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Research Article

Cancer Prevention Research

Clinical Profiles Predict Early Nonadherence to Adjuvant Endocrine Treatment in a Prospective Breast Cancer Cohort

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Abstract

Nonadherence to adjuvant endocrine breast cancer treatment adversely affects disease-free and overall survival. Clinical predictors of nonadherence may allow for specific interventions to reduce nonadherence and improve survival. The aim was to investigate whether clinical characteristics predict nonadherence. Clinical characteristics and information on adherence were obtained from 417 patients with breast cancer in a population-based prospective cohort from southern Sweden using patient charts, pathology reports, and questionnaires filled out at the 1- and 2-year follow-up visits. At the 1- and 2-year follow-up visits, 36 (8.6%) and 33 (9.7%) patients were nonadherent, respectively. Thirteen of the nonadherent patients declined treatment and were never prescribed endocrine treatment. A body mass index (BMI) < 25 kg/m^2, preoperative current smoking, and drinking alcohol less often than twice a month predicted nonadherence at the 1-year [relative risk (RR), 5.24; 95% confidence interval (CI), 2.75–9.97] and the 2-year visits (RR, 4.07; 95% CI, 2.11–7.84) in patients with at least two of these clinical characteristics. When low histologic grade (I) was added to the model, having at least two of these four clinical characteristics predicted nonadherence at the 1-year (RR, 4.94; 95% CI, 2.46–10.00) and the 2-year visits (RR, 4.74; 95% CI, 2.28–9.87), the two profiles had a sensitivity ranging from 60.6% to 72.7%, whereas the specificity ranged from 68.0% to 78.4%. Nonadherence at the 1-year visit was associated with an increased risk for early breast cancer events (HR, 2.97; 95% CI, 1.08–8.15), adjusted for age and tumor characteristics. In conclusion, two clinical profiles predicted early nonadherence and may allow for targeted interventions to increase adherence if validated in an independent cohort. *Cancer Prev Res; 5(5); 735–45. ©2012 AACR.*

Introduction

In Sweden, more than 7,000 women are diagnosed with breast cancer every year (1). A majority these women have estrogen receptor (ER)-positive tumors (2). About 70% of women with ER-positive tumors receive adjuvant endocrine treatment (Per Malmström, personal communication). Hence, every year, 4,000 to 5,000 patients with breast cancer in Sweden start endocrine treatment.

Adjuvant endocrine treatment significantly prolongs disease-free survival and overall survival for patients with breast cancer with hormone receptor–positive tumors (3–6). Recommended endocrine treatment duration is 5 years for tamoxifen and 2 to 5 years for aromatase inhibitors (AI; ref. 7). Patients treated with tamoxifen for only 1 or 2 years have higher breast cancer mortality than patients who complete 5 years of tamoxifen therapy (6, 8).

Nonadherence to adjuvant endocrine treatment has been associated with overall mortality and a shorter disease-free survival in patients with breast cancer (9, 10). Previous publications suggest nonadherence as high as 23.6% after the first year of follow-up (11, 12). Nonadherence increases with each consecutive year (11, 12). Several studies report that nonadherence rates are close to 50% before the end of the recommended 5-year treatment period (11–13). Tamoxifen users seem less adherent than AI users (12, 14, 15), possibly due to differing side effect profiles (4).

Nonadherence has been associated with both psychologic and biologic factors. Studies have identified, with often conflicting results, that factors associated with poor adherence to breast cancer therapy such as type of breast cancer surgery (16, 17), severity of side effects (18, 19), number of tablets (20–22), age (11–13, 15, 20, 23, 24), depression and/or the use of antidepressants (24, 25), socioeconomic disadvantage (26, 27), smoking (28), the impact of breast cancer therapy on quality of life, and the perceived risk–benefit ratio (29).

Clinically accessible markers that individually or in combination reliably predict that nonadherence may allow for

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interventions that decrease nonadherence and improve survival in women treated with adjuvant endocrine breast cancer therapy (30). The aim of this study was to investigate whether constitutional factors such as body mass index (BMI) and waist-to-hip ratio (WHR), lifestyle factors such as smoking, alcohol intake, and natural remedy use, tumor characteristics, detection mode, and type of surgery predict nonadherence to adjuvant endocrine breast cancer therapy, alone or in combination.

Materials and Methods

Women assessed preoperatively for a primary breast cancer at the Skane University Hospital in Lund, Sweden, were invited to take part in an ongoing prospective study about genetic and nongenetic factors that could be associated with breast cancer prognosis. A total of 819 patients were included between October 2002 and June 2010. The patients were invited to participate regardless of age, stage, or ethnic background (most women were ethnic Swedes). Those who had been diagnosed and treated for another type of cancer within the past 10 years were not eligible to participate. We excluded 47 pretreated patients [interstitial laser thermotherapy ($n = 11 + 1$ uncertain) or neoadjuvant systemic therapy ($n = 34 + 1$ patient who received treatment for another cancer between the primary surgery and reoperation)]. Patients with a follow-up shorter than 1 year were excluded as well, leaving 629 patients. After excluding patients with ER-negative tumors and patients who had not been advised to use adjuvant endocrine therapy, the cohort consisted of 417 patients, Fig. 1. The study was approved by the Ethics Committee of Lund University (Lund, Sweden; LU75-02).

