Breast Cancer Research and Treatment (2019) 177:185–195
https://doi.org/10.1007/s10549-019-05294-w

EPIDEMIOLOGY

Drug monitoring of tamoxifen metabolites predicts vaginal dryness and verifies a low discontinuation rate from the Norwegian Prescription Database

Thomas Helland[1,2] · Kari Britt Hagen[2,3] · Martha Eimstad Haugstøyl[1,2] · Jan Terje Kvaløy[4,6] · Siri Lunde[5] · Kirsten Lode[6] · Ragna Anne Lind[2] · Birgitta Haga Gripsrud[7] · Kristin Jonsdottir[5,6] · Jennifer Gjerde[1,2] · Ersilia Bifulco[2,8] · Steinar Hustad[2,8] · Janne Jonassen[5] · Turid Aas[3] · Tone Hoel Lende[5,9] · Ernst Asbjørn Lien[1,2] · Emiel Adrianus Maria Janssen[4,10] · Håvard Søiland[2,5] · Gunnar Mellgren[1,2]

Received: 16 May 2019 / Accepted: 22 May 2019 / Published online: 29 May 2019

Abstract

Purpose Tamoxifen is an important targeted endocrine therapy in breast cancer. However, side effects and early discontinuation of tamoxifen remains a barrier for obtaining the improved outcome benefits of long-term tamoxifen treatment. Biomarkers predictive of tamoxifen side effects remain unidentified. The objective of this prospective population-based study was to investigate the value of tamoxifen metabolite concentrations as biomarkers for side effects. A second objective was to assess the validity of discontinuation rates obtained through pharmacy records with the use of tamoxifen drug monitoring.

Methods Longitudinal serum samples, patient-reported outcome measures and pharmacy records from 220 breast cancer patients were obtained over a 6-year period. Serum concentrations of tamoxifen metabolites were measured by LC–MS/MS. Associations between metabolite concentrations and side effects were analyzed by logistic regression and cross table analyses. To determine the validity of pharmacy records we compared longitudinal tamoxifen concentrations to discontinuation rates obtained through the Norwegian Prescription database (NorPD). Multivariable Cox regression models were performed to identify predictors of discontinuation.

Results At the 2nd year of follow-up, a significant association between vaginal dryness and high concentrations of tamoxifen, Z-4′-OHtam and tam-NoX was identified. NorPD showed a tamoxifen-discontinuation rate of 17.9% at 5 years and drug monitoring demonstrated similar rates. Nausea, vaginal dryness and chemotherapy-naive status were significant risk factors for tamoxifen discontinuation.

Conclusions This real-world data study suggests that measurements of tamoxifen metabolite concentrations may be predictive of vaginal dryness in breast cancer patients and verifies NorPD as a reliable source of adherence data.

Keywords Tamoxifen · Metabolism · Adherence · Discontinuation · Side effects · Endocrine therapy

Introduction

Tamoxifen was the first and is still one of the most important targeted endocrine therapies in the adjuvant treatment of estrogen receptor-positive (ER +) breast cancer. The drug inhibits estrogen-mediated growth by antagonistic binding to the ER and has been shown to reduce breast cancer recurrence by 50% [1]. At present, tamoxifen is mainly used in pre-menopausal breast cancer patients, while aromatase inhibitors (AIs) alone or in concert with tamoxifen are recommended for post-menopausal patients [2]. Although the number of patients using tamoxifen may have decreased since AIs entered the marked, tamoxifen treatment-duration has been doubled from 5 to

Håvard Søiland and Gunnar Mellgren shared last author.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-019-05294-w) contains supplementary material, which is available to authorized users.

✉ Gunnar Mellgren
gunnar.mellgren@uib.no

Extended author information available on the last page of the article

10 years [2] due to significant outcome benefits demonstrated by the ATLAS and aTTom trials [3, 4]. Worryingly, studies reviewing pharmacy records show that more than 40% of patients outside clinical trials do not complete the first 5 years of tamoxifen treatment [5, 6]. Moreover, the true numbers may be even higher as no studies have investigated tamoxifen discontinuation by monitoring systemic tamoxifen drug concentrations. Side effects have been identified as a significant predictor of tamoxifen discontinuation [7] and as many as 73% of patients experience some form of side effects which they attribute to tamoxifen-use [8]. Common side effects of tamoxifen include menopausal symptoms such as hot flashes, vaginal dryness and discharge, night sweats and decreased libido [9, 10], as well as symptoms that could impair quality of life such as depression, anxiety, mood swings and fatigue. More severe, but less frequent symptoms include endometrial cancer and thromboembolic events [11].

To increase adherence to tamoxifen, there is a need for reliable predictive factors of side effects of the anti-estrogen treatment. Such biomarkers might help clinicians identify patients at high risk of discontinuing endocrine treatment and thus improve clinical outcome. One such putative biological predictor may be systemic concentrations of tamoxifen and its metabolites. Tamoxifen is a prodrug which is metabolized by highly polymorphic enzymes resulting in formation of various metabolites at different concentrations between individuals [12]. Particular attention has been drawn to the two most active tamoxifen metabolites, 4OHtam and 4OHNDtam (endoxifen), in which serum levels have consistently been shown to be associated with CYP2D6 phenotypes [13–15]. Several studies have reported adverse clinical outcome for patients with low levels of active tamoxifen metabolites [15–17] or impaired enzyme activities [18] leading to argumentation for therapeutic thresholds [19], dose escalation [20, 21] and administering active metabolites as single drugs [22]. However, studies on tamoxifen metabolites and their possible association to side effects, are rare and have reported inconsistent findings [8, 23, 24].

In the present study, we analyzed repeated serum measurements of tamoxifen and 7 metabolites, side effects through patient-reported outcome measures (PROM) data, and prescription data from the Norwegian Prescription Database (NorPD) over a 6-year period in 220 breast cancer patients. We aimed to elucidate possible associations between side effects and tamoxifen metabolite concentrations and to evaluate the reliability of NorPD-determined adherence.

Methods

Participants

Patients using tamoxifen ($N = 220$) were recruited through the Prospective Breast Cancer Biobank (PBCB) (Fig. 1). Established in 2011, PBCB is a prospective population-based biobank project comprising liquid biopsies, clinical- and PROM-data from breast cancer patients recruited at Haukeland and Stavanger University Hospitals [25]. Patients comprising ER-positive tumors ≥ 0.1 cm (pT1a) i.e. tumors with ER positivity ≥ 1% and/or PR positivity > 10% were enrolled. All patients received 20 mg of tamoxifen daily and were able to read and write Norwegian.

