From THE DEPARTMENT OF PHARMACOLOGY AND PHYSIOLOGY
Karolinska Institutet, Stockholm, Sweden

SENSE OF COHERENCE (SOC) IN WOMEN TREATED FOR BREAST CANCER AND ITS RELATION TO TREATMENT OUTCOME

Carina Lindblad

Karolinska Institutet

Stockholm 2016

SENSE OF COHERENCE (SOC) IN WOMEN TREATED FOR BREAST CANCER AND ITS RELATION TO TREATMENT OUTCOME
THESIS FOR LICENCIATE DEGREE

By

Carina Lindblad

Principal Supervisor:
Professor Kerstin Sandelin
Karolinska Institutet
Department of Molecular Medicine and Surgery

Co-supervisor(s):
Professor Ann Langius-Eklöf
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society

Lena-Marie Petersson PhD
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society

Karl-Fredrik Sjölund MD, PhD
Karolinska Institutet
Department of Pharmacology and Physiology

Examination Board:
Professor Pernilla Lagergren
Karolinska Institutet
Department of Molecular Medicine and Surgery

Professor emerita Berit Lundman
Umeå University
Department of Nursing

Professor Beatrice Melin
Umeå University
Department of Radiation Sciences and Oncology

To Johnny, Jonatan and Johanna

ABSTRACT

Breast cancer incidence has, on average increased by 1.4 % annually during the last decades. Early detection and advances in treatment are the main contributing factors for the favourable outcome in terms of five- and ten-year survival rates. The biological factors that influence disease progression and mortality in breast cancer have been well studied. Comparatively less is known about the overall coping ability and their relevance for outcome in the breast cancer-population. The concept of sense of coherence (SOC) reflects a person´s orientation to life and was established to describe why people remain healthy during times of considerable strain, and manage to make sense out of difficult experiences or situations. In the current thesis SOC is measured by the Sense of Coherence Scale (SOC-13). It contains 13 items that reflects the three core components; comprehensibility, manageability and meaningfulness. Higher SOC scores indicate higher sense of coherence.

The main aim of the thesis was to evaluate the SOC scale´s stability and predictive value regarding progression and mortality in breast cancer patients. This was done utilizing a prospective design with a long-term follow-up in a multicenter cohort at four different Swedish hospitals. Two studies were performed. Of the total cohort, 75% and 87% respectively, participated in the two studies.

In paper I, support for the SOC scale´s stability over time (ICC 0.68, effect size 0.06) was demonstrated. The result of the cross-sectional factor analysis revealed a modified three-factor and a second order factor model meeting criteria for goodness of fit. The longitudinal modified second-order factor model confirmed the construct stability character of the SOC scale with an acceptable goodness-of-fit criteria.

In paper II, patients with high SOC had a 60% lower risk of breast cancer progression and a 80% lower risk of mortality than patients with low SOC over a median follow-up time of 10 years. The mortality risk declined by 2.3% for every one-unit increase in SOC (breast cancer mortality HR, 0.98; 95% CI, 0.96 to 0.99 and all-cause mortality HR, 0.98; 95% CI, 0.96 to 0.99). After adjusting for potential cofounders, the risk declined by 1.7% (breast cancer mortality) and 1.5% (all-cause mortality). The risk of progression declined by 1.4% for every one-unit increase in SOC (HR, 0.99; 95% CI, 0.97 to 1.00). After adjusting for potential cofounders, the decline was 0.7%.

In conclusion, the results from this thesis have shown that the SOC scale and its underlying construct is stable over time when applied to women with breast cancer. In addition, the SOC scale demonstrates a predictive value for disease progression, breast cancer caused mortality and for all-cause mortality among women with breast cancer and can be a valuable instrument for assessment of women at risk.

Keywords: *Breast cancer, Factor analysis, Progression, Psychometrics, Mortality, Sense of coherence, SOC, Stability*

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I. **Stability of the 13-item sense of coherence (SOC) scale: a longitudinal prospective study in women treated for breast cancer**
Lindblad C, Sandelin K, Petersson L-M, Rohani C, Langius-Eklöf A
Quality of Life Research (2016) 25:753–760

II. **Sense of Coherence (SOC) scale a predictor of survival: a longitudinal prospective study in women treated for breast cancer**
Lindblad C, Langius-Eklöf A, Petersson L-M, Sackey H, Bottai M, Sandelin K
Submitted March 2016.

CONTENTS

LIST OF ABBREVIATIONS

aHR	Adjusted hazard ratio
AIC	Akaike's information criterion
AMOS	Analysis of Moment Structures
ANOVA	Analysis of variance
AUC	Area under the receiver operating characteristic curve
CFI	Comparative fit index
Df	Degrees of freedom ratio
GFI	Goodness-of-fit index
HR	Hazard ratio
ICC	Intra-class correlation coefficient
OLQ	Orientation of life questionnaire
R^2	Squared multiple correlation
RMSEA	Root-mean square error of approximation
ROC	Receiver operating characteristic curve
SOC	Sense of coherence
SOC-29	Sense of Coherence Scale (the 29-item version)
SOC-13	Sense of Coherence Scale (the 13-item version)
SPSS	Statistical Packages of Social Sciences
TNM	T =tumor size and invasiveness, N =lymph node status, M =distant metastasis
X^2	Chi-square

1 BACKGROUND

1.1 BREAST CANCER

Worldwide more than 1.2 million women are diagnosed with breast cancer every year, making it the second most common cancer form after lung cancer (1). In the Western hemisphere, breast cancer is the most common cancer among women. In Sweden, one in every eight women will get a breast cancer diagnosis during her lifetime and 8691 invasive breast cancer cases were diagnosed in Sweden 2014 (2). Sex and age are the most important determinants of breast cancer incidence. In Sweden, the mean age of onset is 64 years (2). The average annual increase in breast cancer has been 1.4% during the last two decades, with an increase from 80 to 200/100 000 female inhabitants from 1970 to 2014 (2). Both in Sweden and worldwide, lifestyle changes, such as women having fewer children, improved diagnostic methods, screening programs, and an ageing populations contribute to the increase (1).

1.2 TREATMENT AND PROGNOSIS

Sweden has national and regional evidence based treatment guidelines for breast cancer that are regularly updated in line with internationally accepted counterparts (3, 4). The primary treatment for the majority of patients is surgery. In addition, based on prognostic and treatment predictive information, radiotherapy and adjuvant systemic therapy (anti hormonal therapy, chemotherapy and anti-HER2 therapy) is recommended (3, 4). The definition of a disease prognostic factor is that it prognosticates the progression of untreated disease. A treatment predictive factor predicts the most likely therapy response to a certain therapeutic agent. Factors that provide prognostic and/or treatment predictive information for breast cancer are patient´s age, tumor stage according to TNM classification (T = tumor size and invasiveness, N = lymph node metastases, M = distant metastases) (4). In addition, tumor characteristics such as histological grade, expression of biomarkers, estrogen, progesterone receptor status, human epidermal growth factor receptor 2 statuses (HER2) also have prognostic and/or predictive value. More recently molecular sub typing of tumors has been introduced as valuable prognosticators (4).

Post treatment follow-up varies according to risk group and whether the patient is included in any study protocol (4). Most women are referred back to the screening program after completion of adjuvant treatment. The routinely yearly clinical visits are almost non existing based on lack of evidence for such follow-up methods. The results of breast cancer treatment in Sweden measured as survival are among the best in Europe (1). Advances in medical knowledge and technology have reduced the adverse side effects of therapy (5). Long-term prognosis of breast cancer patients has improved significantly over the last 50 years (1). Breast cancer mortality in Sweden has, contrary to the incidence, been stable for many years with about 1 400 deaths per year but now decreases slightly by in average of 1% per year for the last 20 years (6). Breast cancer was up to 2005 the leading cancer causing death among women (6). Just about 94 000 individuals in Sweden live with a breast cancer diagnosis (7). Of those alive, over 83% live 10 years after diagnosis, making breast cancer patients the largest group of long-term cancer survivors (7). This situation also holds true for other countries with the best outcome (1). The improved survival is partly due to earlier detection and more targeted treatment (8). Despite this, a breast cancer diagnosis remains stressful for

most patients (9, 10) and stress may be associated with an elevated risk of breast cancer recurrence (11) and earlier mortality (12).

