Patient Prefer Adherence 2017;11:305–22.
[16] Huiart L, Bouhnik AD, Rey D, Tarpin C, Cluze C, Bendiane MK, et al. Early discontinuation of tamoxifen intake in younger women with breast cancer: is it time to rethink the way it is prescribed? Eur J Canc 2012;48:1939–46.
[17] Ziller V, Kyvernitakis I, Knoll D, Storch A, Hars O, Hadji P. Influence of a patient information program on adherence and persistence with an aromatase inhibitor in breast cancer treatment-the COMPAS study. BMC Canc 2013;13:407.
[18] Shea SC. The medication interest model. How to talk with patients about their medications. second ed. Wolters Kluwer; 2018.
[19] Cheng MK. New approaches for creating the therapeutic alliance: solution-focused interviewing, motivational interviewing, and the medication interest model. Psychiatr Clin North Am 2007;30:157–66.
[20] Chlebowski RT, Kim J, Haque R. Adherence to endocrine therapy in breast cancer adjuvant and prevention settings. Cancer Prev Res 2014;7:378–87.
[21] Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens 2008;10:348–54.
[22] Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: response to authors. J Clin Epidemiol 2011;64:255–7.
[23] Eriksen HR, Ihlebaek C, Ursin H. A scoring system for subjective health complaints (SHC). Scand J Publ Health 1999;27:63–72.
[24] Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570–9.
[25] Box V, Hepworth M, Harrison J. Identifying information needs of people with

multiple sclerosis. Nurs Times 2003;99:32–6.
[26] Hagen KB, Aas T, Lode K, Gjerde J, Lien E, Kvaloy JT, et al. Illness uncertainty in breast cancer patients: validation of the 5-item short form of the Mishel Uncertainty in Illness Scale. Eur J Oncol Nurs 2015;19:113–9.
[27] Norwegian Institute of Public Health. Norwegian prescription database. Oslo, Norway. 2017. Retrieved from:, http://www.norpd.no/. [Accessed 30 October 2016].
[28] Furu K. Establishment of the nationwide Norwegian Prescription Database (NorPD) – new opportunities for research in pharmacoepidemiology in Norway. Nor Epidemiol 2008;18:129–36.
[29] Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin 2009;25:2303–10.
[30] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
[31] Cox DR. Regression models and life-tables. J R Stat Soc Series B Methodol 1972;34:187–220.
[32] Hagen KB, Aas T, Kvaloy JT, Eriksen HR, Soiland H, Lind R. Fatigue, anxiety and depression overrule the role of oncological treatment in predicting self-reported health complaints in women with breast cancer compared to healthy controls. Breast 2016;28:100–6.
[33] Lind R, Arslan G, Eriksen HR, Kahrs G, Haug TT, Florvaag E, et al. Subjective health complaints and modern health worries in patients with subjective food hypersensitivity. Dig Dis Sci 2005;50:1245–51.
[34] Hagen KB, Aas T, Kvaløy JT, Søiland H, Lind R. Diet in women with breast cancer compared to healthy controls. What is the difference? Eur J Oncol Nurs 2013;32:20–4.
[35] Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA. Adherence to tamoxifen over the five-year course. Breast Canc Res Treat 2006;99:215–20.
[36] Wigertz A, Ahlgren J, Holmqvist M, Fornander T, Adolfsson J, Lindman H, et al. Adherence and discontinuation of adjuvant hormonal therapy in breast cancer patients: a population-based study. Breast Canc Res Treat 2012;133:367–73.
[37] Wang PS, Benner JS, Glynn RJ, Winkelmayer WC, Mogun H, Avorn J. How well do patients report noncompliance with antihypertensive medications?: a comparison of self-report versus filled prescriptions. Pharmacoepidemiol Drug Saf 2004;13:11–9.
[38] Atkins L, Fallowfield L. Intentional and non-intentional non-adherence to medication amongst breast cancer patients. Eur J Canc 2006;42:2271–6.
[39] Moon Z, Moss-Morris R, Hunter MS, Hughes LD. Understanding tamoxifen adherence in women with breast cancer: a qualitative study. Br J Health Psychol 2017;22:978–97.
[40] Van Dyk K, Crespi CM, Bower JE, Castellon SA, Petersen L, Ganz PA. The cognitive effects of endocrine therapy in survivors of breast cancer: a prospective longitudinal study up to 6 years after treatment. Cancer 2018. https://doi.org/10.1002/cncr.31858.
[41] Hershman DL, Kushi LH, Hillyer GC, Coromilas E, Buono D, Lamerato L, et al. Psychosocial factors related to non-persistence with adjuvant endocrine therapy among women with breast cancer: the Breast Cancer Quality of Care Study (BQUAL). Breast Canc Res Treat 2016;157:133–43.
[42] Wheeler SB, Roberts MC, Bloom D, Reeder-Hayes KE, Espada M, Peppercorn J, et al. Oncology providers' perspectives on endocrine therapy prescribing and management. Patient Prefer Adherence 2016;10:2007–19.
[43] Verbrugghe M, Verhaeghe S, Decoene E, De Baere S, Vandendorpe B, Van Hecke A. Factors influencing the process of medication (non-)adherence and (non-)persistence in breast cancer patients with adjuvant antihormonal therapy: a qualitative study. Eur J Cancer Care 2017;26.
[44] Lønning PE, Haynes BP, Dowsett M. Relationship of body mass index with aromatisation and plasma and tissue oestrogen levels in postmenopausal breast cancer patients treated with aromatase inhibitors. Eur J Canc 2014;50:1055–64.
[45] Kwan ML, Chen WY, Kroenke CH, Weltzien EK, Beasley JM, Nechuta SJ, et al. Pre-diagnosis body mass index and survival after breast cancer in the after breast cancer pooling project. Breast Canc Res Treat 2012;132:729–39.