Blood sample collection & tamoxifen metabolite measurement

Serum samples were drawn every 6 months and/or yearly in Vacuette™ serum tubes containing clot activator, coagulated for 30–60 min and centrifuged for 10 min at 2200 g and stored at − 80 °C. All patients were given instructions not to take anti-hormonal drugs on the morning blood was drawn and were thus considered drug-fasting.

We used a modification of a previously published LC–MS/MS method [15] to quantify tamoxifen and seven of its metabolites. In brief, serum samples of 20 µL were protein precipitated in acetonitrile containing deuterated internal standards, and 80 µL of the supernatant was evaporated to dryness under nitrogen flow before being reconstituted in 500 µL water:methanol (20:80, v:v). The samples were then injected onto a BEH Phenyl column from Waters (100 mm × 2.1 mm, 1.7 µm particle size) and chromatographically separated on an Aquity UPLC system from Waters (Milford, MA, USA), using a 0.01% aqueous solution of formic acid and methanol and methanol as weak and strong mobile phases, respectively. The compounds were subjected to atmospheric pressure photoionization (APPI) and detected in positive mode using a Xevo TQ-S tandem mass spectrometer (Waters).

Instruments

Questionnaires mapping various side effects were distributed to patients by mail every 6 months and/or yearly between 2011 and 2017 for 124 patients. The remaining 96 patients were issued one set of questionnaires in 2016. Only questionnaires from patients who had answered during the first 3 years of treatment and had started tamoxifen therapy (> 1 month) were included in the analyses. We restricted our analyses to items similar to side effects of tamoxifen described as "very common" or "common" by the Physician's Drug Handbook (www.felleskatalogen.no).

The validated Norwegian version of Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES) version 4 consists of 46-items divided into four subscales that measure social, physical, emotional and functional aspects of Quality of Life (QoL). This instrument is suitable to assess toxicity of endocrine treatment as it includes

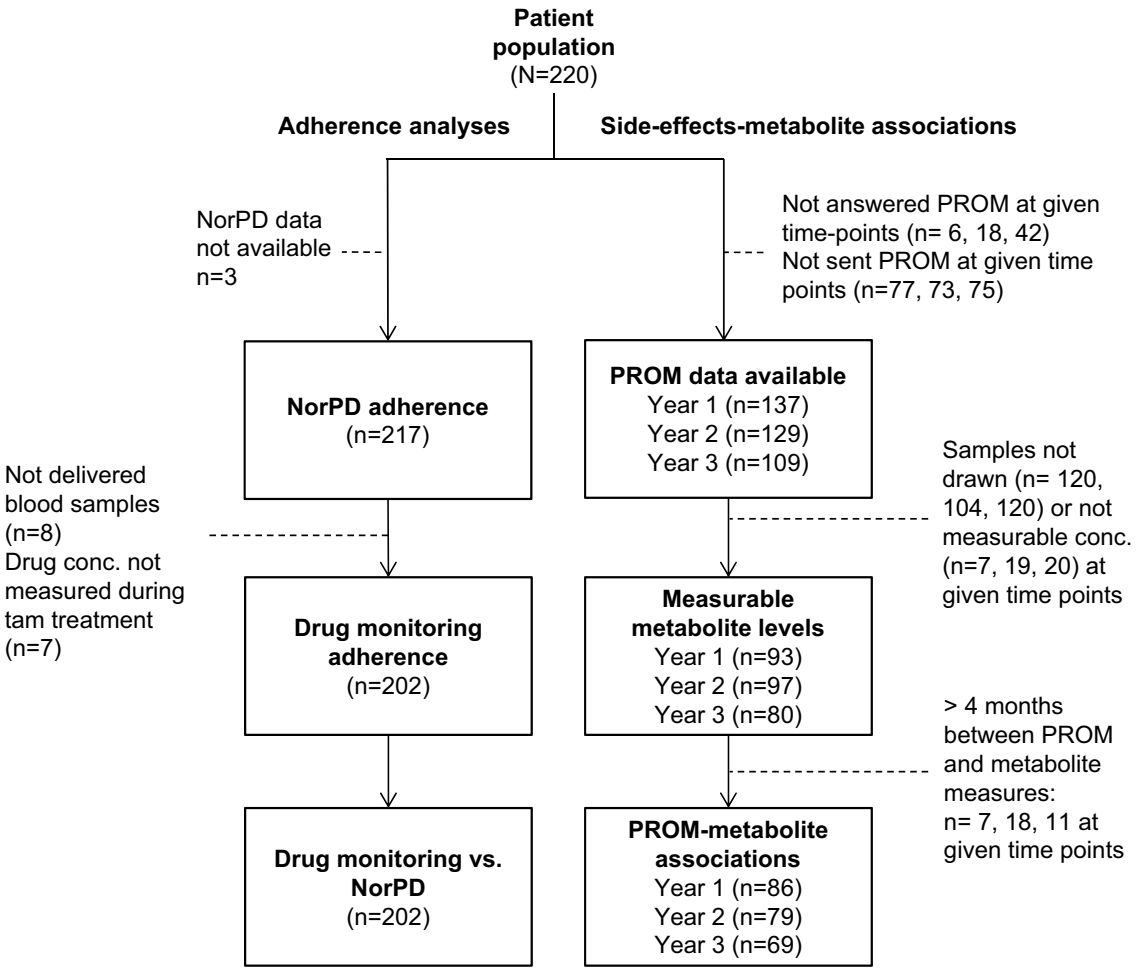


Fig. 1 Study flow diagram. Flow chart of two sub-studies; adherence (left) and side effect-metabolite associations (right). *Conc* concentration(s), *PROM* patient-reported outcome measures, *NorPD* Norwegian prescription database, *tam* tamoxifen

an endocrine symptoms subscale that specifically measures common side effects associated with breast cancer endocrine therapy [26]. Patients rated the statements presented in the questionnaire according to a scale ranging from 0 (not at all) to 4 (very much). The values "quite a bit" (3) and "very much" (4) were considered to be "severe" and the remaining values were recoded to be "not severe". The yes/no variable was coded so that "not at all" was recoded to "no" and all other values were coded to "yes".