1.3   SENSE OF COHERENCE (SOC)

The medical sociologist Aaron Antonovsky conceptualized Sense of Coherence (SOC). This concept reflects a person´s orientation to life and was described as an attempt to explain why some people remain healthy during times of considerable strain, while other people become sick or ill under the same degree of strain (13, 14). Antonovsky studied a group of survivors from the concentration camps of the Second World War. He was intrigued and raised the question why these individuals, regardless of major stressful situations and severe hardships, were able to stay healthy. He postulated that it was because of the way they viewed their life and their essence of existence (14). SOC is defined as a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence (14). The SOC concept contains three components: comprehensibility, manageability and meaningfulness, which together contribute to the unity of SOC. These three components in the construct are dynamically interrelated, and serve as an overall coping resource (14). The SOC construct does not refer to specific types of coping strategies. It is intended to be a prerequisite for the perception and management to overcome a stressful situation (15). According to Antonovsky, people with high SOC possess resources that enable them to cope with various kinds of stressful life events. A person with a high feeling of comprehensibility expects that stimuli/ events that appear in the future will be rational, understandable and predictable, or if they come as surprises; they will be ordered and explicable (14). A person with high feeling of manageability perceives the resources as adequate and available to meet the demands posed by the stimulus, and still feels able to cope adequately with the situation. Finally, a person with high feeling of meaningfulness is more likely to feel that life makes sense and that at least some of the problems and demands are worth investing energy in and worth making commitments for (14).

1.4   THE SOC SCALE

Antonovsky developed the SOC scale, a self-report inventory, also called the Orientation to Life Questionnaire. The original SOC scale consists of 29 items (SOC-29), a shorter form has 13 items (SOC-13) (14). The 13-item version has shown to be as reliable and valid as the 29-item version (16-18). The items of the SOC-13 measure comprehensibility (5 items), manageability (4 items) and meaningfulness (4 items). An example of an item in the component of comprehensibility is "Do you have the feeling that you are in an unfamiliar situation and do not know what to do?" An example of an item in the component of manageability is, "How often do you have feelings that you are not sure you can keep under control?" and of an item in the component of meaningfulness is, "Do you have the feeling that you do not really care about what goes on around you?" The SOC scales have been validated in several settings using cohorts both from within healthcare facilities and from general populations. Reliability and validity have been supported in numerous studies, including cancer populations (19-21), with internal consistency, with Cronbach´s alpha ranging from 0.74 to 0.93 (16). There are no predefined boundaries for high and low SOC respectively (16). A review summarized the research on the SOC scales until 1992 and reported data from 42 different studies (22) and another review analyzed studies from 1992 to 2003 (16). The SOC scales have been widely used in 127 cross-sectional and longitudinal studies with up to 20 000 persons (16). The SOC scales have been used in both Western

countries, including Sweden, and in Japan, China, Thailand and South Africa. They are validated for more than 33 languages in 32 countries. Thus, the SOC-13 scale is considered to be cross culturally applicable (16).

Over the years, the concept of SOC has become well established in public health, in health promotion and has received attention within healthcare research. Antonovsky suggested that one of the most crucial determinants in an individual´s perception of health is the degree of SOC which will have a health-protective behavior pattern and a stress buffering effect (13). Longitudinal studies have supported Antonovsky´s view of the SOC construct as a health-promoting factor (23-26), for both physical (25, 27) and mental well-being (28, 29). Eriksson and Lindström conclude in their review that the SOC scale shows high predictability for health in both the short- (months) and long-term (years) perspective (30). Also, higher degrees of SOC correlates with better self-rated health (21), less chronic disease risk factors (31), better quality of life (32), less prevalence of symptoms (33), less distress (34, 35), better adaptation to a life situation during a disease regardless of disease severity (21, 33, 36) and improved survival (27).

1.5 THE STABILITY OF SOC

Antonovsky considered that SOC represents a stable dispositional orientation; it develops through young adulthood when it stabilizes and remains relatively stable and only fluctuates temporary when radical life events occur (14). This is supported by several studies (17, 37-41). Eriksson and Lindström confirm in a review that variations over time are small in adults (16). However, some studies have questioned the stability of SOC as stated by Antonovsky and propose that SOC depends on a person´s physical and mental state that can change over time (42, 43). Others have claimed that a low SOC score mainly reflects psychiatric morbidity such as anxiety or depression (44, 45). While other studies suggest that high SOC represents more than just the absence of psychopathology (39, 46).

1.6 SOC AND BREAST CANCER

Gibson and Parker found in their study of breast cancer survivors that SOC was a direct predictor of psychological well-being (47). Among 100 patients who had undergone surgery, including some breast cancer surgery, showed that high SOC was positively related to less pain and distress (48). Several studies have concluded that SOC significantly predicts better health status, less distress regardless of disease stage or treatment (21) and lower levels of symptom burden (33, 49) in women with breast cancer. A study by Boman et al. found that higher SOC was associated with better-perceived general health and mental well-being short term after breast cancer surgery (50). Studies have also shown that a higher SOC in breast cancer patients correlated statistically significantly with health related quality of life (21, 51-53). Although several studies have been performed during the course of the breast cancer disease, neither of them has evaluated SOC´s stability over time in this group, nor the stability of SOC´s construct.

1.7   SOC, PROGESSION AND MORTALITY

Although the biological factors that influence disease progression and mortality in cancer have been well studied, comparatively less is known about the coping abilities influence on outcomes in cancer populations. Only one previous study has examined SOC´s prediction of cancer progression. In a sample of 16 patients with acute leukemia and highly malignant lymphoma, patients who did not relapse had a significant higher SOC than those with recurrences during a 2-year study period (54). One study evaluated SOC´s association with cancer incidence and reported an increased overall cancer incidence in a cohort of 5800 men with low SOC. This led to the assumption that a high SOC could putatively delay the onset of cancer (55). Surtees et.al examined SOC´s predictive value for overall cancer mortality and found that a higher SOC was associated with 30% reduced cancer mortality in men (56). However, a high SOC did not improve survival in head and neck cancer (57). A few population-based studies report that higher SOC was associated with a decreased risk of all-cause mortality (27, 56, 58-61). However, there are also studies diverging from these results. Lundman et al. found a significant association with 1-year mortality, but not with 4-year mortality among participants above 85 years of age (59). Haukkla et al. found that the association between higher SOC and a lower risk of all-cause mortality became non statistically significant after adjustment for depressive symptoms (62). No study has yet examined SOC´s prediction on progression, breast cancer mortality and all-cause mortality among breast cancer patients.

2 AIMS

The main aim was to extend the knowledge of the SOC scale´s stability and predictive value with regards to progression and mortality in breast cancer patients.

The specific aims were:
1. To test the stability of the SOC scale over time and to test the stability of the latent construct in patients with breast cancer from the time of diagnosis (preoperatively) to one year postoperatively, and in a subsample two and three years postoperatively.

2. To pursue the SOC scale's predictive value in breast cancer patients with regards to progression and mortality in long term (a median follow up time of 10 years).

3 MATERIAL AND METHODS

The design was a longitudinal prospective cohort study. An overview of subjects and methods (study I and II) is presented in Table 1.

