Pressure pain sensitivity as a marker for stress and pressure pain sensitivity-guided stress management in women with primary breast cancer

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Abstract
Objectives. To validate (1) Pressure Pain Sensitivity (PPS) as a marker for stress and (2) a PPS-guided intervention in women with primary Breast Cancer (BC). Methods. (1) A total of 58 women with BC were examined before and after 6 months of intervention. A control group of 165 women office employees was divided in a High Stress Group (HSG, n = 37) and a Low Stress Group (LSG, n = 128) to evaluate the association between PPS, questionnaire-related Quality of Life (QOL) and self-evaluated stress. (2) A PPS-guided stress management program (n = 40) was compared to a Psychosocial Group Intervention (PGI, n = 91) and no treatment (n = 86) with respect to a European Organization for Research and Treatment of Cancer (EORTC) questionnaire measured QOL. Results. (1) Resting PPS and changes in PPS during the intervention period correlated significantly to EORTC and Short Form 36 (SF 36) main scores: (all $p < 0.05$). Between BC, HSG and LSG there was a significant and positive correlation with respect to PPS, SF 36 main scores, depression, and clinical stress scores (all $p < 0.05$). However, the BC group scored significantly lower than both HSG and LSG (both $p < 0.05$) with respect to self-evaluated stress. (2) The PPS-guided intervention group improved EORTC main score, pain and nausea, when compared to the control groups (all $p < 0.05$). Conclusions. PPS was positively associated with QOL, which was in contrast to self-evaluated stress. PPS-guided intervention improved QOL in women with breast cancer.

Key Words: Acupuncture, acupressure, clinical stress score, EORTC questionnaire, HADS questionnaire, patient education, self-evaluated stress, SF 36 questionnaire

Introduction
Breast cancer diagnosis and treatment are psychologically stressful events [1–3]. No international consensus on biochemical, psychological, or physiological methods for measuring stress exists [4,5].

It is essential to distinguish between transient and persistent stress. Transient stress is characterized by increased preparedness, induced through neural and hormonal signals as a response to perception of a challenge like a dangerous or painful situation, or the demand of an acute performance. When the threat or challenge is over, homeostasis is re-established [6,7]. Persistent stress is caused by prolonged exposure to the same challenges as in transient stress, but without sufficient restitution in between, which leads to a variety of physiological and psychological dysfunctions [8,9]. Persistent stress may affect work performance [10], as well as general health negatively [11], and may be associated with features of the metabolic syndrome [12–14], ischemic heart disease and diabetes Type II [15,16].

The validation process of the Pressure Pain Sensitivity (PPS) (see the abbreviations in Table I) measure as a potential measure for physiological stress is based on the international recommendation for device validation [17] suggesting a minimum of two independent prospective randomized trials as well as including validity and reliability aspects [18].
management program (Ull Care prospective case control studies indicate that a stress potential life-threatening disease, including the cross as a marker for persistent stress in patients with a ground the present study validates the PPS measure has been tested separately [19,20]. On this back-

(4) Rate-Product, and serum cholesterol [21]; and pressure, work of the heart measured as Pressure-Rate-Product [19] as well stress level [20]; (3) PPS was linked to blood pressure, pulse rate, and saliva cortisol [19]; (2) with respect to persistent stress and cross sectional studies that PPS was linked to resting heart rate and work of the heart measured as Pressure-Rate-Product [19] as well as questionnaires associated with persistent stress, such as Short Form 36 (SF 36), Major Depression Inventory (MDI) score, a clinical stress symptom score in healthy people [20] and in patients with ischemic heart disease [19,21]. However, PPS was not linked to the individual personal perception of the stress level [20]; (3) with respect to persistent stress and interventional studies it was found in office workers that a reduction of an elevated PPS measure was associated with concomitant reduction in important health risk factors such as heart rate, blood pressure, work of the heart measured as Pressure-Rate-Product, and serum cholesterol [21]; and (4) measurement reliability and categorization agreement has been tested separately [19,20]. On this background the present study validates the PPS measure as a marker for persistent stress in patients with a potential life-threatening disease, including the cross sectional aspect as well as the interventional aspect.