Persistence, adherence and discontinuation according to Norwegian Prescription database

Data from January 2011 to December 2017 were extracted from the NorPD at the Norwegian Institute of Public Health that records all drugs ordered and prescribed from pharmacies in Norway [27]. The NorPD supplied dates and number of pills from each outtake/refill of breast cancer endocrine treatment drugs for the above-mentioned period. Persistence refers to the total amount of time in which a patient has been using the drug and was calculated as the difference in time between the dates of the first drug-outtake and the last refill + quantity of days from the last refill determined by amount of pills (1 pill = 1 day). Adherence refers to a patient's commitment to follow the prescription guidelines [28] and we used medication possession ratio (MPR) to calculate adherence. MPR is the sum of days covered by the prescriptions divided by the number of days the patient was observed. This is further calculated to percentages and we applied an 80% cut-off for non-adherence. This is a commonly used cut-off for tamoxifen [29], as missing a dose or two is not expected to affect treatment efficacy due to its long half-life. Discontinuation means stopping the treatment before the end of the pre-decided treatment time. Patients with a lapse in treatment of more than 60 days were considered to have discontinued. As we had access to prescription data for all endocrine breast cancer drugs we could account for

patients that had switched from tamoxifen to an aromatase inhibitor and code them accordingly.

Persistence and discontinuation according to tamoxifen concentrations

Persistence according to drug concentrations was calculated as the time period between the first outtake of tamoxifen registered by NorPD to either of the two scenarios; (1) date of the last blood sample drawn with measurable endoxifen concentrations (> 1 nM) or (2) date of the first sample with no-measurable endoxifen concentrations (≤ 0.9 nM). The patients were coded to have continued if the first scenario was true or to have discontinued if the last was true.

Data analyses and statistics

Inter-patient variability and intra-patient variability was calculated by coefficient of variation (CV) calculated as; "standard deviation of the concentration × 100/mean concentration". To identify differences between years in side effects and metabolite concentrations we applied linear mixed models to account for a mixture of pair-wise and independent samples. To analyze associations between metabolite concentrations and side effects we included only patients that had metabolites measured within 4 months of answering the questionnaires to ensure that concentration levels were a valid representation of the toxicity measures. Binary logistic regression was applied to search for a linear association between concentration levels (continuous variable) and reporting a certain side effect (dichotomized categorical variable). Cross tables using Fisher exact test for significance was used to analyze relationships between the highest/lowest quartiles of metabolites and dichotomized side effects. Benjamin-Hochberg's false discovery rate procedure was used to correct for multiple testing and only *p*-values significant after correction were considered significant. Kaplan–Meier curves were applied to illustrate discontinuation over time decided by NorPD and drug monitoring. Uni- and multivariable regression analysis adjusting for clinically relevant variables was performed using the Cox proportional hazards method. To avoid "immortal time bias" conditional Cox analyses and time-dependent covariates were applied when necessary. Statistical analyses were conducted using SPSS Statistical software version 24 (SPSS, Inc., Chicago, IL, USA) and MedCalc for Windows, version 16.4.3 (MedCalc Software, Ostend, Belgium).

Results

Patient characteristics and demographics

The clinical and demographic characteristics of the patients are shown in Table 1. Our patient population is skewed towards younger age and more unfavorable prognosis, which is reflected by the high percentage of patients receiving chemotherapy. As much as 44% of the patients were classified as overweight according to BMI ≥ 25, and 86% of the patients were pre-menopausal according to a 55 years age cut-off.

Table 1 Patient characteristics and demographics

Characteristics	Grouping	Study population ($N = 220$)
Age at diagnosis, years	Mean (median)	48.69 (48.08)
	Range (min–max)	60 (24–84)
Menopause status, n (%)	Pre (< 55 years)	188 (85.50)
	Post (> 55 years)	32 (14.50)
BMI (kg/m^2)	Mean (median)	25.30 (24.57)
Surgery, n (%)	Breast conserving	107 (48.60)
	Mastectomy	109 (49.50)
	Unknown	4 (1.90)
Chemotherapy, n (%)	Yes	196 (89.10)
	No	24 (10.90)
Radiation, n (%)	Yes	165 (75.00)
	No	54 (24.50)
	Unknown	1 (0.50)
Tumor size, n (%)	pT1	108 (49.10)
	pT2	84 (38.20)
	pT3	16 (7.30)
	pT4	7 (3.20)
	pTx	5 (2.30)
Tumor grade, n (%)	G1	30 (13.60)
	G2	113 (51.40)
	G3	64 (29.10)
	Unknown	13 (5.90)
Node status, n (%)	Positive	81 (36.80)
	Negative	138 (62.70)
	Not reported	1 (0.50)
HER2 status, n (%)	HER2$^+$	37 (16.80)
	HER2$^-$	182 (82.70)
	Not reported	1 (0.50)

Total patient population = 220. Menopause status is pseudo-assessed using 55 years of age as cut-off for menopause

BMI body mass index, *pT* pathological tumor size, *G* grade

Tamoxifen metabolite measures

A total of 898 serum samples from 212 patients were available for LC–MS/MS analysis, of which 166 samples were found to be blank (< 0.9 nM endoxifen). The mean and median concentrations separated by years are shown in online resource 1. The first sample from each patient that exhibited concentrations above 0.9 nM Z-endoxifen was used to calculate mean and median concentration of 196 patients at steady state (Table 2). Z-endoxifen was the metabolite with the highest variation between patients (~ 62%). Tamoxifen metabolites varied on average ~ 23% within the patients and tam-NoX demonstrated the highest degree of intra-patient variability ~ 33% (Table 2).

Side effects

The mean scores of tamoxifen-related toxicity items (FACT-ES v.4) at 1, 2 and 3 years after surgery are presented in Table 3. Approximately, 77% of the patients reported that they experienced some form of side effects at the 1st year after surgery and this number did not change significantly over 3 years. The most common side effect in our patient population was hot flashes as ~ 87% of the patients reported hot flashes at year 1 after surgery. Approximately, 40% of patients reported severe hot flashes on average over 3 years and a non-significant increase in severe hot flashes was observed over 3 years. Other side effects reported as severe were vaginal dryness (18.5%), decreased libido (26.1%) and joint pain (30.2%). Baseline data (FACT-ES questionnaires at time of surgery) were obtained from patients included in Stavanger ($N = 78$). We found quality of life and endocrine symptoms to be significantly worsened at 1, 2 and 3 years compared to baseline (online resource 2).