Written informed consent was collected during the preoperative visit at the Department of Surgery at the Skane University Hospital. Body measurements were measured by a trained nurse at the preoperative visit. All patients filled out a preoperative questionnaire, including questions on

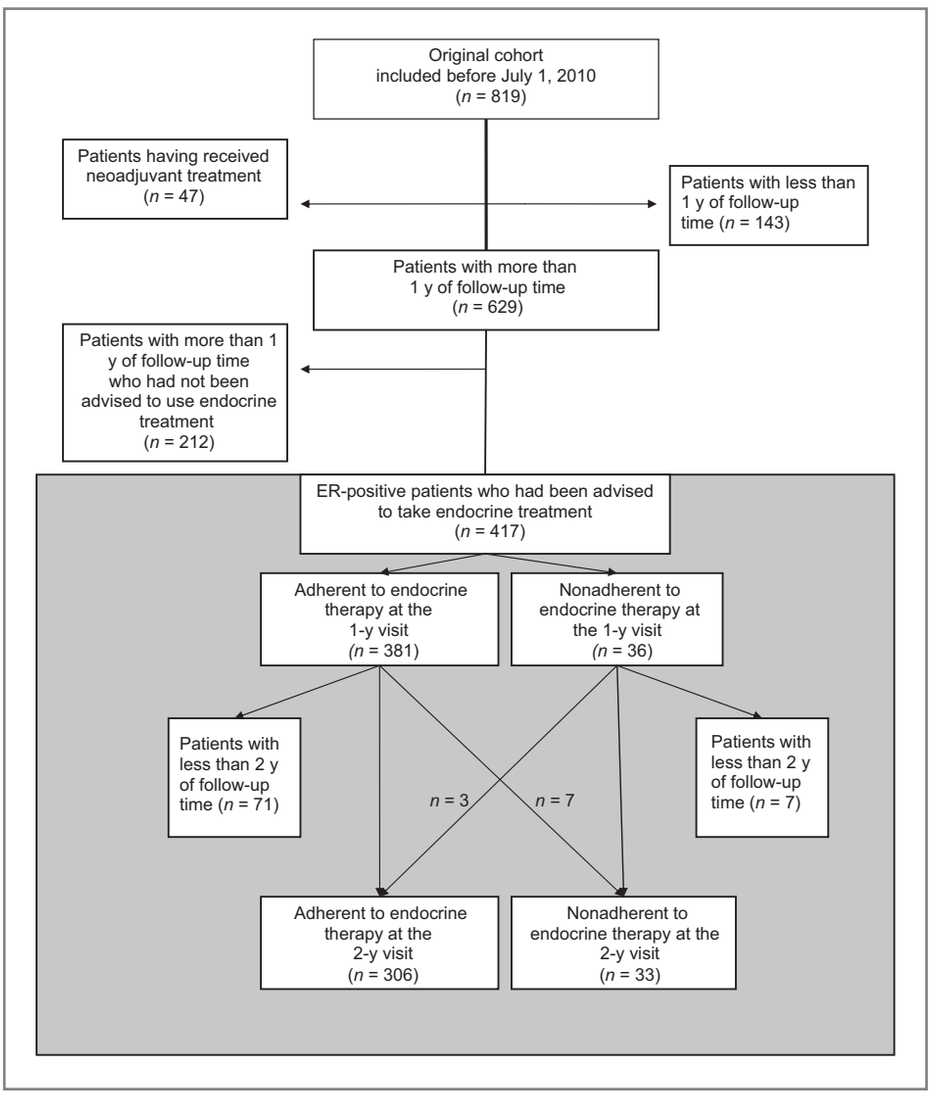

Figure 1. Flowchart of the selection process of patients.

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birth date, coffee consumption, smoking, alcohol intake, reproductive history, use of exogenous hormones, family history of cancer, and concomitant medications. The question about concomitant medications was open, the patients were asked to include all medications used during the past week, including natural remedies and dietary supplements as well as cancer medications. Patients were also asked to specify their food intake on the day they filled out the questionnaire. The number of tablets taken for comorbidities was obtained from the preoperative questionnaire, excluding both vitamins and natural remedies or complementary alternative medications (CAM). Anatomic Therapeutic Chemical (ATC) classification system codes were used to categorize medications; N06A for antidepressants, N06A-N06C and N05A-N05C for psychiatric medications (no patient used medications from the N05D category), A10 for antidiabetic medications, and C01-C10 for heart medications. Use of heart medications, antidiabetic medications, antidepressants, psychiatric medications, and CAMs were coded as dummy variables on the basis of the information obtained from the preoperative questionnaire. CAMs were classified and included according to a previous publication (31). One person was excluded from both the CAM variable and the concomitant medications variable as we could not identify the reported medication. The preoperative visit usually took place a few days before surgery.

Nonadherence to endocrine treatment was assessed at the 1- and the 2-year follow-up visits. Patients were considered nonadherent if they had declined recommended endocrine therapy, were no longer taking an endocrine therapy upon follow-up, or had taken a pause in endocrine therapy exceeding 20% of the treatment period (32). Patients who switched from one endocrine therapy to another and did not take a pause in therapy exceeding 20% of the treatment period were considered adherent, based on a previous publication reporting survival benefits for both prematurely switched patients and guideline-switched patients (33). Adherence information was taken from patient charts, follow-up questionnaires, as well as the clinical follow-up form filled in by the research nurse. The clinical follow-up forms recorded the durations of pauses in treatment since the last visit; this information was not always present in the patients' charts.

The age cutoff points examined in relation to adherence were chosen in concordance with earlier publications (11, 13, 15, 23, 24). A BMI cutoff point at 25 kg/m^2 was used according to World Health Organization (WHO) classifications of overweight (34). Central obesity was considered to be present if the WHR was above 0.85 (34). Alcohol consumption was divided into 5 categories (never, not more than once a month, 2–3 times every month, 2–3 times every week, and 4 or more times a week). Current smokers included both daily smokers and party smokers. The 2 of 3 risk factor profile was based on the strongest factors for nonadherence in the single variable analyses. As low histologic grade was strongly associated with nonadherence in the single variable analysis, it was added to the 2 of 4 risk factor profile as well.