With respect to the used intervention, previous prospective case control studies indicate that a stress management program (Ull Care©, www.ulcare.com) [19] using the PPS measure as a combined tactual and visual biofeedback marker for the patient and/or therapist for stress and using personal reflection on the PPS measure in combination with acupuncture, acupressure and a broad range of physical and cognitive exercises for stress reduction may improve survival in patients with ischemic heart disease and stroke [19,22] and reduce cardiovascular physiological and biochemical risk factors associated with persistent stress in office workers [23]. With this background, the aims of the present study were to use a prospective controlled trial to test the possible link between PPS, generally used questionnaires for QOL, and self-perceived stress in women with primary breast cancer (the validation study), and to evaluate the effect of PPS-guided stress management in these women (the intervention study).

### Material and methods

#### Study design

The validation study consisted of two parts: Part (A) was a cross sectional controlled study including two study groups (Figure 1): a breast cancer group (BC Group) (N = 58) and a healthy control group of female office workers (N = 165). The BC Group inclusion took place in cooperation between two departments of breast surgery (Herlev and Hørsholm Hospitals). The female office workers were employed in a large Danish company within the finance sector. These 165 women were part of a total office study group of 308 women and men. Characteristics of this office study group are described in detail elsewhere [20]. Part (B) was a prospective experimental study testing the longitudinal association between stress measured by PPS and stress measured by Quality of Life (QOL) questionnaires within the BC group, and using a 6-month PPS-guided stress management program to reduce stress during the observation period.

The intervention study was a prospective controlled study including females treated for primary breast cancer and comparing (1) the PPS Group, receiving PPS-guided stress management (N = 40) to (2) two Psychosocial Intervention Groups (PGI, N = 177), who received comprehensive group therapy (PGA, N = 91) and a control group, receiving treatment as usual (PGC, N = 86) (Figure 1). Inclusion criteria were: age ≥ 70 years and operation for primary breast cancer. Exclusion criteria were: women previously treated for cancer, suffering from chronic disease, or who had mental or language problems. Inclusion in the latter two groups took place in a simultaneously conducted randomized study at the Department of Breast Surgery, Herlev Hospital. The details are described elsewhere [24]. Selection and invitation between the PGI and the PPS groups was carried out by the consulting nurse.
Pressure pain sensitivity

1 week after surgery. It was done on a 1/1 basis, but not using a randomized protocol. Women who declined participation in one study were not enrolled in the other study.

Minimizing bias

Within the Pressure Sensitivity Groups, the following were done to minimize bias: PPS measurements were conducted by one group of researchers who had no access to the answers of the used questionnaires; reading of the PPS instrument was not visible during measuring neither for subject nor researcher; a second group of researchers collected questionnaires, and these researchers had no access to the PPS measurements.

Interventions

The **PPS-guided intervention**. The PPS-guided intervention was performed in a non-hospital setting in order to facilitate transition to ‘normal life’ and to prevent a negative impact on the program from potential conditional reflexes as from nausea induced by chemotherapy. All data were collected at baseline and after 6 months. For 15 women of the PPS study, who had not finished chemotherapy at 6 months, an additional measurement was conducted after the end of treatment for that part of the study, which tested the link between PPS and QOL.

The intervention (Ull Care©) consists of a professional part and a self-care part.

The professional part included PPS measurement, acupuncture and patient education conducted by a special instructor. At each professional consultation the PPS measure was conducted as a guideline for the treatment strategy; a decrease in PPS measure suggested a decrease in stress, while an increase in PPS or a persistently elevated PPS suggested the need for supplementary efforts, which could include more frequent professional consultations or adjustment of the self-care based efforts.