Table 2 Concentrations of tamoxifen metabolites in 196 breast cancer patients

Compounds	Concentrations mean (median)	Inter-patient variability (%)	Mean intra-patient variability
Tamoxifen	296.41 (284.41)	42.31	22.95
NDtam	604.29 (567.86)	40.99	21.74
Z-endoxifen	29.79 (26.44)	61.92	24.76
Z-4OHtam	5.32 (4.97)	49.86	21.45
Z-4′-endoxifen	23.45 (22.16)	39.72	19.08
Z-4′OHtam	7.60 (7.15)	40.47	19.51
Tam-NoX	20.10 (17.43)	55.35	32.91
NNDDtam	88.50 (84.38)	42.10	22.02

Analysis is limited to patients with measurable tamoxifen metabolite levels (Z-endoxifen > 0.9 nM). Intra-patient variability is calculated from patients with ≥ 3 longitudinal measures and presented as mean. Concentrations are in nM

Table 3 Patient-reported side effects

Side effect	Year 1[a]	Year 2	Year 3	*P*-val.
Any side effects	1.62	1.60	1.58	0.92
I feel sick	0.57	0.66	0.58	0.56
Thrown up	0.06	0.10	0.13	0.43
Nausea	0.29	0.33	0.38	0.54
Hot flushes	2.21	2.09	2.15	0.40
Light headed	0.55	0.58	0.58	0.90
Vaginal discharge	0.86	0.74	0.86	0.21
Vaginal bleeding	0.10	0.13	0.17	0.53
Vaginal dryness	1.07	1.16	1.38	0.09
Vaginal irritation	0.44	0.52	0.55	0.46
Lost interest in sex	1.39	1.47	1.65	0.20
Pain in joints	1.49	1.90	1.77	0.21
Mood swings	1.18	1.28	1.19	0.45

Side effects represent mean scores from 5-point (0–1–2–3–4) FACT-ES scale. Higher score indicates higher degree of side effect

P value test for difference in mean score between years, mixed models

[a]Years after commencing of primary treatment

Side effects in association with tamoxifen metabolite concentrations

To identify associations between tamoxifen metabolite concentrations and side effects, we applied two approaches described in the method section using dichotomized FACT-ES items (no/yes) (online resource 3 and 4). We only considered associations that replicated in both approaches after correction for multiple testing to be clinically significant. After applying these strict criteria we observed that patients who reported vaginal dryness on year 2 after surgery had significantly higher levels of tamoxifen, tam-NoX and Z-4′OHtam (Table 4). No significant associations were found when analyzing vaginal dryness on year 1 and 3. Multivariate analyses including age, BMI, surgery method and chemotherapy did not change these results. Additional analyses on the year 2 association showed a significant linear increase of tamoxifen for each point of the 5-point scale for vaginal dryness ($p = 0.001$), and that patients with severe vaginal dryness had significantly higher levels of tamoxifen compared to patients without severe vaginal dryness ($p = 0.013$) (online resource 5).

Adherence, persistence and discontinuation

The median follow-up time assessed by NorPD was 3 years. For drug monitoring, the median follow-up time was 2.5 years with an average of four samples per patient. At 5 years, 17.9% of the patients using tamoxifen alone had discontinued according to NorPD (Fig. 2a) and 14.7%

Table 4 Vaginal dryness in association to tamoxifen metabolite concentrations

Metabolite[a]	P	Exp(B)	CI 95 lower	CI 95 upper	n	P	Rel. Risk	CI 95 lower	CI 95 upper	n
Z-endoxifen	0.469	1.008	0.986	1.031	79	0.744	0.925	0.625	1.369	41
Z-4'-endoxifen	*0.019*	*1.067*	*1.011*	*1.127*	*79*	0.062	1.623	0.982	2.682	43
Tamoxifen	**0.023**	**1.006**	**1.001**	**1.011**	**79**	**0.007**	**2.294**	**1.166**	**4.51**	**38**
NDtam	*0.031*	*1.002*	*1*	*1.004*	*79*	0.1	1.472	0.941	2.302	41
TamNoX	**0.027**	**1.067**	**1.007**	**1.131**	**79**	**0.017**	**1.823**	**1.103**	**3.013**	**41**
Z-4OHtam	0.068	1.218	0.986	1.505	79	0.299	1.314	0.831	2.076	39
Z-4'-OHtam	**0.02**	**1.245**	**1.036**	**1.497**	**79**	**0.011**	**2.024**	**1.138**	**3.598**	**41**
NNDDtam	0.103	1.01	0.998	1.021	79	*0.01*	*2.256*	*1.188*	*4.281*	*39*

FACT-ES determined vaginal dryness was dichotomized to no/yes from 5 point scale

Values in italics are significant after correction for multiple testing (false discovery rate). Values in bold indicates significance in both tests

P Fisher's Exact Test (2-sided), *n* number of patients included in analyses, *Exp (B)* odds ratio, *CI 95* confidence interval 95%

[a]Left, binary logistic regression using metabolite concentrations as a continuous explanatory variable. Right, cross table analysis w/relative risk for vaginal dryness highest versus lowest quartile of concentrations

had discontinued according to drug monitoring (Fig. 2b). When including the patients who had switched to an aromatase inhibitor, the rate was 39.9% according to NorPD and 41.8% according to drug monitoring (Fig. 2c,d, respectively). Figure 2e shows that when including all patients in the drug monitoring analysis, most of the "discontinuers" had switched endocrine therapy. The majority (~ 76%) of the patients who switched, had switched in line with treatment guidelines [30]. After switching from tamoxifen to an AI, 11.6% discontinued the AI-treatment before the predetermined duration. Adherence to tamoxifen was overall very well maintained with only 2.8% of the patients being non-adherent (Table 5).

Predictors for discontinuation

Being non-adherent significantly increased the risk of discontinuation (HR = 5.68, CI 95 = 1.94–16.66). Not receiving chemotherapy (HR = 3.72, CI 95 = 1.56–8.91), severe vaginal dryness at 1st year of therapy (HR = 3.72, CI 95 = 1.49–9.72), and reporting nausea at the 1st year after surgery (HR = 4.10, CI 95 = 1.25–13.45) were all predictors of discontinuation in univariate analysis. All variables remained significant after adjusting for age, BMI, surgery method and node status.

