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ORIGINAL ARTICLE

Endocrine symptom assessment in women with breast cancer: what a simple "yes" means

K. Ribi · J. Bernhard · K. Rufibach · B. Thürlimann · R. von Moos · T. Ruhstaller · A. Glaus · C. Böhme

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Abstract
Goals of work To investigate the self-reported symptoms related to endocrine therapy in women with early or advanced breast cancer and the impact of these symptoms on quality of life (QL) indicators.
Materials and methods Symptom occurrence was assessed by the Checklist for Patients on Endocrine Therapy (C-PET) and symptom intensity was assessed by linear analogue self-assessment (LASA) indicators. Patients also responded to global LASA indicators for physical well-being, mood, coping effort and treatment burden. Associations between symptoms and these indicators were analysed by linear regression models.
Main results Among 373 women, the distribution of symptom intensity showed considerable variation in patients reporting a symptom as present. Even though patients recorded a symptom as absent, some patients reported having experienced that symptom when responding to symptom intensity, as seen for decreased sex drive, tiredness and vaginal dryness. Six of 13 symptoms and lower age had a detrimental impact on the global indicators, particularly tiredness and irritability.
Conclusions Patients' experience of endocrine symptoms needs to be considered both in patient care and research, when interpreting the association between symptoms and QL.

Keywords Breast cancer · Self-reported endocrine symptoms · Symptom intensity · Quality of life

K. Ribi (✉) · J. Bernhard
International Breast Cancer Study Group (IBCSG),
Coordinating Center,
Effingerstrasse 40,
3008 Bern, Switzerland
e-mail: karin.ribi@ibcsg.org

J. Bernhard
Department of Medical Oncology, Inselspital,
3010 Bern, Switzerland

K. Rufibach
(formerly Department of Statistics,
Stanford University, Stanford, CA 94305, USA),
Swiss Group for Clinical Cancer Research (SAKK),
Effingerstrasse 40,
3008 Bern, Switzerland

B. Thürlimann
Senology Centre of Eastern Switzerland, Kantonsspital St. Gallen,
Rorschacherstrasse 95,
9006 St. Gallen, Switzerland

R. von Moos
(formerly Kantonsspital St. Gallen),
Oncology, Kantonsspital Graubünden,
7000 Chur, Switzerland

T. Ruhstaller
(formerly Onkologie, Innere Medizin,
Kantonsspital Münsterlingen),
Oncology, Kantonsspital St. Gallen,
Rorschacherstrasse 95,
9006 St. Gallen, Switzerland

A. Glaus
Centre for Tumour Prevention,
Detection and Treatment,
Rorschacherstrasse 150,
9006 St.Gallen, Switzerland

C. Böhme
Oncology, Kantonsspital St. Gallen,
Rorschacherstrasse 95,
9006 St. Gallen, Switzerland

Introduction

In the past two decades, a large number of randomised trials have been conducted to determine the role of adjuvant endocrine therapy for women with hormone-sensitive breast cancer [18]. The findings of these studies indicate that endocrine therapy should be recommended as a standard adjuvant treatment in those patients irrespective of age, menopausal status or tumour stage. Tamoxifen is the most extensively used endocrine treatment for all stages of breast cancer. Other common endocrine approaches are the application of fulvestrant (a selective downregulator of estrogen receptors) or aromatase inhibitors, ovarian ablation through luteinizing hormone-releasing hormone (LHRH) analogues and the combination of endocrine therapy [35]. Regarding aromatase inhibitors, several newer drugs have been investigated to determine their efficacy and safety in advanced disease and in the adjuvant setting [4, 12, 26].