Additional clinical information, including type of surgery, sentinel node biopsy, and axillary node dissection, was obtained from each patient's chart. Invasive tumor size and/or extent of the primary tumor (pT; ref. 35), histologic type and grade, axillary node involvement (pN), signs of distant metastases, and ER and progesterone receptor (PR) status were obtained from each patient's pathology report. Tumors with more than 10% positive nuclear staining were considered receptor-positive. All tumors were analyzed at the Department of Pathology at Skane University Hospital, Lund. HER-2/neu status was routinely analyzed as of November 2005 (36).

Skane University Hospital, Lund is 1 of 7 hospitals in the South Swedish Health Care Region conducting breast cancer surgery. Its catchment area serves almost 300,000 inhabitants. Patients with breast cancer are not referred to other hospitals for surgery. Hence, this study population is population-based. During the same period as this cohort was accrued, there were 1,543 patients who went through breast cancer surgery in Lund. The mean age was 61.15 years, ER status was reported in 91.2% of the patients, and PR status was reported in 90.6% of the patients; 85.7% of the tumors were ER-positive and 69.8% of the tumors were PR-positive. Approximately 50% of the patients in Lund were included in this study and were similar to nonincluded patients with respect to age, ER, and PR status. Most nonincluded patients were missed because of lack of available research nurses. Approximately 5% of the patients were missed because of unverified diagnosis at the time of surgery.

Statistics

The statistical analyses were conducted with the software SPSS 19.0. BMI and WHR were not normally distributed. Therefore, the variables were either dichotomized or transformed using the natural logarithm. The χ^2 and logistic regression analyses were used to analyze categorical variables: pT (0–4 or 0–1 vs. 2+), pathologic axillary lymph node involvement (pN; yes/no) or number of involved axillary lymph glands (0, 1–3, 4+), and histologic grade (I-III or I vs. II-III) in relation to adherence. Kaplan–Meier and adjusted Cox regression were used in the survival analyses. Only patients with invasive cancers were included in the survival analyses. A breast cancer event was defined as an ipsilateral, contralateral, regional, or distant metastasis. In the present cohort, there were 55 patients with any type of breast cancer event during the 7-year follow-up. Breast cancer–free survival was calculated from inclusion to diagnosis of a breast cancer event or last study follow-up visit or death due to non–breast cancer–related causes up to June 30, 2010. A P value <0.05 was considered significant. All P values were 2-tailed.

Results

Patient characteristics for the 417 patients with ER-positive tumors who had been advised to use endocrine treatment and who had been followed at least until the 1-year follow-up visit are shown in Table 1. Age at breast cancer

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Table 1. Characteristics of patients with ER-positive tumors who had been advised to take endocrine treatment (N = 417)

	All patients, N = 417, median (IQR) or %	Missing
Age at diagnosis, y	60.3 (52.7–66.3)	—
Age at menarche, y	13 (12–14)	2
Parous (%)	86.3	—
Parity (no. of children)	2 (1–3)	—
Antidepressant use (%)	10.6	—
CAM use (%)	23.6	1
Alcohol use		1
Never	40 (9.6)	
Not more than once a mo	102 (24.5)	
2–3 times/mo	162 (38.9)	
2–3 times/wk	91 (21.9)	
4 or more times a wk	21 (5.0)	
Ever HRT use (%)	47.8	1
Smokers (%)	19.2	—
Height, cm	166 (162–170)	2
Weight, kg	69.0 (62.0–77.3)	3
Number of medications last wk	1 (0–3)	—
BMI, kg/m^2	24.8 (22.5–27.9)	4
WHR	0.84 (0.79–0.89)	2

Abbreviation: IQR, interquartile range.

diagnosis ranged from 25 to 99 years, with a median age of 60.3 years.

Characteristics of the nonadherent patients

At the 1-year follow-up visit, 36 of 417 patients (8.6%) were nonadherent to their endocrine treatment. Among these nonadherent patients, 13 never commenced endocrine therapy, despite being advised to do so, 3 patients had less than 80% adherence due to pauses in treatment before the 1-year visit, and 20 patients stopped prematurely. At the 2-year follow-up visit, 33 of 339 patients (9.7%) were nonadherent. Three patients who were nonadherent at the 1-year visit were considered adherent at the 2-year visit. Seven patients had discontinued treatment between the 1- and 2-year visits and 26 patients remained nonadherent since the 1-year visit; Fig. 1.

Adherence in relation to tamoxifen and AI use

At the 1-year visit, 13 of the 295 patients (4.4%) treated with tamoxifen but not AI were nonadherent compared with 2 of 77 nonadherent patients (2.6%) who had been treated with AI but not tamoxifen. The highest nonadherence was found in the group of prematurely switched patients, 8 of 29 (27.6%) were nonadherent. Three patients had not yet started endocrine treatment at the time of the 1-year visit (1 patient was still receiving goserelin and 2 patients were receiving trastuzumab). Thirteen patients declined treatment despite being recommended endocrine therapy and were not included in this analysis.

At the 2-year visit, 17 of the 222 patients (7.7%) treated with tamoxifen but not AI were nonadherent compared with 2 of 54 nonadherent patients out (3.7%) who had been treated with AI but not tamoxifen. In the group of prematurely switched patients, 4 of 53 (7.5%) were nonadherent. Ten patients declined treatment despite being recommended endocrine therapy and were not included in this analysis.