Table 1. Overview of Subjects and Methods

	Study I	Study II
Study Design	Longitudinal prospective cohort study	Longitudinal prospective cohort study
Sample	Women with invasive breast cancer included in the multicenter trial who answered SOC-13 at T1 and T2 (n=417) and a subsample (n=80) who answered SOC-13 additionally at T3 and T4	Women with invasive breast cancer included in the multicenter trial who answered SOC-13 at T1 (n=487)
Data Sources	SOC-13, medical charts, the Swedish Cancer Registry	SOC-13, medical charts, the Swedish Cancer Registry, the Swedish Cause of Death Registry
Inclusion period	1999- 2004	1999- 2004
Follow-up period	1999- 2007	1999- 2012
Outcome	SOC stability	SOC´s predictive value for breast cancer progress and mortality

3.1 SAMPLE

The patient cohort originates from a Swedish multicenter trial that recruited patients from four breast cancer units at three university hospitals and at one county university-affiliated hospital. The primary aim of the study was to assess subjective and objective arm morbidity, health related quality of life and SOC after different surgical procedures of breast cancer at the time of introducing the sentinel node biopsy concept (63, 64). The participating units performed 4283 breast cancer operations on patients potentially eligible for the study during the time of data collection (1999-2004). Postoperative adjuvant treatment (chemotherapy, radiotherapy and hormonal treatment) was given according to the national guidelines.

The patients were included consecutively. The study cohort included 557 women with invasive breast cancer. In addition to the surgical procedure, eligible patients had undergone either sentinel node biopsy or axillary lymph node dissection. Exclusion criteria were difficulties in understanding the Swedish language, mental or physical inability to participate in the pre- and postoperative evaluation, bilateral breast cancer, previous axillary treatment or clinically fixed axillary metastases.

The recruitment process for the two studies is described in Figure 1. Those 417 patients (75%) who answered a complete SOC scale both preoperatively (T1) and 1 year postoperatively (T2) formed the main cohort of study I and a sub cohort consisting of 80 patients from one of the study sites (university hospital) was evaluated additionally two (T3) and three (T4) years postoperatively. Those 487 (87%) of the included patients who answered the complete SOC scale preoperatively formed the cohort of study II.
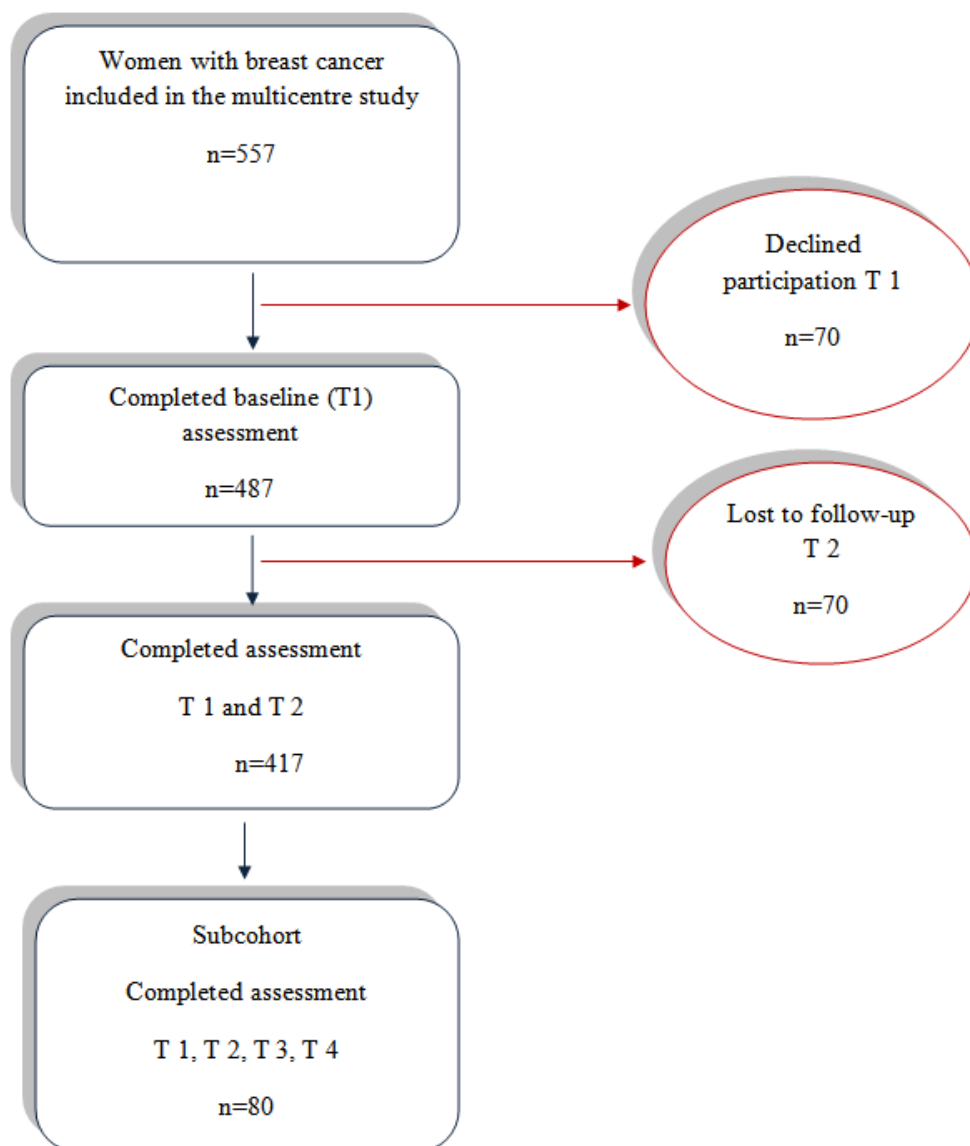
Figure 1 *Number of women included in the study. T1 = preoperative, T2 = one year postoperative, T3= two years postoperative, T4= three years postoperative.*

3.2   DATA COLLECTION

Demographic data (including age, employment and marital status at surgery), and medical data (including type of breast surgery, tumor size, lymph node status and type of adjuvant treatment given) were collected from medical charts and recorded.

Data on disease progression (including first local/regional/distant event) was obtained from the National Cancer Registry (65). It has since 1958 covered the whole population and approximately 60 000 malignant cases of cancer are registered every year in Sweden. Since the mid-80's six regional registries are associated with the Regional Cancer Centers in Sweden, where coding, major check-up and correction work is performed. The estimated underreporting of the coverage rate in comparison to the inpatient registry is approximately 4% (66, 67).

Mortality data (including date and cause of death) was obtained from the Cause of Death Registry (6). It has since 1961 provided the basis for the official statistics on cause of death in Sweden and is updated every year.

SOC was assessed using the Swedish version of the self-assessment questionnaire, SOC-13 as shown in appendix. After informed consent had been provided by the patients, the study-affiliated nurses at each of the participating centers handed out the SOC scale before surgery (study I and II) and during follow-up visits (one, two and three years postoperatively) (study I). The SOC-13 scale has a semantic-differential format ranging from one to seven points with two anchoring responses (for example never and very often). Five of the items are formulated negatively and have to be reversed in scoring, so that a high score always expresses a high SOC. After reversing the scores, a total sum score, ranging from 13 to 91, is obtained. Higher SOC scores indicate a higher sense of coherence.

3.3 STATISTICAL ANALYSIS

The statistical methods used in study I and II, their functions and criteria are described in Table 2. In all analyses, a *p* value < 0.05 was regarded as statistically significant.