Studies of self-reported symptoms related to endocrine therapy are limited. Two randomised controlled prevention trials demonstrated that vasomotor and gynaecologic symptoms are substantially more frequent in women using tamoxifen than in women receiving placebo [17, 20]. Menopausal symptoms are also an important concern of pre-menopausal women with breast cancer receiving adjuvant treatment [33]. Patients treated with goserelin (LHRH analogue) reported higher levels of symptoms than tamoxifen-treated patients or controls and tamoxifen-treated patients reported higher symptom levels than controls. In the arimidex, tamoxifen, alone or in combination (ATAC) trial examining post-menopausal breast cancer patients, most patients experienced a worsening of symptoms related to adjuvant endocrine therapy in the first 3 months after study entry, regardless of the treatment arm [19]. Subsequently, these symptoms stabilised until the 24-month follow-up. The Intergroup Exemestane Study (IES) reported high severity of vasomotor symptoms and sexual problems in post-menopausal women at entry and during the study [21]. A randomised placebo-controlled trial of letrozole after 5 years of tamoxifen in post-menopausal women (MA.17) found symptoms to be bothersome in a minority of patients both in the letrozole and placebo groups [37]. Small but statistically significant differences of mean change scores from baseline to months 6, 12 and 24 showing a worsening for the letrozole group were seen for vasomotor symptoms (i.e. hot flushes and night sweats).

Furthermore, physical and menopausal symptoms appear to remain a problem over the long-term course for breast cancer survivors. Patients with no evidence of disease reported a high frequency and severity of menopausal symptoms [13, 16, 23], also in comparison with healthy age-matched women [24].

Regarding the impact of endocrine treatment on quality of life (QL), findings are not consistent. Two non-controlled case series studies suggested that menopausal symptom severity is significantly related to lower physical and emotional QL [13, 16]. Due to methodological flaws, the results of these studies have to be considered with caution [15]. In contrast, randomised trials revealed that the frequency of symptoms did only moderately affect the overall physical and emotional well-being [17, 19, 20, 33, 37].

Endocrine agents, particularly aromatase inhibitors like anastrozole, letrozole and exemestane are promising new treatment options for patients with breast cancer. Their use will extend in earlier stages and for longer periods of time. It's of increasing importance to better understand patients' menopausal symptoms related to endocrine treatments. The main objective of the available studies was to compare treatment groups rather than to evaluate the association between endocrine symptoms and QL indicators. The aim of this study was to examine the experience of endocrine symptoms in women with early or advanced breast cancer by evaluating a confirmative statement of having a particular symptom with symptom intensity and by assessing the impact of endocrine symptoms on various global QL indicators.

Materials and methods

Patients and procedures

For this study, 405 patients with early or advanced breast cancer receiving endocrine therapy were consecutively approached whilst attending an outpatient visit in a Swiss cancer centre (Kantonsspital St. Gallen, Herisau and Münsterlingen) or affiliated oncological settings within a period of 12 months. No further inclusion or exclusion criteria have been specified, except that only patients with sufficient ability to understand German or Italian were asked for participation. Ethical approval was obtained by the institutional review board of the Kanton St. Gallen (valid for all three centres). Before their consultation, patients received an envelope containing patient information on the study, informed consent form and two questionnaires. Those patients who agreed to participate (N=373) were first asked to sign the informed consent and afterwards invited to fill in the questionnaires without assistance of the staff.

Questionnaires

Patient-reported symptoms related to endocrine therapy was assessed with the Checklist for Patients on Endocrine Therapy (C-PET) [27]. C-PET is a simple clinical checklist

to assess patients' experience with endocrine treatment and to facilitate communication between patients and their treatment teams about those experiences. The original checklist was developed by the 'Working Group on Living with Advanced Breast Cancer Hormone Treatment' and piloted with patients in three UK oncology centres for feedback on the coverage of items, understandability of wording of items, appropriateness of response categories and to clarify the purpose of the checklist, its style and format. After feedback and review, the checklist was piloted in 148 patients from 7 European centres. Over 95% felt that the symptoms listed were appropriate [27, 32]. The C-PET comprises a list of 13 symptoms related to endocrine therapy: hot flushes/sweats, weight gain, nausea, low energy, fluid retention, irritability, decreased sex drive, skin rash, pain at needle injection site, breathlessness, vaginal bleeding, vaginal discharge and vaginal dryness. The patient is asked to mark for each symptom, whether she is currently experiencing it. The checklist was translated into German and Italian. In the German version, the C-PET symptom "low energy" was translated to "tiredness".