At each consultation acupuncture was performed in agreement with traditional Chinese practice [25]. After obtaining needle sensation (or the arrival of qi), the needles were left in situ for 20 minutes with no further stimulation. Five classical points were used: C.V. 17, U.B. 14 and 15, Per. 6, and St. 36.

The self-care part included a ‘must do part’ with (a) daily recording of the PPS measure and to use a cognitive feedback measure for the current stress level and (b) daily acupressure conducted by the patient and her husband in accordance with instructions obtained during the professional part, and with the aim to reduce the PPS (e.g. reduce stress), prevent and treat nausea before and during chemotherapy and reduce pain and inflammation during radiation therapy, and a ‘free-of-choice’ selection of additional self-care-based modalities: physical and relaxation exercises, cognitive therapy and exercises as well as nutrition suggestions, described in detail previously [26].

Acupressure was conducted twice daily as application of firm painless finger pressure. After 20–30 seconds of acupressure the patient evaluated whether any underlying soreness had decreased. If not, the procedure was repeated with a slight increased pressure bringing acupressure time to one minute. The acupressure point for nausea was Neiguan (Per 6) between the tendons of m. flexor carpi radialis and m. palmaris longus [27]. Acupressure points for stress management were on the sternum (Shanzhong, C.V. 17) and on the back 1.5-inch lateral to the spinal process of the fourth and fifth thoracic vertebra (Jueyinshu and Xinshu, U.B. 14 and 15). Acupressure on the back was preferably conducted by the spouse.

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**Figure 1.** Case materials and study groups.

**A Pressure Sensitivity Groups**

<table>
<thead>
<tr>
<th>Breast Cancer patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC Group: All patients; (N = 58)</td>
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<tr>
<td>PPS Group: BC ≤ 70 years; (N = 40)</td>
</tr>
</tbody>
</table>

**B Psychosocial Intervention Groups (PGI)**

<table>
<thead>
<tr>
<th>Breast Cancer patients, (N = 177)</th>
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<tbody>
<tr>
<td>PGA: active group; (N = 91)</td>
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<tr>
<td>PGC: control group; (N = 86)</td>
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</table>

**C Healthy control group**

<table>
<thead>
<tr>
<th>Female office workers, (N = 165)</th>
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<tbody>
<tr>
<td>HSG: High Stress Group; (N = 37)</td>
</tr>
<tr>
<td>LSG: Low Stress Group; (N = 128)</td>
</tr>
</tbody>
</table>

Study design:

Validation Study = A (BC Group) + C
Intervention Study = A (PPS Group) + B
taught the patient that control was possible and was considered a compliance enhancer. The sensitivity on the sternum served as a feedback measure for the patient in evaluation of stress level and to monitor effects of daily stress reducing efforts, with an elevated sensitivity reflecting an elevated stress level.

**Psychosocial intervention.** This intervention had two parts: 12 hours of education conducted as two weekly sessions. Teachers were surgeons, oncologists, nurses, dieticians, a social worker, a psychologist and a physiotherapist. In the second part of the intervention, groups of 8 women met 8 times over 8 weeks for 2.5 hours sessions. A psychologist led the group in cooperation with two nurses. The main purpose was to share ‘cancer stories’, to reveal negative thinking and to integrate elements of cognitive therapy smoothly. Homework was added and the results were shared in the group [18].

The Control intervention was treatment as usual and described in detail elsewhere [18].

**Effect variables**

**The PPS measure.** This measure was used in both the Validation Study and the Intervention Study (Figure 1): An algometric instrument (UllMeter; UllCare LtD., Lemchesvej 1, DK 2900 Hellerup, Denmark) was used for measurement of the PPS. The measurement site is the sternum within the area between third, fourth and fifth intercostal spaces reflecting the area of segmental innervation of the heart. The instrument transforms pain threshold mathematically into a logarithmic scale of sensitivity levels (from 30 to 100 PPS units). An increase in 30 PPS units corresponds to a 100% increase in sensitivity [19,20]. A high score indicates a high level of stress. The measurement was conducted in the supine position after 10 minutes of rest. For analysis the mean of two consecutive measurements was used; if the difference was more than 10 PPS units the mean of two consecutive measurements was used; if the difference was more than 10 PPS units a third measurement was performed and the result was the mean of all three.