Table 2. Statistical methods

Method		Function	Criteria
Descriptive statistics: mean, SD, range, percentage	Studies I-II	Describe demographic and clinical data of the study cohort	
Cronbach´s alpha reliability coefficient	Study I	Test the reliability of SOC-13	≥ 0.70 is satisfactory
Student´s *t*-test, ANOVA, Intra-class correlation (ICC), Cohen´s effect size	Study I	Analyse differences in SOC´s mean value over time	ICC; < 0.4 is poor, 0.4 to 0.75 is moderate, > 0.75 is good agreement. Cohens effect size; $d = 0.20$ is small, $d = 0.50$ is medium, $d = 0.80$ is large.
Cross-sectional factor analysis, Chi-square test	Study I	Explore the theoretical construct of the SOC-13 scale by goodness of fit	Criteria of goodness of fit: X^2/df ratio (criteria < 3), GFI (criteria ≥ 0.90), RMSEA (criteria < 0.08), CFI (criteria ≥ 0.90).
Longitudinal factor analysis, Chi-square test	Study I	Assess the construct stability character of SOC-13 by goodness of fit	Criteria of goodness of fit: X^2/df ratio (criteria < 3), GFI (criteria ≥ 0.90), RMSEA (criteria < 0.08), CFI (criteria ≥ 0.90). $R^2 \geq 0.40$ is satisfactory. Cut off level for factor loading is > 0.40.
Univariate and multivariate analyses	Study II	Identify significant independent predictors for progress and mortality	
Cox proportional-hazard regression	Study II	Estimate hazard ratios associated with increasing SOC over time	
Logistic Regression	Study II	Estimation of probability of progress or mortality	
Receiver operating characteristic (ROC) analyses	Study II	Assess sensitivity and specificity of the logistic regression	

3.3.1 Study I

The descriptive statistics was used to characterize the demographic and clinical data of the study cohort. When evaluating the Cronbach's alpha reliability coefficient of the SOC scale, a Cronbach's alpha coefficient equal to or greater than 0.70 was considered satisfactory (68).

3.3.1.1 Test-retest

The student's *t*-test was used to analyze the differences in mean values over time in the main sample. Analysis of variance (ANOVA) was used to analyze the differences in mean values over time in the sub cohort, and in addition to that intra-class correlation coefficient (ICC). As suggested (69), ICC is interpreted to be poor <0.4, moderate 0.4 to 0.75, or good agreement >0.75. Cohen's effect size was used to evaluate the clinical relevance of mean changes between the two time points and according to Cohen (70), d = 0.20 indicates a small; d = 0.50 a medium; and d = 0.80 a large effect-size.

3.3.1.2 Factor analyses

When further assessing the SOC scale´s stability, cross sectional and longitudinal factor analysis models were used, based on the 417 patients in the main cohort. The theoretical construct was analyzed cross-sectionally separately for the two time points (T1 and T2) in three steps: one-factor, three-factor and second-order factor models, in accordance with earlier studies and Antonovsky's theoretical modeling (14, 17, 18).

By combining the cross-sectional models together with evaluation of the stability of the hypothetical underlying constructs, the longitudinal factor analysis models were created. The goodness-of-fit describes the factor models fit and were evaluated by Chi-square to the degrees of freedom ratio (criteria: ratio<3), goodness-of-fit index (GFI) (criteria: ≥0.90), comparative fit index (CFI) (criteria: ≥0.90) (71, 72) and root-mean square error of approximation (RMSEA) (criteria: <0.08) (71). The Akaike information criterion (AIC) is a measure of the relative quality of the factor models. A decrease in Akaike's information criterion (AIC) is a sign of the improvements in the cross-sectional and longitudinal factor model fit (73). The squared multiple correlation (R^2) indicates how well data fits in the statistical model and is thereby a prediction of future outcomes of the final longitudinal factor model. If the relation between the latent factors (*i.e.* SOC T1 and SOC T2) does not change over time (proportion of variance) the longitudinal factor analysis model fits (74). The squared multiple correlation (R^2) equal to the proportion of variance at T2 explained by the estimation at T1. In line with recommendations based on previous research , a factor loading greater than 0.40 was used as cutoff level (70). R^2 ≥0.40 is considered as satisfactory (72).

The Statistical Packages of Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA) for Windows (version 20), and the Analysis of Moment Structures (AMOS) structural equation modeling program version 16.0 were used for the analyses.

3.3.2 Study II

Descriptive statistics were used for the demographic and clinical data of the study cohort. The breast cancer patients were followed from inclusion to tumor progression, death from breast cancer or death from all causes or end of study, whichever came first. The analyses were performed for each event separately. The definition of progression-free survival was the time elapsing from surgery to progression or to breast cancer caused death. Breast cancer survival and overall survival was defined as the time elapsing from surgery to death. End of follow up represented a censoring event. To assess progression-free survival and survival Kaplan-Meier survival curves were used in three equal sized groups of SOC.

3.3.2.1 Cox proportional-hazard Regression

To identify significant independent predictors, Cox proportional-hazard regression was used to estimate the effect of one-unit increase in SOC for the crude (univariate) and adjusted (multivariate) hazard ratios (HR and aHR). The means of natural cubic spline variables were assessed by the linearity of the relationship between the log-hazard and SOC. By including, a time-varying interaction between time and SOC, the assumption of proportional hazards was tested. Potential cofounders were identified through univariate analyses. The multivariate analysis included the following potential cofounders in the adjusted model in addition to SOC: age (26 to 51, 52 to 57, 58 to 65, 66 to 89 years), married/cohabitant (yes or no), employed (yes or no), breast surgery (breast-conserving surgery or mastectomy), lymph node status (positive or negative). To cross validate SOC as a predictor the recalibration coefficient was calculated for the estimates of the hazard ratio associated with one-unit increase in SOC with a thousand Monte Carlo bootstrap samples (75).

3.3.2.2 Logistic Regression

With logistic regression the probability of experiencing tumor progression, death of breast cancer, and death of all causes within 5 years after inclusion was estimated. No data were censored before this time period (*i.e.* follow-up time for the present study was 8-12 years). The sensitivity and specificity of the predictive model by receiver operating characteristic (ROC) analyses was summarized thus obtaining the area under the receiver operating characteristic curve (AUC). To quantify the predictive value of SOC per se, SOC was excluded but all the other predictors from the multivariate analysis were included.

The Statistical Packages of Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA) for Windows (version 20) and the statistical software Stata version 14 (Statacorp, College Station, TX) was used for all analyses.

3.4 ETHICAL CONSIDERATIONS

The regional Ethics Committee approved study I and II (Dnr 500: 16 979/99, 2011 1916: 32 and Dnr 500: 16 979/99, 2011 1916: 32). The researchers involved in these studies had no conflicts of interest.

Enrollment followed WMA Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects. Patients were informed about the study and that participation or non-participation would not affect treatment and care. The ethical principle of respect for human dignity and justice includes the right to self-determination, full disclosure, fairness and privacy *i.e.* patients must be reassured that their decision is voluntary and without pressure when they are asked to participate in a study (76, 77).

Participation in research can be agreed to for several reasons such as; hope for direct benefit from the study or that other patients can benefit from the research results in the future (76, 77). In study I and II there were no obvious benefits for the participating patients. Furthermore, participating in study I and II was not considered harmful other than the burden the patients may feel when answering the self-assessment questionnaire.

4 RESULTS

4.1 STUDY I

The mean age of the study cohort (n=417) at inclusion was 58.8 years (SD 10.4, range 26-89). Most were married or cohabiting and employed. The majority had breast-conserving surgery and had received at least one of the postoperative adjuvant therapies (chemotherapy, radiotherapy and/or anti hormonal treatment) (Table 3).

The sub cohort (n=80) were statistically significantly younger (mean 56.6 years SD 8.8, range 40–81 years vs. 58.8, SD 10.4, range 26–89 years). Fewer underwent breast conserving surgery (64 vs. 73 %), and also received radiotherapy less often (70 vs. 83 %).