Discussion

In the present study we have shown that patients with high levels of tamoxifen, Z-4′OHtam and tam-NoX reported significantly more vaginal dryness at the 2nd year after surgery compared to patients with lower levels. We further showed that NorPD-determined tamoxifen discontinuation was in concordance with drug monitoring of serum concentrations of tamoxifen metabolites.

Hot flashes are recognized as the main side effect of tamoxifen and were reported by 86% of the patients in our cohort, which is somewhat higher than what has previously been reported [31]. The high number may be associated to the high percentage of patients receiving chemotherapy in this study (89%). In addition, healthy women frequently experience several endocrine symptoms of tamoxifen during menopause [32]. Since the median age of our patient population was 48 years, the endocrine symptoms measured by FACT-ES could in part have been menopause related. We therefore compared endocrine symptoms reported before and after start of endocrine treatment, and found a significant worsening of endocrine symptoms at years 1 through 3 compared to baseline (online resource 2). This indicates that the endocrine symptoms reported by our patients were more likely related to tamoxifen-use and not naturally occurring menopause symptoms.

To the best of our knowledge, only four other studies [8, 23, 24, 33] have investigated the association between tamoxifen metabolite concentrations and side effects. Our study is the first to report that vaginal dryness increases significantly

with increasing tamoxifen, tam-NoX and Z-4′OHtam serum concentrations. Earlier studies linking tamoxifen metabolites to side effects have not identified this association. On the contrary, Gallicchio et al. [23] found tamoxifen concentrations to be higher in patients that did *not* report vaginal dryness. However, Gallicchio's finding did not reach statistical significance. We found that three separate metabolites were associated with vaginal dryness and this pattern (several metabolites being associated to the same side effect) is also evident in other studies associating tamoxifen metabolites to side effects [8, 23, 33]. This phenomena is likely caused by the strong correlation between metabolites in our dataset (Spearman's Rho ranging from 0.388 to 0.813, $p < 0.0001$) which makes it difficult to single out possible side effects related to one specific metabolite. However, further analyses (online resource 5) on the association between vaginal dryness and metabolites, only tamoxifen remained significant. Tamoxifen has been reported to have both estrogenic and anti-estrogenic effects on vaginal tissue [34]. Our data imply that vaginal dryness from tamoxifen is not a direct effect of reduced estrogenization, as the active metabolites were not predictive of this condition. We, therefore, speculate that the lipophilic nature of the mother drug tamoxifen has a higher relevance for vaginal dryness than the more hydrophilic metabolites. Tamoxifen accumulates in the phospholipid bilayer of cell membranes where it can alter the membrane integrity and function [35, 36], which may in turn disturb the lubrication function of the vaginal epithelial cells.

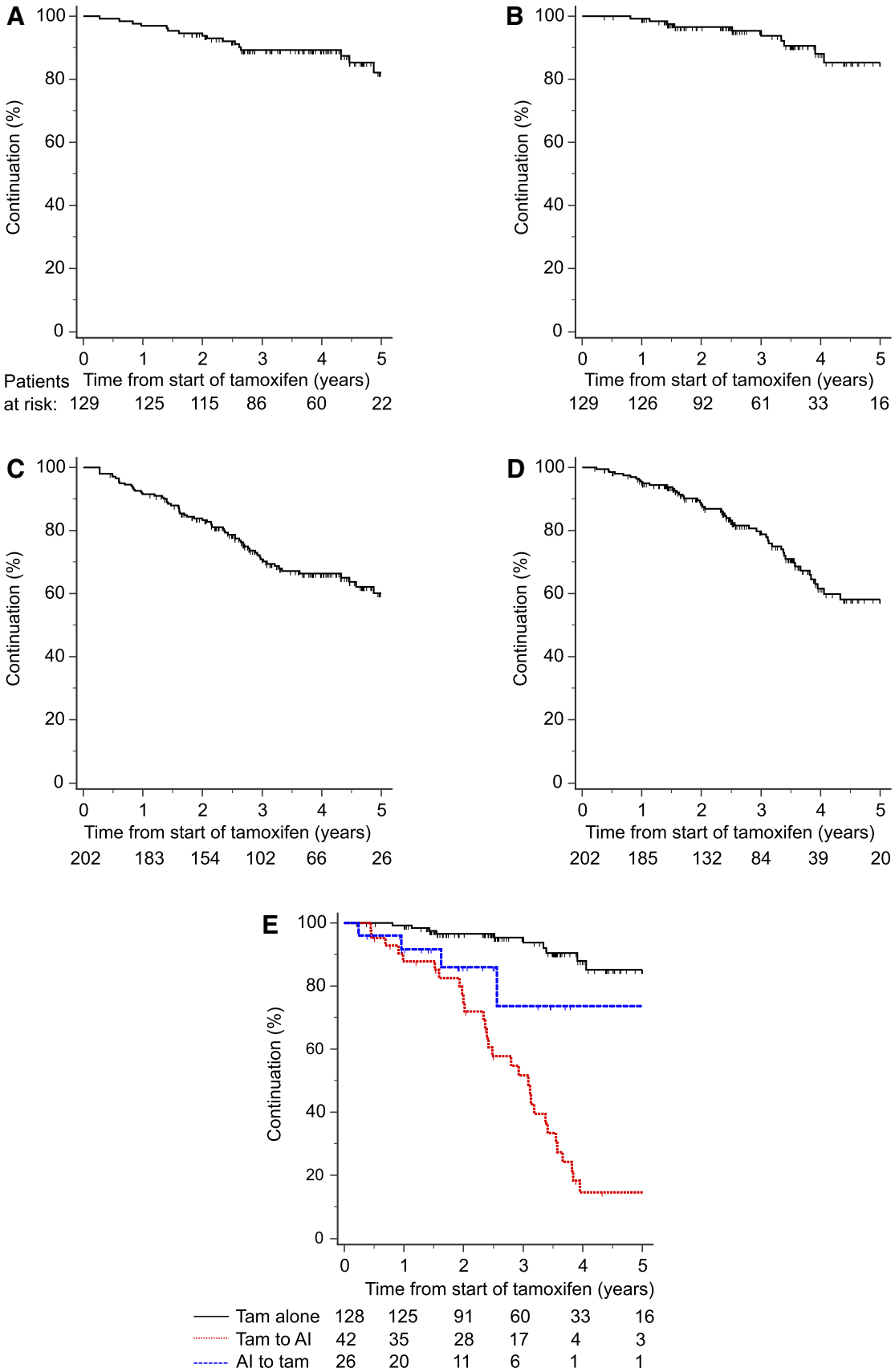
To our knowledge, this is the first study comparing discontinuation of tamoxifen from pharmacy records (NorPD) and longitudinal drug monitoring. Using NorPD, we found a discontinuation rate of 19.4% at 5 years, whereas other studies have reported discontinuation rates ranging from 15 to 60% [5, 28, 37]. As far as we have learned, all discontinuation rates previously reported for tamoxifen are based on information obtained through either self-reported data or prescription databases. Prescription databases are considered superior to self-reported adherence and have been validated through pill counting [38]. However, pill counting does not provide direct evidence for a patients' consumption of a drug. Cross table analysis comparing continuation statues assessed through drug monitoring and NorPD revealed that only 4 out of 55 patients (7.2%) had discontinued according to drug monitoring and not by NorPD. The remaining 51 patients had either switched to an AI or were also identifiable as discontinuers by the NorPD. When comparing Kaplan–Meier curves obtained through the two methods of monitoring adherence, the curves are strikingly similar (Fig. 2a–d). Taken together, our results indicate that measuring discontinuation by pharmacy refill records is a reliable source of information. Interestingly, patients switching from an AI to tamoxifen seem to have a higher chance of discontinuing (Fig. 2e). Switching from an AI to tamoxifen is rarely a pre-determined treatment regime, and these patients have most likely switched due to side effects of an AI. Since our data indicate that these patients are more likely to quit tamoxifen, special attention should be given to this patient group.