In the validation study questionnaire related effect variables were used: SF 36; Hospital Anxiety And Depression Scale (HADS); A specially designed Clinical Stress Score (CSS)[20], the European Organization for Research and Treatment of Cancer (EORTC) questionnaire; Self-evaluated stress level; and Reduced QOL measured by the included questionnaires.

The SF 36 assesses general mental and physical health by two main scales (Mental Component Summary (MCS) and Physical Component Summary (PCS), and eight subscales. A high score indicates high QOL [28]. The SF 36 and the depression questionnaires have been internationally recognized as stress measurement methods [29–31]. The HADS questionnaire assesses the level of anxiety and depression [32]. The CSS was calculated from a symptom check-list, on which the participants registered the occurrence of 50 different clinical stress symptoms within the previous four weeks (score range 0–100 – arbitrary units) (www.ballegard clinicalstressscore.com). This score has previously shown to be positively correlated to the PPS measure [20]. The endpoints of the EORTC questionnaire were: the main score (Global Health), four function scales (Physical, Role, Cognitive and Social Function), and three symptom scales (Fatigue, Nausea and Pain). A high score indicates high well-being with respect to Global Health and the function scales, and a high level of symptoms on the symptom scales. Self-evaluated stress was measured on a four-point scale from No Stress (= 0) to Very Stressed (= 3). QOL was considered reduced when the questionnaire scores were: (1) HADS depression score: ≥ 8 [32]; (2) MDI score for depression: ≥ 20 as used in the office-workers study [20]; (3) CSS: ≥ 50 arbitrary units; (4) SF 36 MCS and PCS scores: ≥ 25% percentile when matched for age as in previous PPS evaluating study [20]; and (5) self evaluated stress score: ≥ 25% percentile within study group.

In the intervention study, the EORTC questionnaire was used, exclusively. Compliance to treatment was included in the PPS Group, only. Compliance was evaluated from the questions: ‘Do you presently use the obtained knowledge in your handling of the disease?’ (‘Yes’, ‘No’ or ‘Do not know’); ‘Did you experience an effect from the treatment as a whole or from part of it: (a) in general, (b) with respect to tolerance, and (c) with respect to side effects from chemo- or radiation therapy? This was answered by a 7-step ordinal scale from negative (0) to positive (6).

**Statistics**

**PPS validation study.** Between-group data were analyzed by unpaired sample t-test. To test the possible cross sectional association between PPS and QOL in breast cancer women against healthy office-working women, the ratio of reduced QOL score was calculated as the number of persons having that score divided by the total number of persons in that study group. Furthermore, when creating a step-wise classification of study groups with respect to level of stress, PPS was used as a classification variable. In calculations the office-working women were divided into a High Stress Group (HSG) (n = 37) and a Low Stress Group (LSG) (n = 128) using a resting PPS = 60 as the discrimination point as this has shown to be a useful discrimination point with respect to questionnaire-related QOL [20].

To test the possible association between PPS and answers to QOL questionnaires related to persistent...
For between-group differences.

Statistical analyses. The SPSS version 18 for Windows (SPSS Inc. Chicago, IL, USA) was used for the statistical analyses with the significance level set at 5%.

Ethics

The study was conducted according to the Declaration of Helsinki 1983 and in compliance with Good Clinical Practice and local ethical and legal requirements. Written informed consent was obtained from all participants.

Results

PPS validation study

For all used questionnaire-related effect variables the correlation between pre- and post observation period variables were significant (all correlation coefficients > 0.6; all \( p < 0.001 \)), thus supporting the hypothesis that they are not significantly influenced by unknown confounding factors during the observation period, which makes pooling of pre- and post-observation period data for analysis possible.