Adherence in relation to preoperative patient characteristics

Adherence in relation to preoperative patient characteristics is shown in Table 2. Patients with a preoperative BMI < 25 kg/m^2 were more likely to be nonadherent at the 1-year visit [relative risk (RR), 2.77; 95% confidence interval (CI), 1.33–5.73; $P = 0.004$] and at the 2-year visit (RR, 1.92; 95% CI, 0.94–3.91; $P = 0.064$). Patients who were current smokers at the preoperative visit were more likely to be nonadherent at the 1-year (RR, 3.01; 95% CI, 1.62–5.57; $P < 0.001$) and 2-year visits (RR, 2.74; 95% CI, 1.44–5.22; $P = 0.002$). Party smokers and smokers had similar frequencies of nonadherence. No association was seen between adherence and age, family history of breast cancer in a first- or second-degree relative, WHR, hormone replacement therapy (HRT) use, alcohol use, CAM use, antidepressant use, psychiatric medication use, or the number of medications taken during the past week. No association was seen between adherence and heart medication use or antidiabetic medication use. Furthermore, neither antidepressant use at the 1-year follow-up nor alcohol use at the 1-year follow-up was significantly associated with adherence at the 1- or 2-year follow-up visits.

Adherence in relation to tumor characteristics, mammography detection, and type of surgery

Tumor characteristics, mode of tumor detection, and type of surgery for the 417 women in relation to adherence are presented in Table 3. Patients with invasive tumors ≤20 mm or *in situ* tumors were more likely to be nonadherent at the 1-year visit than patients with larger primary tumors (RR, 2.94; 95% CI, 1.17–7.38; $P = 0.014$). Histologic grade (I) was associated with nonadherence at the 1-year (RR, 3.66; 95% CI, 1.99–6.71; $P < 0.001$) and 2-year follow-up visits (RR, 3.68; 95% CI, 1.96–6.91; $P < 0.001$). Patients who had received breast-conserving surgery were more likely to be nonadherent at the 1-year visit than patients who had received a mastectomy (RR, 2.58; 95% CI, 1.25–5.36; $P = 0.007$). Finally, patients who had not received chemotherapy were more often nonadherent at the 1-year (RR, 7.18; 95% CI, 1.00–51.6; $P = 0.017$) and 2-year visits (RR, 1.12; 95% CI, 1.08–1.18; $P = 0.014$). No associations between adherence and axillary lymph node involvement, PR status, or mammography detection were seen.

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Table 2. Preoperative characteristics in relation to adherence for the 417 patients with ER-positive tumors who had received or had been advised to take endocrine treatment

	Total number of patients, 1-y follow-up (%), N = 417	Adherent, 1-y follow-up (%), N = 381	Nonadherent, 1-y follow-up (%), N = 36	RR (95% CI)	*P*	Total number of patients, 2-y follow-up (%), N = 339	Adherent, 2-y follow-up (%), N = 306	Nonadherent, 2-y follow-up (%), N = 33	RR (95% CI)	*P*
Age, y										
<60	201 (48.2)	183 (91.0)	18 (9.0)	1.07 (0.58–2.01)	0.82	167 (49.3)	149 (89.2)	18 (10.8)	1.24 (0.64–2.37)	0.52
≥60	216 (51.8)	198 (91.7)	18 (8.3)	1		172 (50.7)	157 (91.3)	15 (8.7)	1	
Missing	0	0	0			0	0	0		
BMI, kg/m^2										
<25	215 (52.1)	188 (87.4)	27 (12.6)	2.77 (1.33–5.73)	0.004	183 (54.5)	160 (87.4)	23 (12.6)	1.92 (0.94–3.91)	0.064
≥25	198 (47.9)	189 (95.5)	9 (4.5)	1		153 (45.5)	143 (93.5)	10 (6.5)	1	
Missing	4	4	0			3	3	0		
WHR										
≤0.85	235 (56.6)	213 (90.6)	22 (9.4)	1.20 (0.63–2.29)	0.57	201 (59.3)	180 (89.6)	21 (10.4)	1.18 (0.60–2.33)	0.62
>0.85	180 (43.4)	166 (92.2)	14 (7.8)	1		136 (40.4)	124 (91.2)	12 (8.8)	1	
Missing	2	2	0			2	2	0		
Alcohol use										
Never	40 (9.6)	36 (90.0)	4 (10.0)			35 (10.4)	29 (82.9)	6 (17.1)		
Not more than once a mo	102 (24.5)	89 (97.3)	13 (12.7)	1.73 (0.93–3.22)	0.083	85 (25.1)	76 (89.4)	9 (10.6)	1.51 (0.79–2.89)	0.21
2–3 times/mo	162 (38.9)	151 (93.2)	11 (6.8)			124 (36.7)	113 (91.1)	11 (8.9)		
2–3 times/wk	91 (21.9)	85 (93.4)	6 (6.6)	1		74 (21.9)	68 (91.9)	6 (8.1)	1	
4 or more times/wk	21 (5.0)	19 (90.5)	2 (9.5)			20 (5.9)	19 (95.0)	1 (5.0)		
Missing	1	1	0			1	1	0		
Smoker										
Yes	80 (19.2)	65 (81.2)	15 (18.8)	3.01 (1.62–5.57)	0.0003	65 (19.2)	52 (80.0)	13 (20.0)	2.74 (1.44–5.22)	0.002
No	337 (80.8)	316 (94.8)	21 (6.2)	1		274 (19.2)	254 (92.7)	20 (7.3)	1	
Missing	0	0	0			0	0	0		
Natural remedy use										
Yes	98 (23.6)	88 (89.8)	10 (10.2)	1.25 (0.62–2.50)	0.53	81 (24.0)	73 (90.1)	8 (9.9)	1.02 (0.48–2.16)	0.97
No	318 (76.4)	292 (91.8)	26 (8.2)	1		257 (76.0)	232 (90.3)	25 (9.7)	1	
Missing	1	1	0			1	1	0		
Antidepressant use										
Yes	44 (10.6)	40 (90.9)	4 (9.1)	1.06 (0.39–2.86)	0.91	33 (9.7)	30 (90.9)	3 (9.1)	0.93 (0.11–2.87)	0.90
No	373 (89.4)	341 (91.4)	32 (8.6)	1		306 (90.3)	276 (90.2)	30 (9.8)	1	
Missing	0	0	0			0	0	0		
Psychiatric medication use (sedatives, sleeping pills, antidepressants)										
Yes	83 (20.0)	74 (89.2)	9 (10.8)	1.34 (0.66–2.74)	0.42	64 (18.9)	55 (85.9)	9 (14.1)	1.61 (0.79–3.30)	0.19
No	334 (80.0)	307 (91.9)	27 (8.1)	1		275 (81.1)	251 (91.3)	24 (8.7)	1	
Missing	0	0	0			0	0	0		