It is generally believed that tamoxifen's side effect profile is central for women who decide to abandon therapy early [6, 7, 39, 40], but also demographic and clinical characteristics including age and comorbidities have been reported to be associated with early discontinuation [5]. Our data confirm side effects as an important predictor of discontinuation of tamoxifen, as we have shown that women who reported nausea were more likely to quit tamoxifen. Moreover, we found that women who reported severe vaginal dryness at the 1st year of therapy were more likely to stop treatment early. The latter finding was contradicted by Aiello et al. who found that vaginal dryness was associated with decreased odds of stopping tamoxifen [7]. However, their study was based on self-reported adherence data, hence differences in methods for assessment of adherence might have caused the discrepancy with our findings.

We found that patients who did not receive chemotherapy had a higher risk of discontinuation. Patients receiving chemotherapy undergo ovarian suppression with lower estrogen levels as a consequence [41]. Thus, these patients may become accustomed to low systemic estrogen levels before the transition to tamoxifen or AIs take place after termination of chemotherapy. They will likely report fewer and less severe side effects than those who start off directly on tamoxifen or aromatase inhibitor. In addition, these patients will be followed by a specialist/health care provider, who may give advice on endocrine treatment, which may have contributed to the lower the rates of discontinuation among these patients. Furthermore, having more serious disease may increase the motivation for long-term tamoxifen-use. In contrast to earlier findings [5, 42] we did not find age to be a significant predictor of tamoxifen discontinuation.

Our results should be evaluated in the context of certain weaknesses. Firstly, neither the follow-up for blood samples, nor the PROM data were complete. This caused some gaps when linking metabolite measures to PROM data and lower numbers of patients for the association between side effects and tamoxifen metabolite levels at separate years (Fig. 1) and limited the use of paired analyses and trends over time for this association. The low number of included patients at each time-point calls for caution in interpretation of the association between vaginal dryness and tamoxifen metabolite concentrations, and the result should be validated in larger studies.

On the strong side, as the results are based upon real-world data, they should be considered representative for


A
B
C
D
E
Continuation (%)
100
80
60
40
20
0
0 1 2 3 4 5
Time from start of tamoxifen (years)
Patients at risk: 129 125 115 86 60 22
129 126 92 61 33 16
202 183 154 102 66 26
202 185 132 84 39 20
Tam alone 128 125 91 60 33 16
Tam to AI 42 35 28 17 4 3
AI to tam 26 20 11 6 1 1

◂**Fig. 2** Endocrine treatment persistence. **a**, **b** Tamoxifen continuation for patients using tamoxifen alone decided through NorPD and drug monitoring, respectively. **c** NorPD tamoxifen continuation, including switch to AIs. **d** Drug monitoring decided continuation including all patients. **e** Drug monitoring continuation compared between patients who have used tamoxifen alone (Non-stippled black line), switched from tamoxifen to an AI (red-dotted line), and switched from AI to tamoxifen (blue-dashed line)

Table 5 Adherence, persistence and discontinuation in breast cancer patients treated with tamoxifen

Factor	*N*	%
Adherence tamoxifen (80% cut-off), NorPD		
Adherent	211	97.2
Not adherent	6	2.8
Discontinuation tamoxifen, NorPD		
Continued tamoxifen	143	65.9
Discontinued tamoxifen	26	12
Switched to AI	48	22.1
Mean (median) follow-up time, years	3.09 (2.97)	–
Discontinuation tamoxifen, drug monitoring		
Continued tamoxifen	147	72.8
Discontinued tamoxifen	55	27.8
Mean (median) follow-up time, years	2.80 (2.53)	–
Tamoxifen alone or switch, NorPD		
Tamoxifen alone	139	64.1
Switch to alternative endocrine treatment	78	35.9
Switch Tamoxifen to AI, NorPD		
Changed according to guidelines	38	77.6
Changed because of side effects	11	22.4
Switch AI to tamoxifen, NorPD		
Changed according to guidelines	24	75
Changed because of side effects	8	25
Continuation after switch to AI, NorPD		
Continued after switch to AI	38	88.4
Discontinued after switch to AI	5	11.6

AI aromatase inhibitor, *NorPD* Norwegian prescription database

*Medication Possession Rate (MPR) of 80% meaning patients taking 80% of pills during a given period and is a proxy for adherence

**Discontinuation determined by NorPD means patients stopping tamoxifen for > 60 days

***Discontinuation by drug monitoring means patients that presented with a blank serum sample during pre-determined tamoxifen treatment period

Norwegian breast cancer patients on endocrine adjuvant systemic therapy.