Table 3. Demographic and clinical data

Characteristics	Study I (n=417)		Study I (n=80)		Study II (n=487)	
Age*						
Mean, (SD)	58.8 (10.4)		56.6 (9.8)		58.8 (10.6)	
Range	26-89		40-81		26-89	
	n	%	n	%	n	%
Married/Cohabitants*						
Yes	287	68.8	52	65.0	328	67.4
No	130	31.2	28	35.0	159	32.6
Employed*						
Yes	209	66.3	58	72.5	284	58.3
No	106	33.7	22	27.5	203	41.7
Breast surgery						
Breast conserving surgery	305	73.1	51	63.8	354	72.7
Mastectomy	112	26.9	29	36.3	133	27.3
Tumor size						
≤ 20 mm	284	68.1	53	66.3	319	65.5
21-50 mm	122	29.3	26	32.5	155	31.8
> 50 mm	11	2.6	1	1.3	13	2.7
Lymph node status						
Negative	285	68.3	52	65.0	320	65.7
Positive	132	31.7	28	35.0	167	34.3
Postoperative adjuvant treatment**						
Antihormonal treatment						
Yes	323	77.5	62	77.5	378	77.6
No	94	22.5	18	22.5	109	22.4
Chemotherapy						
Yes	153	36.7	33	41.3	183	37.6
No	264	63.3	47	58.8	304	62.4
Radiotherapy						
Yes	346	83.0	56	70.0	409	84.0
No	71	17.0	24	30.0	78	16.0
Disease progession***						
No	329	78.9	68	85.0	386	79.3
Yes	88	21.1	12	15.0	101	20.7
Deceased***						
Breast cancer	55	13.2	9	11.3	75	15.4
Another reason	14	3.4	1	1.3	21	4.3

* At inclusion   ** More than one regime could be given   *** 8-12years

4.1.1 Test-retest

The mean SOC of the study cohort (n=417) at T1 was 70.9 (SD 10.3, range 42–90) and at T2 70.2 (SD 11.4, range 33–91) (Fig 2). There was no significant difference in mean values between T1 and T2. The intra-class correlation coefficient (ICC) between the two time points was 0.68 and the effect size was 0.06.
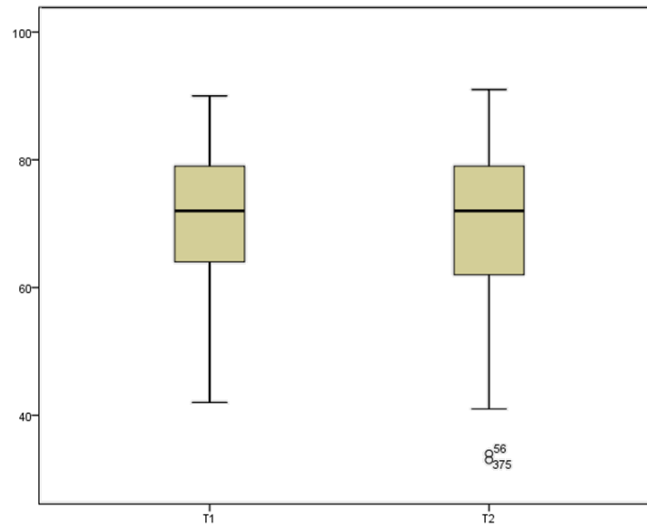

Figure 2. *SOC sum (n=417) at T1 and T2. Data is presented with 25th and 75th percentile range in boxes, whiskers represent 10th and 90th percentiles and dots are outliers.*

The mean SOC values in the sub cohort (n=80) at T1 was 69.9 (SD 10.4, range 44–89), at T2 71.1 (SD 11.0, range 33–91), at T3 72.3 (SD 11.2, range 39–90) and at T4 71.3 (SD 11.0, range 43–91). There was a significant difference ($p = .026$) in the sub cohort between T1 and T3 (Fig 3). The ICC in the sub cohort ranged from 0.68 to 0.74, and the effect size ranged from 0.10 to 0.21 during the four time points.
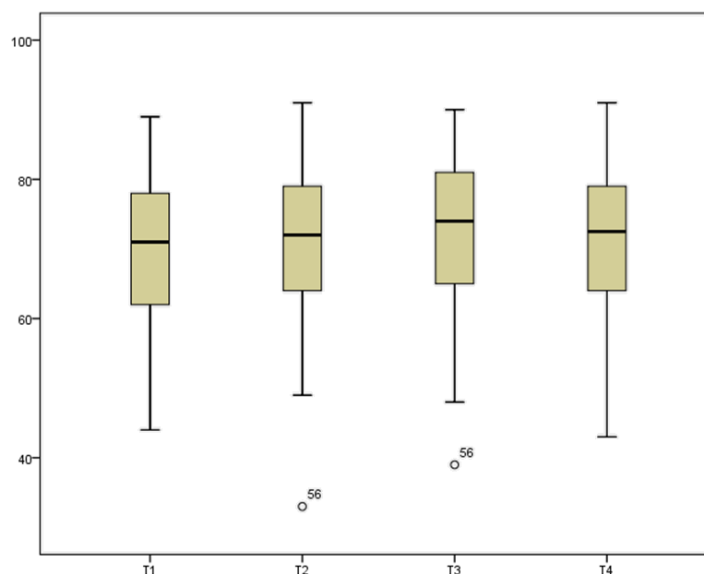

Figure 3. *SOC sum (n=80) at T1, T2, T3 and T4. Data is presented with 25th and 75th percentile range in boxes, whiskers represent 10th and 90th percentiles and dots are outliers.*

Cronbach's alpha at all measurement time points in both samples (n=417 and n=80) was above 0.80.

4.1.2 Cross-sectional factor analysis

To address the construct validity of SOC, a cross-sectional factor analysis was performed separately for T1 and T2. As seen in Table 4, the results showed that the one-factor, three-factor and second-order factor models did not reach all the criteria of goodness-of-fit at the two time points. The main measurement errors occur mainly between the meaningfulness item 1 ("Do you have feeling that you don't really care about what goes on around you?"), the comprehensibility item 2 ("Has it happened in the past that you were surprised by the behavior of people whom you thought you knew well?") and the manageability item 3 ("Has it happened that people whom you counted on disappointed you?") at T1 and T2 (Table 4 and 5). All models improved after a modification of the models allowing correlation between measurement errors between items, both at T1 and T2. The three-factor and the second-order factor models met all criteria for model fit at the two time points.

Table 4 Goodness-of Fit Indices for the Cross-Sectional Factor Analysis Models of the Sense of Coherence Scale at Baseline (T1) and 1 Year Later (T2) in Women with Breast Cancer (n = 417)

Measurement models	T1					T2				
	X^2/df : Ratio[a]	GFI[b]	RMSEA[c]	CFI[d]	AIC[e]	X^2/df ; Ratio	GFI	RMSEA	CFI	AIC
One-factor model	393.3/65; 6.05	0.87	0.11	0.75	445.30	366.5/65; 5.63	0.89	0.11	0.80	418.5
Modified one-factor model [f]	187.1/62; 3.01	0.93	0.07	0.91	245.1	185.5/62; 2.99	0.93	0.07	0.92	243.5
Three-factor model	344.4/62; 5.55	0.89	0.10	0.79	402.4	344.1/62; 5.55	0.89	0.10	0.81	402.1
Modified three-factor model [f]	134.7/59; 2.28	0.95	0.06	0.94	198.7	151.9/59; 2.57	0.95	0.06	0.94	215.9
Second-order factor model	344.4/62; 5.55	0.89	0.10	0.79	402.4	344.1/62; 5.55	0.89	0.10	0.81	402.1
Modified second-order factor model [f]	134.7/59; 2.28	0.95	0.06	0.94	198.7	151.9/59; 2.57	0.95	0.06	0.94	215.9

[a]The criteria of goodness-of-fit: X^2/df Ratio (criteria: < 3); [b] GFI: goodness of index (criteria: $\geq$ 0.90); [c] RMSEA; root mean square error of approximation (criteria: < 0.08); [d] CFI; comparative fit index (criteria: $\geq$ 0.90); [e]Akaike Information Criterion.

[f]Modified factor models allow correlation between measurement errors of the items 2& 3, 1& 2 and 1& 3 for T1 and items 2, 3; 1, 2 & 5, 6 at T2.