Patient-reported symptom intensity was assessed using five key symptoms (i.e. tiredness, hot flushes/sweats, weight gain, decreased sex drive and vaginal dryness). Based on the literature and on clinical experience, these were prospectively selected to cover the most frequent symptoms. They were measured by linear analogue self-assessment (LASA) indicators, which are lines of 100 mm length anchored at both ends with words describing the 2 extremes of the item content (from "none" to "severe"). The patient is asked to mark the line according to her current self-estimation. Higher scores mean more severe symptoms. LASA scales can discriminate between effects of endocrine and cytotoxic treatment [5] and between responders and non-responders to endocrine treatment for advanced breast cancer [10].

Three global LASA indicators were included to assess relevant QL dimensions in the adjuvant and metastatic setting [5, 9–11, 14, 30]: physical well-being ("good"–"lousy" [34]), mood ("happy"–"miserable" [29]) and coping effort ("no effort at all"–"a great deal of effort" [28]). Validation studies are summarised elsewhere [7]. One further global indicator was included for treatment burden ("not at all"–"severely"). This indicator has been validated regarding the side effects of anti-emetic and cytotoxic therapies [8] and is expected to be similarly responsive to endocrine symptoms. Responses on global measures assessed with single items are expected to reflect the summation of the individual meaning and importance of various factors to each patient. For all LASA indicators, lower scores reflect a better condition (i.e. better physical well-being and mood, less coping effort and less treatment burden).

Table 1 Patient and treatment characteristics

	Participants (*N*=373)		Non-participants (*N*=32)	
	N	%	*N*	%
Age				
<50	74	20	2	6
51–65	153	41	8	25
>65	146	39	22	69
Treatment				
Early disease	302	81	27	84
Advanced disease	71	19	5	16
Endocrine treatment				
Tamoxifen	259	69	21	66
Other anti-estrogens	11	3	1	3
GnRH[a]	11	33	1	3
GnRH+tamoxifen or aromatase inhibitor	13	3	–	–
Aromatase inhibitor	46	12	7	22
BIG I-98[b]	25	7	2	6
Gestagen	2	0.5	–	–
Tamoxifen/arimidex blinded	6	1.5	–	–
Prior chemotherapy				
Yes	212	57	11	66
No	161	43	21	34

[a] Gonadotropin releasing hormone.
[b] Four randomised double-blind treatment arms (i.e. tamoxifen alone, letrozole alone, sequential combination of tamoxifen and letrozole or letrozole and tamoxifen).

Statistical considerations

Distribution of self-reported symptom intensity between patients indicating a symptom as absent and those indicating a symptom as present by a simple checklist (C-PET) were assessed with descriptive statistics.

To analyse the impact of the endocrine symptoms on the global QL indicators, simple linear regression models were performed. In addition to the 13 symptoms assessed by the C-PET, the continuous variables age, treatment (adjuvant vs metastatic setting), previous chemotherapy (yes vs no) and time since endocrine therapy started were included as covariates.

The scores of the dependent variables physical well-being, mood, coping effort and treatment burden were skewed towards positive values, implying the same tendency for the residuals of the linear models. After adding 1 and taking the logarithm, the residuals were approximately normally distributed. All analyses were performed using these transformed scores.

In a first step, univariate regression models were computed for each dependent variable. Subsequently, two multiple regression analyses were performed, either based