In conclusion, NorPD-determined tamoxifen discontinuation is very low, which was confirmed by longitudinal serum tamoxifen metabolite measurements. Predictors of discontinuation of tamoxifen are non-adherence, chemotherapy naive status, 1st year nausea and vaginal dryness—which for the latter was predicted by high serum concentrations of tamoxifen and two of its metabolites.

Acknowledgements We would like to thank all the patients that currently are, or have been, participating in the Prospective Breast Cancer Biobank (PBCB) project.

Funding The present study was funded by the Western Norway Regional Health Authority, Folke Hermansen Foundation and Inge Steenslands Foundation.

Conflict of interest All authors declare no conflict of interest.

Ethical approval The Prospective Breast Cancer Biobank in which this population was obtained was approved by the Norwegian Regional Ethical Committee (2010/1957 and 2011/2161).

Informed consent All participants provided written informed consent before enrolling. All personal identifiers for each case in this population cohort were removed before analyses.

References

1. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM et al (2005) Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. J Nat Cancer Inst 97(22):1652–1662. https://doi.org/10.1093/jnci/dji372
2. Jackisch C, Harbeck N, Huober J, von Minckwitz G, Gerber B et al (2015) 14th St. Gallen International Breast Cancer Conference 2015: evidence, controversies, consensus - primary therapy of early breast cancer: opinions expressed by German experts. Breast Care 10(3):211–219. https://doi.org/10.1159/000433590
3. Davies C, Pan H, Godwin J, Gray R, Arriagada R et al (2013) Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381(9869):805–816
4. Gray RG, Rea D, Handley K, Bowden SJ, Perry P et al (2013) aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol. https://doi.org/10.1200/jco.2013.31.18_suppl.5
5. Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A et al (2010) Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 28(27):4120–4128. https://doi.org/10.1200/jco.2009.25.9655
6. Owusu C, Buist DSM, Field TS, Lash TL, Thwin SS et al (2008) Predictors of tamoxifen discontinuation among older women with estrogen receptor–positive breast cancer. J Clin Oncol 26(4):549–555. https://doi.org/10.1200/jco.2006.10.1022
7. Aiello Bowles EJ, Boudreau DM, Chubak J, Yu O, Fujii M et al (2012) Patient-reported discontinuation of endocrine therapy and related adverse effects among women with early-stage breast cancer. J Oncol Pract 8(6):e149–e157. https://doi.org/10.1200/jop.2012.000543
8. Lorizio W, Wu AHB, Beattie MS, Rugo H, Tchu S et al (2012) Clinical and biomarker predictors of side effects from tamoxifen. Breast Cancer Res Treat 132(3):1107–1118. https://doi.org/10.1007/s10549-011-1893-4