When pre-treatment and post-treatment data were pooled, the correlation coefficients between the PPS measure and the included QOL measures: All SF 36 scales, both HADS scales, the CSS score and for most EORTC scores were significant (all \( r \geq 0.2 \), all \( p < 0.05 \)) (Table II).

During the intervention period, the median PPS was reduced from 80 (interquartile range (IQR)): 97–62 units) to 56 (IQR: 69–43) (\( p < 0.001 \)) (\( n = 58 \)). The change in PPS during the observation period correlated significantly to changes in EORTC scores: Global health score, physical function, role function, fatigue, and pain (\( r = 0.3, p < 0.05 \)), the main SF 36 scores, and seven out of eight SF 36 subscales (all \( r \geq -0.2 \); all \( p < 0.05 \)). No significant correlation was found between changes in PPS and changes in HADS scales and CSS score, although a significant and concomitant reduction to the PPS reduction was observed for all three during the observation period: Anxiety score (mean score reduction from 6.2 to 4.1 (\( p < 0.001 \)), Depression score (mean reduction 3.4 to 2.5 arbitrary units (a.u) (\( p < 0.05 \)), and CSS (mean score reduction from 48 to 34 (\( p < 0.001 \)).
Including the healthy office-working women, and when using PPS as classification variable with respect to level of persistent stress, the office working women LSG had the lowest PPS measure (median PPS 46, IQR 35–50) (named Stress Group 1, Figure 2), the BC group had the highest PPS (median PPS 79; IQR 63–97 units) (Stress Group 3); and the office HSG women had a PPS in-between the two other groups (median PPS 76, IQR: 66–88) (Stress Group 2). A positive and significant correlation was found between this three-step stress group classification and the ratio of having a reduced QOL measured by SF 36 MCS score ($r = 0.375$, $p < 0.001$), SF 36 PCS score ($r = 0.16$, $p = 0.02$), CSS score ($r = 0.230$, $p = 0.002$), and Depression score ($r = 0.13$, $p = 0.05$). However, with respect to Self-evaluated Stress score, this correlation was negative ($r = -0.12$, $p = 0.08$).

The ratios for having a reduced QOL for the three groups were: SF 36 PCS score (ratios: study group 1 = 18%, study group 2 = 23%, study group 3 = 35%) ($p$ for trend < 0.05); SF 36 MCS score (ratios: 1 = 20%, 2 = 42%, 3 = 61%) ($p$ for trend < 0.05); CSS (ratios: 1 = 30%, 2 = 52%, 3 = 63%) ($p$ for trend < 0.05); Depression score (ratios: 1 = 4%, 2 = 7%, 3 = 12%) ($p$ for trend = 0.05). For elevated Self-evaluated Stress score the ratios were: 1 = 17%, 2 = 24%, 3 = 4% with the BC Group scoring significantly lower than both HSG ($p = 0.0013$) and LSG groups ($p = 0.042$), and with no significant difference between LSG and HSG ($p > 0.1$). Figure 2 shows the corresponding trend lines between stress groups 1, 2 and 3, and the ratios of having a reduced QOL measured by SF 36 MCS score, SF 36 PCS score, CSS, and Depression score and on the other side, the contrasting trend line between the Stress grouping and Self evaluated stress score. Abbreviations: QOL, Quality of Life; SF 36, Short Form 36 Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; CSS, Clinical Stress Score.

### Intervention study

Between-group variables in the PPS, PGI and PGC groups were non significant with respect to age, type of operation, tumor size, nodal status, degree of malignancy, receptor status, and conducted treatment postoperatively, and similarly with respect to the included effect variables: EORTC scores for global health, physical function, role function, cognitive function, fatigue, pain, and nausea (all $p > 0.1$; data not shown).

In the PPS study, 98 patients were offered participation; 58 women (59%) accepted inclusion. A total of 51 patients (89%) completed the study. Seven patients dropped out as they found the distance to the clinic too long (two patients) or found themselves too busy (five patients). The patients received a combination of irradiation, chemotherapy, and anti-hormonal therapy and received a mean of 15 treatments (IQR: 9–19) during the 6-month observation period.