(Continued on the following page)

Table 2. Preoperative characteristics in relation to adherence for the 417 patients with ER-positive tumors who had received or had been advised to take endocrine treatment (Cont'd)

	Total number of patients, 1-y follow-up (%), N = 417	Adherent, 1-y follow-up (%), N = 381	Nonadherent, 1-y follow-up (%), N = 36	RR (95% CI)	P	Total number of patients, 2-y follow-up (%), N = 339	Adherent, 2-y follow-up (%), N = 306	Nonadherent, 2-y follow-up (%), N = 33	RR (95% CI)	P
Number of medications last										
<2	221 (53.0)	202 (91.4)	19 (8.6)	1		181 (53.4)	162 (89.5)	19 (10.5)	1	
≥2	196 (47.0)	179 (91.3)	17 (8.7)	1.01 (0.54–1.89)	0.98	158 (46.6)	144 (91.1)	14 (8.9)	0.84 (0.12–1.63)	0.61
Missing	0	0	0			0	0	0		
Family history of breast cancer (first- or second-degree relatives)										
Yes	147 (36.8)	135 (91.8)	12 (8.2)	1		111 (34.2)	100 (90.1)	11 (9.9)	1	
No	253 (63.3)	229 (90.5)	24 (9.5)	1.16 (0.60–2.25)	0.66	214 (65.8)	192 (89.7)	22 (10.3)	1.04 (0.52–2.06)	0.92
Missing	17	17	0			14	14	0		
Ever HRT use										
Yes	199 (47.8)	180 (90.5)	19 (9.5)	1.22 (0.65–2.28)	0.53	163 (48.1)	146 (89.6)	17 (10.4)	1.14 (0.60–2.18)	0.69
No	217 (52.2)	200 (92.2)	17 (7.8)	1		175 (51.8)	159 (90.9)	16 (9.1)	1	
Missing	1	1	0			1	1	0		

Exogenous hormone use in adherent and nonadherent patients during follow-up

No data about side effects from treatment were routinely collected as part of the present study. However, at the 1-year follow-up, 11 (2.9%) of the adherent patients reported current use of either a local estradiol ($n = 9$), systemic combined estradiol and progestin ($n = 1$), or a progestin intrauterine device ($n = 1$). Three (8.3%) of the nonadherent patients reported using a local estradiol ($n = 2$) or medroxyprogesterone injections ($n = 1$). At the 2-year visit, 8 (2.6%) of the adherent patients reported current use of either local estradiol ($n = 7$) or systemic combined estradiol and progestin ($n = 1$), whereas 1 (3%) nonadherent patient reported using a local estradiol.

Clinical profiles predicting nonadherence

Two clinical profiles predicted nonadherence at the 1- and the 2-year follow-up visits; Table 4. Patients with 2 or more of the 3 preoperatively measured risk factors, BMI < 25 kg/m^2, current smoking, or drinking alcohol less often than twice a month, were significantly more often nonadherent at the 1-year (RR, 5.24; 95% CI, 2.75–9.97; $P < 0.001$) and the 2-year visits (RR, 4.07; 95% CI, 2.11–7.84; $P < 0.001$). This profile captured 63.9% of nonadherence at the 1-year visit and 60.6% at the 2-year visit. When low histologic grade (I) was added to the model, having at least 2 of the 4 clinical characteristics identified 72.2% of the nonadherent patients at the 1-year (RR, 4.96; 95% CI, 2.46–10.00; $P < 0.001$) and 72.7% of the nonadherent patients at the 2-year visit (RR, 4.74; 95% CI, 2.28–9.87; $P < 0.001$), the specificity of the clinical profiles ranged between 68.0% and 78.4%. Receiver operating characteristic curves are presented in Fig. 2A and B. The P values of both models remained statistically significant after Bonferroni correction. Similarly, sensitivity analyses where patients with 1% to 20% reported nonadherence were excluded showed that the 2 clinical profiles remained significantly associated with nonadherence (all $P < 0.0001$). Addition of type of breast cancer surgery to create a "three or more out of five" clinical prediction rule resulted in decreased sensitivity for nonadherence.

Disease-free survival in relation to adherence

The 417 patients had a median disease-free survival of 3.02 years (interquartile range, 2.01–4.98). In a multivariate Cox regression model, nonadherence at the 1-year visit was significantly associated with an increased risk for early breast cancer events (HR, 2.97; 95% CI, 1.08–8.15; $P = 0.034$), adjusted for age and tumor characteristics. Nonadherence at the 2-year visit showed a similar risk (adjusted HR, 2.42; 95% CI, 0.75–7.80; $P = 0.14$) but was no longer statistically significantly associated with an increased risk of early events.