4.1.3 Longitudinal factor analysis

The stability of SOC was investigated by using longitudinal factor analysis models. As seen in Table 5, the models allowed correlation between measurement errors of the same items over time (T1→ T2). The model fit was improved. The last longitudinal modified second-order factor model had a satisfactory goodness-of-fit. The Chi-square to the degrees of freedom ratio and RMSEA values met standard criteria, although the values of the fit indices GFI and CFI were slightly lower than the suggested fit levels. The last longitudinal modified second-order model showed the best goodness-of-fit of the data with the lowest Chi square and AIC.

Table 5 Goodness-of-Fit Indices for the Longitudinal Factor Analysis Models of the Sense of Coherence Scale from Baseline (T1) to 1 Year Later (T2) in Women Treated for Breast Cancer (n = 417)

Longitudinal measurement model	T1 ⟶ T2				
	X^2 / df ; Ratio[a]	GFI[b]	RMSEA[c]	CFI[d]	AIC[e]
Longitudinal modified two-factor model [f]	915.4/292; 3.13	0.85	0.07	0.81	1033.4
Longitudinal modified six-factor model [f]	1049.5/287; 3.65	0.83	0.08	0.77	1177.5
Longitudinal modified second-order factor model [f]	832.3 /286; 2.91	0.87	0.07	0.84	962.3

[a] The criteria of goodness-of-fit: X^2/df Ratio (criteria: < 3);
[b] GFI: goodness of index (criteria: ≥ 0.90);
[c] RMSEA; root mean square error of approximation (criteria: < 0.08);
[d] CFI; comparative fit index (criteria: ≥ 0.90);
[e] Akaike Information Criterion;
[f] Modified factor models allow correlation between measurement errors of items 2& 3, 1& 2 and 1& 3 for T1and items 2, 3; 1, 2 & 5, 6 at T2.

Finally, when comparing the longitudinal modified two-factor and second order factor models the result revealed that the factor loadings were similar in both models with standardized parameter estimates, at T1 between 0.26 and 0.81 and at T2 between 0.35 and 0.78. Items 1, 2 and 3 had factor loadings < 0.40 at T1 and item 1 and 2 at T2. As seen in Figure 4, the correlation coefficient between the latent factors (*i.e.* SOC T1 and SOC T2) was 0.65, and the proportion of variance in the final model was $R^2 = 0.42$.
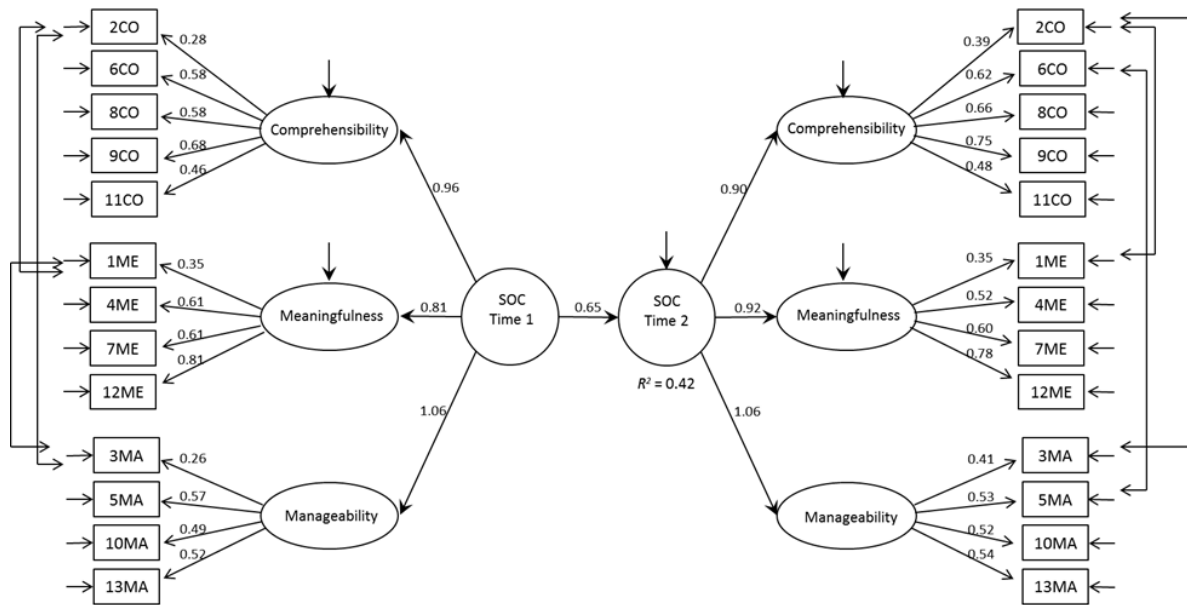
Figure 4. *The longitudinal second-order factor model with standardized parameter estimates allowing correlations between measurement errors of the items at T1 and T2 CO= Comprehensibility, ME= Meaningfulness, and MA=Manageability*

4.2 STUDY II

The majority of the 487 woman had breast-conserving surgery. Two-thirds had a tumor size ≤20 mm and no lymph node metastases. Most had received at least one of the postoperative adjuvant therapy regimens (chemotherapy, radiotherapy and/or anti hormonal treatment) (Table 3).

The study cohort accumulated 4552.2 person-years of follow-up time in a median of 10- year follow-up. A total of 126 progressions were observed, with a rate of 0.030 tumor progressions/person-year (95% CI, 0.03 to 0.04). Seventy-five breast cancer caused deaths with a mortality rate of 0.016 deaths/ person-year (95% CI, 0.01 to 0.02) and 96 deaths from all causes with a mortality rate of 0.021 deaths/ person-year (95% CI, 0.02 to 0.03) occurred during the follow-up period.

4.2.1 Progression-free survival, breast cancer survival and overall survival

The mean SOC score of the study cohort at baseline (T1) was 67.2 (SD 13.4, range 20-90). Tumor progression was more prevalent in patients with the lowest SOC values. Breast cancer survival and overall survival was also lower in this group. The patients with higher SOC had a lower risk of progression and dying during the follow-up time. Compared with patients reporting low levels of SOC, those reporting high levels of SOC had a 60% reduced risk of breast cancer progression, and an 80% reduced risk of breast cancer and all-cause mortality in the 10-year follow up.

In the Cox proportional-hazard regression model, the spline variables were not significant, which provided evidence against a non-linear relationship between log-hazard and SOC. No evidence of lack of proportionality in the interaction between time and SOC was found. Results illustrated a declining risk of progression by 1.4% for every unit increase in SOC (HR, 0.99; 95% CI, 0.97 to 1.00). A slightly weaker association that became borderline statistically non-significant, when adjusted for the potential cofounders (high age, unmarried/not cohabitant, unemployed, having a mastectomy and having positive lymph nodes). The adjusted decline was 0.7% (aHR, 0.99; 95% CI, 0.98 to 1.01).

For every unit increase in the SOC scale, the risk of dying (breast cancer caused mortality and all-cause mortality) declined by 2.3% for breast cancer mortality (HR, 0.98; 95% CI, 0.96 to 0.99) and all-cause mortality (HR, 0.98; 95% CI, 0.96 to 0.99). When adjusted for potential cofounders, the statistically significant association persisted. The decline was then 1.7% (breast cancer) (aHR, 0.98; 95% CI, 0.97 to 1.00) and 1.5% (all-cause) (aHR, 0.99; 95% CI, 0.97 to 1.00).

The result of the ROC analyses showed that the AUC for five-year progression-free survival was 0.58 (95% CI, 0.51 to 0.65), with a cut-off value of SOC at 70. Sensitivity and specificity were 50.2% and 58.4% respectively. The AUC for five-year breast cancer and overall survival was 0.61 (95% CI, 0.52 to 0.70). With a cut-off value of SOC at 70, sensitivity and specificity were 50.0% and 62.2% respectively.