**Table II.** Correlations between PPS and other effect variables ($N = 51$). Baseline and follow-up data pooled ($r_1$). Change from before to after intervention period ($r_2$). Correlation coefficients ($r$) and $p$ values for significance (one-tailed).

<table>
<thead>
<tr>
<th>Effect variable</th>
<th>$r_1$</th>
<th>$r_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status/QOL</td>
<td>$-0.4^{***}$</td>
<td>$-0.2^a$</td>
</tr>
<tr>
<td><strong>Functional scales:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>$-0.3^{***}$</td>
<td>$0.5^{***}$</td>
</tr>
<tr>
<td>Role functioning</td>
<td>$-0.3^{***}$</td>
<td>NS</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>$-0.2^*$</td>
<td>$0.3^*$</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Social functioning</td>
<td>$-0.2^*$</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Symptom scales/items:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>$0.4^{***}$</td>
<td>$0.5^{***}$</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pain</td>
<td>$0.3^{***}$</td>
<td>$0.3^a$</td>
</tr>
<tr>
<td><strong>SF 36</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function</td>
<td>$-0.4^{***}$</td>
<td>$0.3^a$</td>
</tr>
<tr>
<td>Role physical</td>
<td>$-0.4^{***}$</td>
<td>$-0.5^{***}$</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>$-0.3^*$</td>
<td>$-0.2^*$</td>
</tr>
<tr>
<td>General health perception</td>
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<tr>
<td>Vitality</td>
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<td>$-0.2^*$</td>
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<tr>
<td>Social function</td>
<td>$-0.2^*$</td>
<td>NS</td>
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<td>Role emotional</td>
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<td>$-0.2^*$</td>
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<tr>
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<tr>
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<tr>
<td><strong>HADS</strong></td>
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<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>$0.3^{**}$</td>
<td>NS</td>
</tr>
<tr>
<td>Depression</td>
<td>$0.3^{**}$</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical Stress score</td>
<td>$0.4^{**}$</td>
<td>NS</td>
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</tbody>
</table>

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. NS, not significant.
When compared to the PGI group, the patients of the PPS study group obtained a significant increase in EORTC Global Health (mean increase $+15$ a.u versus $+5$ a.u; $p < 0.05$), a significant reduction with respect to nausea (mean reduction $-26$ vs $-16$ a.u), and pain (mean reduction $-17$ vs $-7$ a.u; both $p < 0.01$).

**Compliance**

In the PPS study group, 49 out of 51 (96%) patients stated that they had integrated the program into daily life, all 51 patients (100%) stated a positive general outcome ($\geq 4$ on the 7-point ordinal scale), and 49 patients (96%) stated a marked positive general outcome (score 5 or 6); 40 patients (78%) stated higher tolerance, and 36 patients (71%) stated less side effects from chemo- or radiation treatment.

**Discussion**

In patients with primary breast cancer the PPS measure seemed well correlated with several measures for QOL and depression, which has been found prognostic for breast cancer survival [34]. Secondly, the biofeedback stress management program using the PPS measure as a marker for stress, improved Global Health and reduced pain and nausea when compared to a comprehensive psychosocial intervention program (PGI study). Importantly, 90% of the patients completed the PPS program, all of these patients reported a positive outcome, and had a 96% compliance rate. Thirdly, when compared to healthy office-working women, the link between PPS and QOL was meaningful with respect to four individual questionnaires related to different aspects of QOL, which was in contrast to the self-evaluated stress level.

The evaluation of stress intervention is difficult as no simple objective parameter exists. Questionnaires were used as an important substitute. We demonstrated that PPS correlated to EORTC, SF 36 and HADS scores, and to the clinical stress symptom score. Similar findings with respect to measurement of persistent stress have been found in office workers [20]. In the present study, we found that the PPS measure was reduced significantly and this reduction was significantly correlated to increase in QOL measured by the EORTC Global Health and to reduced fatigue, pain, and the level of persistent stress as measured by the SF 36.