Discussion

This study identified 2 clinical profiles associated with a 4- to 5-fold increased relative risk for nonadherence to adjuvant endocrine breast cancer therapy at the 1- and 2-year

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Table 3. Tumor characteristics, treatment, and mammography screening detection in relation to adherence for patients with ER-positive tumors who had been advised to take endocrine treatment

	Total number of patients, 1-y follow-up (%), N = 417	Adherent, 1-y follow-up (%), N = 381	Nonadherent, 1-y follow-up (%), N = 36	RR (95% CI)	*P*	Total number of patients, 2-y follow-up (%), N = 339	Adherent, 2-y follow-up (%), N = 306	Nonadherent, 2-y follow-up (%), N = 33	RR (95% CI)	*P*
pT										
In situ	1 (0.2)	1 (100)	0			1 (0.3)	1 (100)	0		
I	282 (67.6)	251 (89.1)	31 (10.9)	2.94 (1.17–7.38)	0.014	234 (69.0)	207 (88.5)	27 (11.5)	1.99 (0.85–4.68)	0.10
II	125 (30.0)	120 (96.0)	5 (4.0)			97 (28.6)	92 (94.8)	5 (5.2)		
III	8 (1.9)	8 (100)	0	1		6 (1.8)	5 (83.3)	1 (16.7)	1	
IV	1 (0.2)	1 (100)	0			1 (0.3)	1 (100)	0		
Missing	0	0	0			0	0	0		
Histologic grade										
I	82 (19.7)	65 (79.3)	17 (20.7)	3.66 (1.99–6.71)	<0.0001	69 (20.4)	53 (76.8)	16 (23.2)	3.68 (1.96–6.91)	<0.0001
II	260 (62.4)	244 (93.8)	16 (6.2)			222 (65.5)	205 (92.3)	17 (7.7)		
III	75 (18.0)	72 (96.0)	3 (4.0)	1		48 (14.2)	48 (100)	0	1	
Missing	0	0	0			0	0	0		
Nodal involvement										
0 positive nodes	219 (52.6)	195 (89.0)	24 (11.0)	1.80 (0.92–3.50)	0.078	177 (52.4)	155 (87.6)	22 (12.4)	1.82 (0.91–3.63)	0.083
1–3 positive nodes	151 (36.3)	142 (94.0)	9 (6.0)			127 (37.6)	116 (91.3)	11 (8.7)		
≥4 positive nodes	46 (11.1)	43 (93.5)	3 (6.5)	1		34 (10.1)	34 (100)	0	1	
Missing	1	1	0			1	1	0		
PR status										
PR-positive	328 (78.7)	297 (90.5)	31 (9.5)	1.68 (0.67–4.20)	0.25	265 (78.2)	237 (89.4)	28 (10.6)	1.56 (0.63–3.91)	0.33
PR-negative	89 (21.3)	84 (94.4)	5 (5.6)	1		74 (21.8)	69 (93.2)	5 (6.8)	1	
Missing	0	0	0			0	0	0		
Type of surgery										
MRM	193 (46.3)	184 (95.3)	9 (4.7)	1		147 (43.4)	137 (93.2)	10 (6.8)	1	
BCS	224 (53.7)	197 (87.9)	27 (12.1)	2.58 (1.25–5.36)	0.007	192 (56.6)	169 (88.0)	23 (12.0)	1.76 (0.87–3.58)	0.11
Missing	0	0	0			0	0	0		
Mammography detected[a]										
Yes	219 (57.9)	197 (90.0)	22 (10.0)	1.60 (0.78–3.28)	0.20	182 (58.3)	162 (89.0)	20 (11.0)	1.41 (0.68–2.90)	0.35
No	159 (42.1)	149 (93.7)	10 (6.3)	1		128 (41.3)	118 (92.2)	10 (7.8)	1	
Missing	0	0	0			0	0	0		
Chemotherapy										
Yes	71 (17.0)	70 (99.0)	1 (1.0)	1		48 (14.2)	48 (100)	0	1	
No	346 (83.0)	311 (89.9)	35 (10.1)	7.18 (1.00–51.6)	0.017	291 (85.8)	258 (88.7)	33 (11.3)	1.12 (1.08–1.18)	0.014
Missing	0	0	0			0	0	0		
Radiotherapy										
Yes	254 (60.9)	229 (90.2)	25 (9.8)	1.46 (0.74–2.88)	0.27	210 (61.9)	190 (90.5)	20 (9.5)	0.94 (0.49–1.83)	0.87
No	163 (39.1)	152 (93.3)	11 (6.7)	1		129 (38.1)	116 (89.9)	13 (10.1)	1	
Missing	0	0	0			0	0	0		

Abbreviations: BCS, breast-conserving surgery; MRM, modified radical mastectomy,

[a]Women younger than 45 ($n = 39$ and $n = 29$ for the 1- and 2-year follow-up, respectively) were excluded as women previously started mammography at age of 45 years in Lund.

Table 4. The relative risk of nonadherence at the 1 and 2-year follow-up visits in patients, according to 2 different profiles

	Total number of patients, 1-y follow-up (%), N = 417	Adherent, 1-y follow-up (%), N = 381	Nonadherent, 1-y follow-up (%), N = 36	RR (95% CI)	P	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Two of 3 risk factors[a]									
Yes	105 (25.2)	82 (78.1)	23 (21.9)	5.24 (2.75–9.97)	<0.0001	63.9	78.4	21.9	95.8
No	311 (74.8)	298 (95.8)	13 (4.2)	1					
Missing	1	1	0						
Two of 4 risk factors[b]									
Yes	143 (34.4)	117 (81.8)	26 (18.2)	4.96 (2.46–10.00)	<0.0001	72.2	69.2	18.2	96.3
No	273 (65.6)	263 (96.3)	10 (3.7)	1					
Missing	1	1	0						

	Total number of patients, 2-y follow-up (%), N = 339	Adherent, 2-y follow-up (%), N = 306	Nonadherent, 2-y follow-up (%), N = 33	RR (95% CI)	P	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Two of 3 risk factors[a]									
Yes	93 (27.4)	73 (78.5)	20 (21.5)	4.07 (2.11–7.84)	<0.0001	60.6	76.1	21.5	94.7
No	246 (72.6)	233 (94.7)	13 (5.3)	1					
Missing	0	0	0						
Two of 4 risk factors[b]									
Yes	122 (36.0)	98 (80.3)	24 (19.7)	4.74 (2.28–9.87)	<0.0001	72.7	68.0	19.7	95.9
No	217 (64.0)	208 (95.9)	9 (4.1)	1					
Missing	0	0	0						

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

[a]BMI < 25 kg/m^2, alcohol intake less than twice a month, and preoperative current smoking.