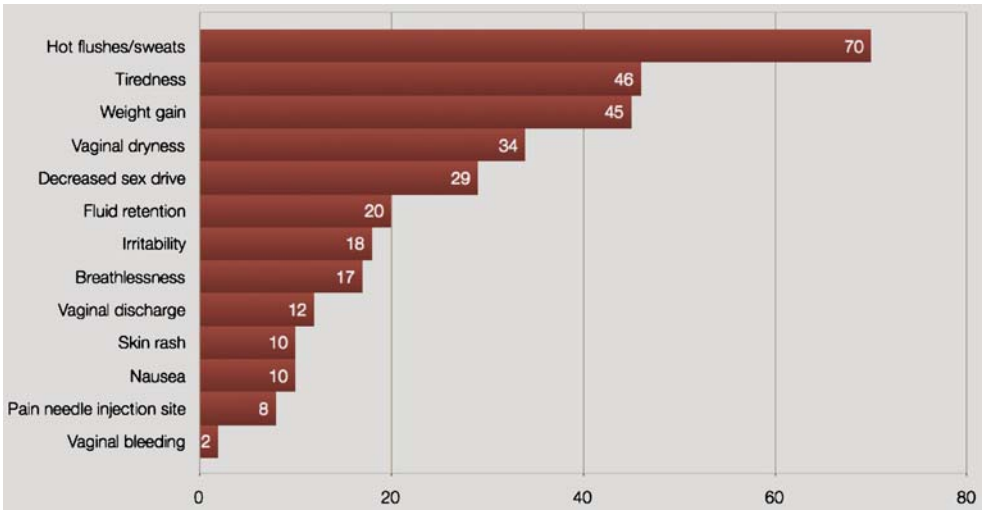

Fig. 1 Percentages of women reporting symptoms

on the set of all variables considered or based on the variables with a borderline significant p value ($p \leq 0.1$) in the univariate regressions. Variables were eliminated using a backwards selection. For each dependent variable, the models resulting from both initial sets of variables were consistent.

Results

Sample

Of the 405 women approached, 373 (92%) agreed to participate in this study. Reasons given by non-participating patients included "no reason" (N=15), poor condition (N=7), linguistic problems (N=1), no time (N=1), currently no endocrine treatment (N=1), lack of comprehension (N=3) or "other reasons" (N=4). The patient and treatment characteristics of the 373 patients included in this study and the 32 non-participating patients are summarised in Table 1. The median age of the total sample was 62 years (range 29 to 88 years). Non-participating patients tended to be older than participating patients. The majority (81%) of participating patients were patients with early disease. The most frequently administered endocrine drug was tamoxifen, which was received by almost 72% of the patients. Fifty-seven percent of the patients received prior chemotherapy. None of the patients received concurrent chemotherapy. The median time since endocrine treatment started was 18 months (median of absolute deviation (MAD)=15.5).

Frequency and intensity of endocrine symptoms

Figure 1 shows the percentages of women reporting symptoms. Hot flushes/sweats (70%), tiredness (46%) and

Fig. 2 Distribution of symptom intensity assessed by LASA indicators separated by women indicating a symptom as present (yes) vs absent (no). *Horizontal lines within the solid boxes* are median values; *solid boxes* show 25th to 75th percentiles; *whisker bars* represent minimal and maximal values of a standard range (within 1.5 times the interquartile distance from the median). *All other horizontal lines* represent outliers beyond this standard range. Varying total numbers reflect missing responses

Table 2 Descriptive statistics for global QL indicators

QL indicator	*N*	Min	Max	Mean	SD
Physical well-being	358	0	97	19.83	22.75
Mood	354	0	98	24.23	22.96
Coping effort	353	0	99	27.14	24.78
Treatment burden	347	0	99	22.31	23.54

Lower scores indicate a better condition (e.g. better mood, less burden) for all global QL indicators.

weight gain (45%) were the most frequent symptoms, followed by vaginal dryness (34%) and decreased sex drive (29%). All other symptoms assessed were experienced by less than 20% of the women. Scores of the five key symptoms assessed additionally by LASA indicators are displayed in Fig. 2. The figure shows visual comparisons of women who marked experiencing the symptom with those who did not. Patients indicated that they experienced certain symptoms even though they reported that symptom to be absent (not marking it); seen for decreased sex drive, tiredness and vaginal dryness. Of the patients that reported a symptom to be present, considerable variation in symptom intensity is observed.

Relevance of symptom experience

Descriptive statistics for the indicators for physical well-being, mood, coping effort and treatment burden are shown in Table 2. With the exception of coping effort all mean scores were within the lowest quartile of possible scale range. Lower scores represent a better condition.