In Danish patients with breast cancer an increased prevalence of depression has been found [35]. Depression is generally accepted as associated with persistent stress [36]. The present study demonstrated that PPS was linked to both anxiety and depression. Although PPS, anxiety and depression scores all improved concomitantly and significantly, the changes between these variables were not internally significantly correlated. This may be explained by a possible non-linear, a partial, or a conditional correlation between PPS, depression and anxiety as well as by low number of patients who had an elevated baseline Anxiety or Depression score.

It was suggested that stress protects women against BC [37]. The hypothesis was based on the finding of a negative correlation between self-evaluated stress and prevalence of breast cancer. The present findings challenges this hypothesis with the finding of an invert association between self-evaluated stress and internationally-validated QOL questionnaires associated with stress as well as to PPS as a physiological marker for stress.

In BC patients, other groups have shown that mindfulness [38,39], yoga [40], and massage [41] reduce stress, and that psychological anti-stress intervention improves survival [42]. In USA, in contrast to Denmark, acupuncture has for a decade been recommended supplementary to chemotherapy in order to reduce or avoid nausea [43,44].

With respect to the possible mechanisms by which the used intervention works, it is important to emphasize that the multiple aspects of the intervention excludes the possibility to assess the potential effect from the individual components, which in other studies have shown clinically-relevant effects [19,26]. The effects of sensory stimulation, as in acupuncture and acupressure, and the effect on nausea and general pain perception were found before [43,45,46]. Effects of sensory stimulation on sympathetic tone and thus the stress level is at least partly mediated by a reduction of sympathetic tone [47,48] and that the effect may be a modulation of the sympathetic tone mediated from the control center of the autonomic nervous system of the brain: the hypothalamus [49].

**Strengths and limitations**

A strength of the validation study is the fact that it represents the fourth consecutive cross sectional study finding an association between PPS and effect variables associated with persistent stress, thus supporting the findings in out-clinic patients [19], healthy office workers [20] and patients with ischemic heart disease [21]. Furthermore, the included study groups are representative for two major population groups for whom stress measurement may be relevant: persons with a potential life-threatening situation, represented by BC patients, and the everyday working life of ordinary citizens, represented as office-working women. With respect to the interventional part, the positive findings correspond to long-term prospective clinical studies in patients with ischemic heart disease [48] and stroke [26] and one short-term (3 months) prospective study in office workers [23].
The present study has limitations: a low number of included patients, which, however, with respect to the association between PPS and used questionnaires, is met by the findings of other studies [19, 20]; the study did not use a strict randomization protocol. However, at baseline, no significant differences between the study groups were observed; the intervention was a comprehensive treatment and educational program, which excludes the possibility of identifying one modality as the more important modality.

Conclusions

In combination with previous studies [19, 20], the present study provides a level ‘A’ evidence for the recommendation of the PPS measure as a marker for persistent stress [17]. The study invites a second and larger study to provide a full evidence-based evaluation before general clinical recommendations of the intervention in BC patients, although the lack of side effects or complications from the used intervention in combination with the prevalence and severity of the disease may suggest a preliminary recommendation.

It is concluded that, in women with primary BC, PPS was found to be useful as a marker for persistent stress, while the value of self-perceived stress was found not useful. Additionally a clinically relevant and physiologically meaningful reduction in stress and improved QOL from the present intervention was observed, and with a high compliance.

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Declaration of interest: Dr Søren Ballegaard is a shareholder of Ull Care A/S who owns the patents for the instrument Ull Meter (patent numbers: PA 2004-00359; PA 2004-00550) that makes the PPS measure possible; for that reason he was not involved in the treatment of patients, the collection or the analysis of data. CK Axelsson: no conflicts; Benny Karpatschof: no conflicts; Peer Schousen: no conflicts.

References

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