[b]BMI < 25 kg/m^2, alcohol intake less than twice a month, preoperative current smoking, and histologic grade I.

follow-up visits. The profiles consisted in combinations of readily accessible clinical information, namely, BMI < 25 kg/m^2, preoperative current smoking, alcohol intake less often than twice a month, and low histologic grade. The profiles identified the majority of nonadherent patients (sensitivity ranging from 60.6% to 72.7%) and the majority of adherent patients (specificity ranging from 68.0% to 78.4%). To our knowledge, no single marker has been shown to have similar accuracy in predicting nonadherence.

The present study found that preoperative BMI < 25 kg/m^2, preoperative current smoking, a smaller tumor size, a low histologic grade, breast-conserving cancer surgery, and no chemotherapy were significantly associated with nonadherence. Alcohol intake of less than twice a month was not significantly associated with nonadherence. No association was seen between adherence and previous HRT use, family history of breast cancer, tumor detection method, or CAM use; to our knowledge, these 4 factors have not yet been studied as potential markers of adherence to endocrine treatment. In assessing the number of concomitant medications, both vitamins and CAMs were excluded. Although prescribed as treatment for several illnesses, a vast number of patients used vitamin supplements and it was impossible to separate prescription users from other users using the questionnaire, including vitamins in the number of medications did not materially change the results. Many of the previously identified markers for nonadherence were not significant in the present study. However, previous studies of risk factors for nonadherence have shown contradictory results, which may reflect a true heterogeneity of the nonadherent group of patients. An alternative explanation is that this study, based on a cohort of 417 patients, lacked sufficient statistical power to detect certain associations between risk factors and nonadherence.

Alcohol intake of less than twice a month was not significantly associated with nonadherence in itself, but it strengthened the association between BMI, smoking, and nonadherence when combined in the clinical profiles. This phenomenon may reflect a synergistic effect between risk factors. A lower-than-average alcohol consumption and smoking are associated with low socioeconomic status (37, 38), and it is possible that the clinical profiles reflect an association between nonadherence and low socioeconomic status. Previous studies suggest that alcohol abstainers are more likely to be on psychotropic drugs (38), which may indicate a psychologic background to the increased nonadherence. In the present study, no significant associations between alcohol consumption and antidepressant use or psychiatric medication use were found (data not shown). Another study found that smokers were more likely to be nonadherent. Komenaka and colleagues suggested considering current smoking as a proxy marker for a certain personality type unwilling to adhere to medical guidelines (28). While a low BMI is associated with a high socioeconomic status in the Western world (37, 39), its inclusion in the clinical profiles increased the profiles' predictive accuracy. A recent study reported that patients with breast cancer with a higher BMI were more persistent in taking their

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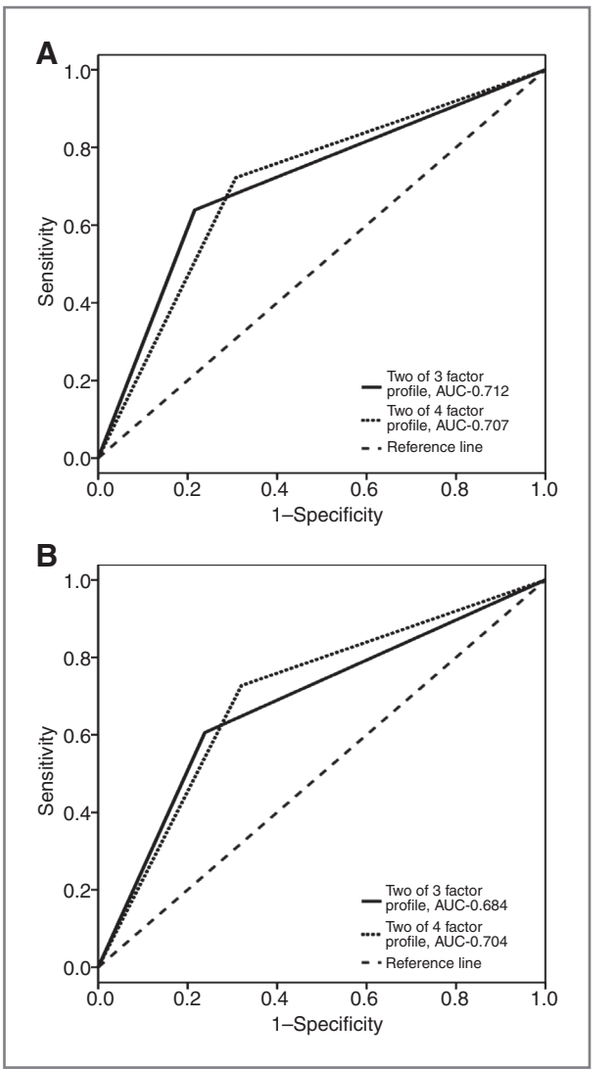

Figure 2. A, at the 1-year follow-up visit, the 2 of 3 factor profile (solid line) yielded a receiver operating characteristic (ROC) area under the curve (AUC) of 0.712 and the 2 of 4 factor profile (dotted line) yielded an ROC AUC of 0.707 for prediction of nonadherence. B, at the 2-year follow-up visit, the 2 of 3 factor profile (solid line) yielded an ROC AUC of 0.684 and the 2 of 4 factor profile (dotted line) yielded an ROC AUC of 0.704 for prediction of nonadherence.

endocrine therapy than patients with a lower BMI, which is in line with our finding (40).