Table 3 shows the results of the final linear regression models. For *physical well-being*, nausea, tiredness, irritability, breathlessness and younger age were significantly associated with poorer physical well-being. When *mood* was used as dependent variable, irritability, tiredness, breathlessness and age were significant predictors: Women indicating one of these symptoms or younger women showed higher scores (i.e. poorer condition) than older women and those not having marked these symptoms. *Coping effort* was associated with nausea, tiredness, irritability, hot flushes/nausea and younger age. More *treatment burden* was associated with symptoms of irritability, tiredness, vaginal dryness and younger age. The coefficient of determination (R^2) of the 4 models varied between 0.17 and 0.22.

To illustrate the clinical interpretation of these findings, we investigated hypothetical scenarios. The magnitude of effect of the significant symptoms on the global QL indicators was evaluated by comparing the situation of having none of these symptoms marked with the situation of having 1 or more of these symptoms marked (with age set to 60 years). Figure 3 shows the symptoms that significantly contributed to the global QL indicators in decreasing order of their magnitude of effect. Mean scores increase substantially by the number of symptoms experienced.

Taking age as a significant predictor of all QL indicators into account, we compared the QL indicators between women at the age of 45 years with those at the age of 60 years who experienced the same symptoms. With respect to *all four Ql indicators*, mean scores were higher in the younger (45 years) than in the older (60 years) age group: Younger women perceived their physical well-being and their mood as being poorer and they experienced more treatment burden than older women irrespective of symptomatology.

Discussion

Endocrine therapy is recommended as standard adjuvant treatment in women with hormone-sensitive breast cancer. Studies investigating the impact of endocrine symptoms on

Table 3 Final models for physical well-being, mood, coping effort and treatment burden

	Physical well-being			Mood			Coping effort			Treatment burden		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Intercept	2.83	0.29	$<10^{-3}$	3.22	0.30	$<10^{-3}$	3.48	0.34	$<10^{-3}$	3.10	0.33	$<10^{-3}$
Hot flushes/sweats							0.38	0.12	.002			
Nausea	0.49	0.19	.008				0.49	0.19	.009			
Tiredness	0.60	0.12	$<10^{-3}$	0.50	0.12	$<10^{-3}$	0.35	0.11	.002	0.43	0.12	$<10^{-3}$
Irritability	0.45	0.15	.002	0.54	0.15	$<10^{-3}$	0.41	0.14	.005	0.50	0.15	.001
Breathlessness	0.37	0.15	.012	0.40	0.15	.009						
Vaginal dryness										0.43	0.12	$<10^{-3}$
Age	−0.01	0.01	.003	−0.01	0.01	.002	−0.02	$<10^{-2}$	$<10^{-3}$	−0.16	$<10^{-2}$	.003
R^2	0.22			0.17			0.19			0.17		
p	$<10^{-4}$			$<10^{-4}$			$<10^{-4}$			$<10^{-4}$		

Positive β values indicate a worse condition (e.g. worse mood, more burden) for all indicators.
Presence/absence of symptoms was used as predictor.