When SOC was included in addition to the other predictors from the multivariate analysis, the risk of progression in 6.8 % of the patients (95% CI, 4.7% to 9.4 %) would be classified more accurately. Likewise having SOC included in the analysis showed a more accurate risk classification; both for the risk for breast cancer caused mortality in 23.8% (95% CI, 20.1% to 27.9%), and that of the risk for all-cause mortality in 17.5% (95% CI, 14.2% to 21.1%) of the patients.

5 DISCUSSION

5.1 STUDY I

The results support Antonovsky's theory that the SOC scale is reflecting a trait by showing stability over time (14). However, it is possible that radical life-events might temporarily alter the individuals SOC (14, 40). This may be reflected in the present study where there was a minor but statistically significant difference in the sub cohort between T1 and T3. This difference was not observed at T4. The finding may reflect a temporary increase in SOC, indicating a transient state characterized by feeling of optimism and strength in these women who have recently gone through a life-threatening situation. The results concur with Eriksson and Lindström who postulate that SOC variations over time are small (16). In conclusion, no clinically significant SOC changes were found in mean values when measured one, two and three years postoperatively confirming the robustness of the SOC concept (17, 37-41).

The study also supports Antonovsky's theory by confirming the SOC structure's stability in that the overall scale reflects one higher-order construct: comprising three dynamically interrelated components (*i.e.* comprehensibility, manageability and meaningfulness) (13, 14). The results give the strongest support for the longitudinal second-order factor model (although allowing correlation between measurement errors of some items) as the most adequate model in assessing the stability of sense of coherence at both time points. Similar findings have been detected in previous studies that examined the SOC scale´s factorial validity. They provide support for a stable second-order factor structure *i.e.* that the SOC scale reflects a single latent factor, although with a three-factor structure approximately or partly corresponding to comprehensibility, manageability and meaningfulness (16, 18, 78-80), whereas others only support the one-factor structure (22, 81).

The findings are also consistent with other studies in different populations and cultural settings. Lower factor loadings of item 1, 2 and 3 have been found (78). Further, misfit of item 1 was described in two Rasch analyses (82, 83) and finally measurement error correlations of items 2 and 3 have been reported (18, 78, 84). Future studies should calibrate the SOC scale for example by deleting item 1 to see if the factor structure improves or by using a scale with less scale steps as suggested by Holmefur et al (82). Also, future factorial analyses without item 2 are needed. The lower factor loadings and the correlated measurement errors of item 3 might depend on the misfit of item 2.

5.2 STUDY II

The current longitudinal prospective cohort study is the first to examine SOC´s prediction for breast cancer progression, mortality and all-cause mortality. The results show that breast cancer patients with higher SOC had a decreased risk of breast cancer caused mortality and all-cause mortality compared with those with lower SOC. The results are in line with the few population-based studies that have reported higher SOC to be associated with a decreased risk of all-cause mortality (27, 56, 58-61). Further, the results indicate that a higher SOC score is associated with decreased risk of breast cancer progression. However, the SOC as an independent predictor becomes non-significant when adjusted for other potential cofounders (high age, unmarried/not cohabitant, unemployed, having a mastectomy, and having positive lymph nodes), this may be associated with the sample size. As mentioned earlier, survival after breast cancer has improved, partly due to earlier detection and advances in treatment (8). Despite established prognostic factors such as; age, tumor stage, histological grade,

expression of receptors and biomarkers and gene expression (5), there are still variations in breast cancer prognosis that cannot be fully explained by the established prognostic factors.

A link between low SOC and increased risk of breast cancer progression and mortality may be a bio-psychosocial pattern with a physiological stress response. The overall stress response involves activation of several body systems. Chronic stress may contribute to deleterious effects on regulation of the stress response systems as well as many organ systems (85). Major stressors may therefore be associated with an elevated risk of breast cancer (86, 87), recurrence (11) and earlier mortality (12). A breast cancer diagnosis is considered stressful for almost all patients (9, 10). According to Antonovsky, SOC does have a stress buffering effect and those with a high SOC possess resources that enable them to cope with various kind of stressful life experiences (14). There is evidence to support that a higher SOC correlates with less distress (21, 29, 30, 88). Antonovsky discussed high and low SOC, but did not define boundaries for a normal SOC (13, 14), and there is no consensus in the literature on what constitutes high, normal and low SOC (16). This needs to be considered when interpreting the results. Hypothetically, the patients with a lower SOC *i.e.* lower ability to manage life strains, experience life with or after breast cancer as more stressful and with more intense physiological stress response. This may contribute to a higher risk of tumor progression and breast cancer mortality. This possible connection between SOC, stress and breast cancer mortality needs to be further explored.

Another link between low SOC and increased risk of breast cancer progression and mortality may be psychosocial factors. Studies have shown that depressive symptoms (89-91) and depressive or passive coping styles (92) are associated with increased mortality among cancer patients. Similar findings have been shown among breast cancer patients where depressive symptoms are associated with higher breast cancer mortality (93-95) and a decreased survival time among women with metastatic breast cancer (96). This link between depressive symptoms, breast cancer progression, and mortality may be due to modulation of the immune system (97, 98). Although SOC and mental health are interrelated, they are considered as independent concepts (30, 39). Previous studies support Antonovskys prediction that SOC is associated with successfully coping with life stress, psychological anxiety and depression (14, 81, 99, 100). However, a study by Henje Blom et al. saw an inverse prediction (101) and in a study by Haukkla et al. the association between SOC and all-cause mortality became non statistically significant after adjustment for depressive symptoms (62). Psychosocial factors such as depressive symptoms and passive coping styles may be a link between SOC and breast cancer progression and mortality, trough physiological stress response and behavior pattern. This possible connection also needs further assessment.

Finally, another explanation to our findings may coincide with how breast cancer patients cope with their disease and the new life situation, adhere to medical or health advice (102), and how they adjust to care and medical treatment. SOC is considered to reflect successful coping with stressful situations *i.e.* characterizes good adaptation to the disease and its treatment (36, 37), and predicts adherence to treatment (103-105). Patients with a low SOC may not find it comprehensible, manageable and meaningful to comply with for example hormonal therapy because of the side effects. A systematic review concluded that many breast cancer patients fail to adhere to long term hormonal therapy despite its proven clinical efficacy (106). SOC may be related to mortality through to which extent the breast cancer patient´s behavior corresponds with medical recommendations, care and treatment.

28

5.3 METHODOLOGICAL CONSIDERATIONS, STRENGTHS AND LIMITATIONS

Strengths of this studies are, the clinical setting, the use of a large sample, a longitudinal prospective data design with a 3-year follow-up regarding SOC (study I), and a median of 10-year follow-up regarding progress and mortality (study II). Particularly, the reliability of registers (66, 67) (the National Cancer Registry (65) and Cause of Death Registry (6)) used. Both studies had a high response rate of 75% (study I) and 87% (study II) of the participants.

Certain shortcomings and limitations of the current study should be considered when interpreting the results. Firstly, no power analysis was preformed, as the aim was to evaluate any type of arm morbidity after different types of axillary surgery. The representativeness of the sample needs to be considered. At the time of data collection (1999-2004), the number of patients declining participation and their reasons for declining were not recorded. This could contribute to a selection bias. However, the sample is representative regarding age, tumor stage (according to TNM classification) and treatment according to the Regional Breast Cancer Registers from each region at the time of inclusion (2), and the sample is also representative regarding breast cancer mortality in Sweden (7). The mean value of SOC is similar to other studies that include women with breast cancer (21, 33).

Second, at the time of inclusion clinical practice focused more on prognostic than on predictive markers. Estrogen and progesterone receptor status were the only predictive markers used and HER2 status was not routinely assessed during the study period. To what extent that information may had an impact on treatment decisions, disease progression and survival, for the included patients remains unclear.