Smoking, BMI, and alcohol intake have been associated with estrogen levels in previous studies. Smoking has been reported to have antiestrogenic effects (41, 42). A high BMI in women correlates with increased levels of estrogen, compared with lower BMIs (43). The association between alcohol intake and estrogen levels is unclear. Alcohol may increase estrogen levels, resulting in lower levels among abstainers and seldom-drinkers (44). However, a pilot study of 59 patients in this cohort suggested that alcohol confers a weaker estrogen metabolite profile (45). As estrogen levels are closely related to hot flashes and other vasomotor symptoms (46) and vasomotor symptoms are commonly reported side effects of endocrine treatment (4), a biochemical basis may account for the increased nonadherence in patients identified by the risk factor profiles. Data about side effects were not routinely collected as part of this study. However, a few patients, both adherent and nonadherent, reported use of exogenous hormones at the follow-up visits, possibly to relieve side effects.

Combining low histologic grade with BMI, alcohol intake, and smoking resulted in a clinical profile with increased sensitivity for nonadherence but lower specificity. The association between low histologic grade and adherence is consistent with earlier publications suggesting a decreased adherence among patients who anticipate less therapeutic gain from endocrine treatment (29). It is also possible that the treating physicians advocate adjuvant therapy more aggressively when the histologic grade is high than when it is low.

The present study had a higher percentage of adherent patients at the 1- and 2-year follow-up visits than in previous publications (11, 13). The study population included 50% of the patients with breast cancer in Lund and was similar, with regard to age, ER, and PR status, to the 50% of patients with breast cancer in Lund who were not included. However, the 417 patients in the present study returned to the hospital for study follow-up visits several times during the 2-year follow-up. During these, visits they had personal contact with a research nurse. This increased contact with health care personnel may have resulted in higher rates of adherence. This was a single-center study in Sweden and we do not know how generalizable the results are to other institutions. To our knowledge, there are no published articles about clinical profiles in relation to endocrine adherence in patients with breast cancer.

Adherence may be measured in several ways, with varying advantages and disadvantages (32). Most methods, including the use of questionnaires, are susceptible to patient self-presentational bias (32). Measurements of medication, estrogen, or metabolite blood levels were not conducted in this study. Questions about medication use, including endocrine treatment, referred to use during the past week, thus minimizing the risk for recall bias. However, we do not know what medications were actually taken between visits. One patient wrote on her questionnaire that she chose to only take her medications every other day (she was considered nonadherent). It is possible that the population included similar cases and that the actual rate of nonadherence is higher than that measured in the present study. When absolute treatment durations and switch dates could not be obtained in the questionnaire, the clinical follow-up form, patient charts, and pathology reports were consulted. In addition, the research nurses recorded pauses, which were not always recorded in the patient charts. Any underreporting would bias the results toward the null. Although other methods of assessing adherence may generate cohorts with larger numbers of patients, gathering information from questionnaires, pathology reports, and patient charts minimizes inaccuracies.

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Many previous publications have assessed nonadherence based on prescription records (9, 10, 12). While it is not certain that the patients who collect their prescriptions take their medicine as prescribed, prescription-based studies may fail to include patients who refuse to start endocrine treatment and who are not issued a prescription in the first place. This study identified 13 nonadherent patients, constituting 36.1% of the nonadherent subgroup, who never commenced recommended endocrine treatment.

Nonadherence was not assessed beyond the 2-year visit due to the smaller number of patients included in the later follow-up visits. Only current smoking status was available in the questionnaires. Hence, former smokers were included in the group of nonsmokers, which may have biased the analyses. Similarly, only current alcohol consumption was recorded at the preoperative questionnaire. Therefore, the category of abstainers may include both former drinkers and lifelong abstainers.

In the current study, nonadherence at the 1-year follow-up visit was associated with a nearly 3-fold increase in the risk of early breast cancer events. Nonadherence impacts negatively on patient survival (5, 6). To justify targeted interventions, screening tests should show both adequate sensitivity and specificity (47). The 2 clinical profiles showed a sensitivity for nonadherence ranging from 60.6% to 72.7% and a specificity ranging from 68.0% to 78.4%.

As reviewed by Hadji (48), strategies for decreasing nonadherence include improving patient education, communication between health care provider and patient, patient access to health care, patient satisfaction, and the management of treatment side effects. None of these strategies are likely to harm patients who are identified by the clinical profiles as at-risk for nonadherence. The potential negative impact of labeling patients as at-risk for nonadherence may be minimized by highlighting the biologic susceptibility for nonadherence (47). The clinical profiles are derived from clinical data readily available to the treating physician and hence applicable in the clinical setting at no extra cost.

A positive relationship between patients and their health care providers as well as frequent monitoring and feedback increase adherence to endocrine treatment (48). The ability to give proper feedback with respect to endocrine therapy–related issues may be suboptimal among nonspecialists and hence decrease adherence. However, a Canadian study reported that primary health care doctors can follow-up patients with breast cancer without adversely affecting outcome (49). As per recent guideline changes in southern Sweden, patients no longer routinely follow-up with their breast cancer physician beyond the first year postsurgery. Instead, patients are referred to the general mammography screening program for patients between the ages of 40 and 72 years or referred to biannual screening for patients ages <40 or >72 years (50). The clinical implication of this change in follow-up warrants close observation.

In conclusion, this study identified 2 clinical profiles strongly associated with nonadherence to adjuvant endocrine breast cancer therapy at both the 1- and the 2-year follow-up visits. Given that nonadherence impacts negatively on survival (5, 6), that the profiles are derived from readily available clinical information, and that targeted interventions to decrease nonadherence are harmless and cheap, these profiles may benefit patient care if they can be validated in independent patient population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Clinical Profiles Predict Early Nonadherence to Adjuvant Endocrine Treatment in a Prospective Breast Cancer Cohort

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