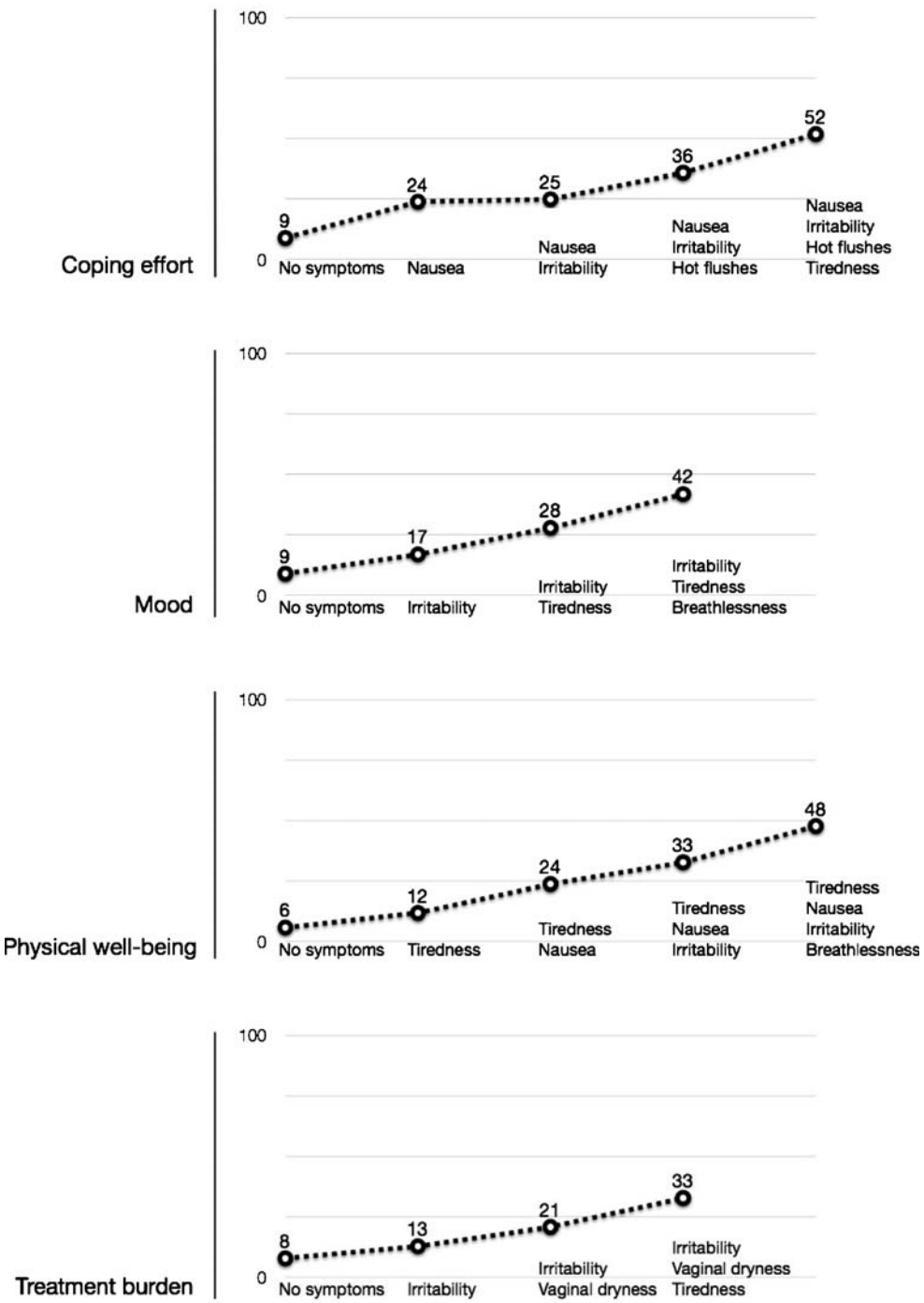

Fig. 3 Scenario to illustrate the clinical interpretation of the impact of symptoms on the global QL indicators: coping effort, mood, physical well-being and treatment burden by accumulated number of experienced symptoms (mean LASA scores). Higher scores indicate a worse condition (e.g. worse mood, more burden) for all indicators

overall QL are inconsistent and none of them was focusing on the subjective meaning of specific symptoms. The aim of this study was twofold: to examine the symptom experienced by evaluating a confirmative statement of having a particular symptom with symptom intensity and to assess the impact of various endocrine symptoms on four different global QL indicators.

In our sample, 70% of the women were experiencing hot flushes and sweats and over 40% suffered from tiredness and weight gain. Similar proportions of these three symptoms have previously been reported [3, 33]. More than one third of the patients reported vaginal dryness. In clinical observation, especially younger women receiving tamoxifen report vaginal dryness and a lack of vaginal lubrication whilst being sexually stimulated.