9. Garreau JR, DeLaMelena T, Walts D, Karamlou K, Johnson N (2006) Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective. Am J Surg 192(4):496–498. https://doi.org/10.1016/j.amjsurg.2006.06.018
10. Ganz PA (2001) Impact of tamoxifen adjuvant therapy on symptoms, functioning, and quality of life. JNCI Monog 2001(30):130–134. https://doi.org/10.1093/oxfordjournals.jncimonographs.a003450
11. Early Breast Cancer Trialists' Collaborative G (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 378(9793):771–784. https://doi.org/10.1016/S0140-6736(11)60993-8
12. Klein DJ, Thorn CF, Desta Z, Flockhart DA, Altman RB et al (2013) PharmGKB summary: tamoxifen pathway, pharmacokinetics. Pharmacogenet Genomics 23(11):643–647. https://doi.org/10.1097/FPC.0b013e3283656bc1
13. Coller JK, Krebsfaenger N, Klein K, Endrizzi K, Wolbold R et al (2002) The influence of CYP2B6, CYP2C9 and CYP2D6 genotypes on the formation of the potent antioestrogen Z-4-hydroxytamoxifen in human liver. Br J Clin Pharmacol 54(2):157–167
14. Gjerde J, Hauglid M, Breilid H, Lundgren S, Varhaug JE et al (2007) Effects of CYP2D6 and SULT1A1 genotypes including SULT1A1 gene copy number on tamoxifen metabolism. Ann Oncol 19(1):56–61. https://doi.org/10.1093/annonc/mdm434
15. Helland T, Henne N, Bifulco E, Naume B, Borgen E et al (2017) Serum concentrations of active tamoxifen metabolites predict long-term survival in adjuvantly treated breast cancer patients. Breast Cancer Res 19:125. https://doi.org/10.1186/s13058-017-0916-4
16. Madlensky L, Natarajan L, Tchu S, Pu M, Mortimer J et al (2011) Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. Clin Pharmacol Therap 89(5):718–725. https://doi.org/10.1038/clpt.2011.32
17. Saladores P, Murdter T, Eccles D, Chowbay B, Zgheib NK et al (2015) Tamoxifen metabolism predicts drug concentrations and outcome in premenopausal patients with early breast cancer. Pharmacogenomics J 15(1):84–94. https://doi.org/10.1038/tpj.2014.34
18. Gm P, Katrin S, Henk-Jan G, Matthias S, Michael P et al (2018) Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and tamoxifen therapy. Clin Pharmacol Therap 103(5):770–777. https://doi.org/10.1002/cpt.1007
19. Jager NG, Linn SC, Schellens JH, Beijnen JH (2015) Tailored tamoxifen treatment for breast cancer patients: a perspective. Clin Breast Cancer 15(4):241–244
20. Barginear MF, Jaremko M, Peter I, Yu C, Kasai Y et al (2011) Increasing tamoxifen dose in breast cancer patients based on CYP2D6 genotypes and endoxifen levels: effect on active metabolite isomers and the antiestrogenic activity score. Clin Pharmacol Therap 90(4):605–611. https://doi.org/10.1038/clpt.2011.153
21. Jr WJI, Walko CM, Weck KE, Ibrahim JG, Chiu WK et al (2011) Genotype-guided tamoxifen dosing increases active metabolite exposure in women with reduced CYP2D6 metabolism: a multicenter study. J Clin Oncol 29(24):3232–3239. https://doi.org/10.1200/jco.2010.31.4427
22. Goetz MP, Suman VJ, Reid JM, Northfelt DW, Mahr MA et al (2017) First-in-human phase I study of the tamoxifen metabolite Z-endoxifen in women with endocrine-refractory metastatic breast cancer. J Clin Oncol 2017(2073):3246
23. Gallicchio L, Lord G, Tkaczuk K, Danton M, Lewis LM et al (2004) Association of tamoxifen (TAM) and TAM metabolite concentrations with self-reported side effects of TAM in women with breast cancer. Breast Cancer Res Treat 85(1):89–97. https://doi.org/10.1023/B:BREA.0000021050.92539.b0
24. Peyrade F, Frenay M, Etienne M-C, Ruch F, Guillemare C et al (1996) Age-related difference in tamoxifen disposition. Clin Pharmacol Therap 59(4):401–410. https://doi.org/10.1016/S0009-9236(96)90108-3
25. Lunde S, Helland T, Jonassen J, Haugstøyl ME, Austdal M et al (2018) A prospective, longitudinal, breast cancer biobank (PBCB) in western Norway. Research Gate. https://doi.org/10.13140/rg.2.2.16266.11201
26. Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D (1999) Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. Breast Cancer Res Treat 55(2):189–199
27. Furu K (2008) Establishment of the nationwide Norwegian Prescription Database (NorPD)–new opportunities for research in pharmacoepidemiology in Norway. Norsk Epidemiologi. https://doi.org/10.5324/nje.v18i2.23
28. Ayres LR, Baldoni AdO, Borges APdS, Pereira LRL (2014) Adherence and discontinuation of oral hormonal therapy in patients with hormone receptor positive breast cancer. Int J Clin Pharm 36(1):45–54. https://doi.org/10.1007/s11096-013-9833-5
29. Partridge AH, Wang PS, Winer EP, Avorn J (2003) Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 21(4):602–606. https://doi.org/10.1200/JCO.2003.07.071
30. NBCG (2017) National action plan with guidelines for diagnosis, treatment and follow up of breast cancer patients. vol IS-2669. Norwegian Directory of Health, www.helsedirektoratet.no
31. Mom CH, Buijs C, Willemse PH, Mourits MJ, de Vries EG (2006) Hot flushes in breast cancer patients. Crit Rev Oncol/Hematol 57(1):63–77. https://doi.org/10.1016/j.critrevonc.2005.04.009
32. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL et al (1996) Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Nat Cancer Inst 88(21):1529–1542. https://doi.org/10.1093/jnci/88.21.1529
33. Jager NG, Koornstra RH, Vincent AD, van Schaik RH, Huitema AD et al (2013) Hot flashes are not predictive for serum concentrations of tamoxifen and its metabolites. BMC Cancer 13:612. https://doi.org/10.1186/1471-2407-13-612
34. Polin SA, Ascher SM (2008) The effect of tamoxifen on the genital tract. Cancer Imaging 8(1):135–145. https://doi.org/10.1102/1470-7330.2008.0020
35. Tsuda K, Nishio I (2005) A selective estrogen receptor modulator, tamoxifen, and membrane fluidity of erythrocytes in normotensive and hypertensive postmenopausal women: an electron paramagnetic resonance investigation. Am J Hypertens 18(8):1067–1076. https://doi.org/10.1016/j.amjhyper.2005.02.009
36. Suwalsky M, Hernandez P, Villena F, Aguilar F, Sotomayor CP (1998) Interaction of the anticancer drug tamoxifen with the human erythrocyte membrane and molecular models. Zeitschrift fur Naturforschung C. J Biosci 53(3–4):182–190
37. Huiart L, Ferdynus C, Giorgi R (2013) A meta-regression analysis of the available data on adherence to adjuvant hormonal therapy in breast cancer: summarizing the data for clinicians. Breast Cancer Res Treat 138(1):325–328. https://doi.org/10.1007/s10549-013-2422-4
38. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS (2006) Validity of a prescription claims database to estimate medication adherence in older persons. Med Care 44(5):471–477. https://doi.org/10.1097/01.mlr.0000207817.32496.cb
39. Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA (2006) Adherence to tamoxifen over the 5-year course. Breast Cancer Res Treat 99(2):215–220. https://doi.org/10.1007/s10549-006-9193-0
40. Demissie S, Silliman RA, Lash TL (2001) Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. J Clin Oncol 19(2):322–328. https://doi.org/10.1200/jco.2001.19.2.322

41. Lambertini M, Del Mastro L, Viglietti G, Ponde NF, Solinas C et al (2017) Ovarian function suppression in premenopausal women with early-stage breast cancer. Curr Treat Options Oncol 18(1):4. https://doi.org/10.1007/s11864-017-0442-8
42. Huiart L, Dell'Aniello S, Suissa S (2011) Use of tamoxifen and aromatase inhibitors in a large population-based cohort of women with breast cancer. Br J Cancer 104(10):1558–1563. https://doi.org/10.1038/bjc.2011.140

Affiliations

Thomas Helland[1,2] · Kari Britt Hagen[2,3] · Martha Eimstad Haugstøyl[1,2] · Jan Terje Kvaløy[4,6] · Siri Lunde[5] · Kirsten Lode[6] · Ragna Anne Lind[2] · Birgitta Haga Gripsrud[7] · Kristin Jonsdottir[5,6] · Jennifer Gjerde[1,2] · Ersilia Bifulco[2,8] · Steinar Hustad[2,8] · Janne Jonassen[5] · Turid Aas[3] · Tone Hoel Lende[5,9] · Ernst Asbjørn Lien[1,2] · Emiel Adrianus Maria Janssen[4,10] · Håvard Søiland[2,5] · Gunnar Mellgren[1,2]

1 Hormone Laboratory, Haukeland University Hospital, 5020 Bergen, Norway
2 Department of Clinical Science, University of Bergen, Bergen, Norway
3 Department of Breast and Endocrine Surgery, Haukeland University Hospital, Bergen, Norway
4 Department of Mathematics and Natural Science, University of Stavanger, Stavanger, Norway
5 Department of Breast and Endocrine Surgery, Stavanger University Hospital, Stavanger, Norway
6 Department of Research, Stavanger University Hospital, Stavanger, Norway
7 Department of Caring and Ethics, Faculty of Health Sciences, University of Stavanger, Stavanger, Norway
8 Core Facility for Metabolomics, University of Bergen, Bergen, Norway
9 Department of Clinical Medicine, University of Bergen, Bergen, Norway
10 Department of Pathology, Stavanger University Hospital, Stavanger, Norway