The distribution of the selected symptoms (i.e. hot flushes, weight gain, tiredness, decreased sex drive or vaginal dryness) showed that even though patients recorded a symptom as absent, some of them reported having experienced that symptom when responding to symptom intensity,

as seen for decreased sex drive, tiredness and vaginal dryness. Presumably, patients record these symptoms less frequently because they may feel embarrassed to talk about symptoms related to sensitive issues. On the other hand, among the patients that reported a symptom to be present, considerable variation in symptom intensity was observed. A simple 'yes' statement of the patient may already be indicative that she is substantially affected by this symptom. From a conceptual point of view, symptom experience comprises not only the perception of the frequency, intensity and distress but also the meaning of symptoms [1]. To learn about the individual meaning of a specific symptom to the patient's overall QL, communication with the patient provides the most accurate information. According to the answers on the C-PET questionnaire, only 5% to 7% of patients expressed the wish to discuss specific symptoms with their physician [25]. A checklist, such as the C-PET, may be an aid for physicians to evaluate patients' experience of symptoms. Yet its value to detect and address symptoms related to sensitive issues such as sexual functioning is not satisfying.

The evaluation of the impact of symptoms on womens' physical well-being, mood, coping effort and treatment burden revealed that 6 of 13 symptoms were significantly associated with 1 or more of these indicators. Tiredness and irritability affected all four indicators. Hot flushes/sweats, nausea, breathlessness and vaginal dryness were associated with selected indicators. It is worthwhile to note that less prevalent symptoms (e.g. breathlessness) may also have a substantial impact on a woman's well-being.

Women suffering from tiredness or irritability were more affected in both their physical well-being and mood, showed more problems in coping with the illness and reported more treatment-related burden than women not experiencing these two symptoms. These results reflect the finding of Nystedt et al. [33] that fatigue (comprising the symptoms of tiredness, irritability and decreased physical fitness) was the most frequent problem during the 2 years of adjuvant treatment and 1 year thereafter. Hot flushes and nausea were associated with coping with the illness whilst vaginal dryness was a predictor of treatment burden, suggesting that the majority of these patients does not perceive symptoms as exclusively illness-related or treatment-related. Our results also indicate that QL was worse when women were suffering from several symptoms concurrently. To illustrate the magnitude of such effects, the average difference in patient-reported mood of having 2 vs 0 of these symptoms (difference: 19) is comparable with having a performance status of 0 vs 1 or 2 in post-menopausal breast cancer patients after failure of tamoxifen (difference: 16.8) [6].

Age showed an effect on all four global indicators. This confirms previous findings showing that younger breast cancer patients are more at risk for impaired QL than older women up to several years after diagnosis [2, 3]. Age-adjusted risk profiles of endocrine side effects are particularly relevant for pre-menopausal patients [11]. In accordance with other studies [3, 22], treatment-related variables (i.e. adjuvant vs metastatic, previous chemotherapy and time since treatment start) did not have a significant impact on these indicators.

This study has several limitations. First, for each global indicator, the amount of variance (R^2), explained by symptoms, age and treatment-related variables was small. One reason may be the dichotomous response format of the C-PET. Some symptoms, even if indicated as present, did not have a statistically significant impact on the global indicators. Thus, symptoms not included in the C-PET such as joint pains and other not symptom-related variables (e.g. anxiety of disease progression) may contribute substantially to the prediction of QL in women with breast cancer. For example, personality traits like dispositional optimism [36], sociodemographic characteristics [31] or social support [22] were identified to have an influence on QL. Second, the sample of the present study is heterogeneous with respect to the type of endocrine treatment received and time-point of treatment. Evidence exists that endocrine agents have different effects on symptom intensity at different time-points during treatment [19, 21, 33]. In addition, due to the cross-sectional design of this study, it was not possible to address changes in self-reported endocrine symptoms and their long-term impact.

In conclusion, our results highlight that the occurrence of symptoms related to endocrine therapy is a considerable burden to breast cancer patients. Less frequently reported symptoms may also have a substantial impact on QL. Patients' experience of endocrine symptoms need to be considered, both in patient care and research when interpreting the association between symptoms and QL. Although sensitive symptoms may be underreported, a symptom checklist is useful to raise the physician's awareness of symptom occurrence.

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