Third, the AUC indicated that SOC is a rather strong predictor but as a single predictor not very sensitive or specific. On the other hand, there exists no predictor that solely can explain the complexity of survival in any model. Our conclusion is that SOC is not the only predictor of survival but an important one.

6 CLINICAL IMPLICATION

These findings are essential to consider in clinical practice, during the initial planning of care and treatment and during the follow-up period. The fact that patients with apparently similar tumors at the time of diagnosis differ significantly in time to tumor progression and in survival, implies that the determinants of outcome could be broader than initially assumed in the purely medical framework. The SOC concept could be used as an adjunct in patient care to achieve specific post-treatment goals for example treatment compliance, reduced morbidity vs. enhanced health related quality of life and prolonged survival. The SOC scale could thus be a complement for assessment of women at risk when designing individual nursing and treatment plans before the start of the treatment period.

7 FUTURE PERSPECTIVES

Future research is warranted both to confirm our results and to replicate the present findings in another population with more advanced disease. Furthermore, research is needed to assess SOC´s predictive value on progress and mortality also in other diseases.

Additionally, potential links between SOC and breast cancer progression and mortality such as physiological stress response, depressive symptoms and patient´s behavior pattern need to be further explored.

Additional work is needed to understand how the SOC concept can improve the health trajectory, particularly in the areas of seeking help and support, adherence and identifying best practices for enhancing coping skills during and after the treatment period.

Although survival is the most important measure of outcome in breast cancer, it would be valuable to assess SOC and its association with health related quality of life, distress and the burden of treatment-related side effects. Interventions such as psychosocial support to those with a low SOC could be assessed before the start of the treatment period.

8 CONCLUSIONS

The present research contributes to further knowledge of the SOC scale´s stability and its predictive value with regards to progression and mortality in breast cancer patients.

1. The SOC scale and the underlying construct is stable over time and can thus be used at different assessment periods in women with primary breast cancer

2. The longitudinal factor analysis demonstrates that the SOC scale is a suitable instrument for measuring the overall ability to cope with life strain, in women with breast cancer.

3. SOC has a predictive value for disease progression, breast cancer caused mortality and for all-cause mortality among women with primary breast cancer and could thus be a complement for assessment of women at risk.

9 SUMMARY IN SWEDISH/SAMMANFATTNING PÅ SVENSKA

Bröstcancer har i genomsnitt ökat med 1.4% årligen under de senaste decennierna. Tidig diagnos och utveckling av nya behandlingsmetoder är de främsta orsakerna till en ökad fem- och tioårs överlevnad. De biologiska faktorer som påverkar sjukdomsutveckling och mortalitet i cancer är väl studerade. De övergripande förhållningssätt som påverkar kliniska resultat hos bröstcancerpatienter är förhållandevis mindre studerade. Begreppet känsla av sammanhang (KASAM) återspeglar en persons orientering i livet och beskrevs för att förklara varför människor förblir friska under tider av stora påfrestningar och ser ett sammanhang vid svåra upplevelser eller situationer. KASAM är mätt med ett formulär bestående av 13 påståenden som mäter de grundläggande KASAM komponenterna: begriplighet, hanterbarhet och meningsfullhet. Högre KASAM värden indikerar en högre känsla av sammanhang.

Huvudsyftet med forskningsprojektet var dels att utvärdera KASAM-skalans stabilitet och dels att studera dess prediktiva värde avseende sjukdomsprogress och mortalitet hos patienter med bröstcancer. Studiepopulationen utgjordes av patienter som rekryterats till en multicenterstudie avseende armmorbiditet vid olika typer av bröstkirurgi. Kvinnorna besvarade KASAM-formuläret preoperativt samt 1, 2 och 3 år postoperativt. Sjuttiofem procent och 87 procent av ursprungskohorten inkluderades i de båda studierna. Resultaten av studie I ger stöd för KASAM skalans stabilitet över tid (ICC 0.68, effektstorlek 0.06). Tvärsnittsfaktoranalysen visade att en modifierad tre-faktor modell och en andra ordningens faktor modell uppfyllde kriterierna för "goodness-of-fit". Den longitudinella modifierade andra ordningens faktormodell bekräftade även KASAM skalans innehållsmässiga stabilitet med en acceptabel "goodness-of-fit".

Resultaten av studie II visar att patienter med en hög KASAM hade en 60% lägre risk för bröstcancerprogress och en 80% lägre risk för död än patienter med en låg KASAM under en medianuppföljningstid på 10 år. Mortalitetsrisken minskade med 2.3% för varje enhetsökning av KASAM (bröstcancermortalitet HR, 0.98; 95 % CI, 0.96–0.99 och mortalitet oavsett orsak HR, 0.98; 95 % CI, 0.96–0.99). Efter justering för andra prediktiva faktorer minskade risken för bröstcancermortalitet med 1.7% och risken för mortalitet oavsett orsak med 1.5%. Risken för sjukdomsprogress minskade med 1.4% för varje enhet ökning av KASAM (HR, 0.99; 95 % CI, 0.97–1.00). Efter justering för prediktiva faktorer, var minskningen 0.7%.

Sammanfattningsvis är KASAM-skalan och dess underliggande struktur stabil över tid hos kvinnor med bröstcancer. Utöver detta har KASAM ett prediktivt värde för sjukdomsprogress, död i bröstcancer och för död oavsett orsak, hos kvinnor med bröstcancer. KASAM-skalan skulle kunna användas för att identifiera högriskpatienter i olika skeenden av bröstcancerprocessen.

10 APPENDIX

10.1 SOC-13, SWEDISH VERSION

SOC

Frågorna gäller hur Du upplever vanliga situationer som är *viktiga* för Dig.

För varje fråga finns det siffror. Din uppgift är att ta ställning till vilken siffra som bäst motsvarar vad Du känner. Rita en ring omkring den siffran.

Här är ett exempel!

9. Händer det att Du har känslor som Du helst inte vill kännas vid?

mycket ofta   1   2   3   4   5   6   7   mycket sällan
eller aldrig

Det är viktigt att Du svarar som Du ***vanligtvis känner*** och inte hur det är just nu.
Arbeta snabbt och fundera *inte länge* på någon fråga.

Översatt från Antonovskys frågeformulär (The Sense of Coherence Questionnarie)
Av H. Björvell och A. Langius, 1987.

1. **Har Du en känsla av att Du faktiskt inte bryr Dig om vad som pågår runt omkring Dig?**

mycket sällan   1   2   3   4   5   6   7   mycket ofta
eller aldrig

2. **Har det hänt att Du förvånats över beteendet hos personer som Du trodde Du kände?**

har aldrig hänt   1   2   3   4   5   6   7   har hänt mycket ofta

3. **Har det hänt att människor som Du litade på har gjort Dig besviken?**

har aldrig hänt   1   2   3   4   5   6   7   har hänt mycket ofta

4. **Tycker Du att Ditt liv fram till nu…**

helt har saknat   1   2   3   4   5   6   7   haft klara mål
mål och mening   och stor mening

5. **Har Du en känsla av att Du blir orättvist behandlad?**

mycket ofta   1   2   3   4   5   6   7   mycket sällan
eller aldrig

6. **Har Du känslan av att vara i en obekant situation utan att veta vad Du skall göra?**

mycket ofta   1   2   3   4   5   6   7   mycket sällan
eller aldrig

7. **Är Dina dagliga sysslor…**

en källa till djup   1   2   3   4   5   6   7   en plåga och en leda glädje och
tillfredställelse

8. **Har Du mycket motstridiga känslor och idéer?**

mycket ofta   1   2   3   4   5   6   7   mycket sällan
eller aldrig

9. Händer det att Du har känslor inom Dig som du helst inte vill känna?

mycket ofta   1   2   3   4   5   6   7   mycket sällan
eller aldrig

10. Många människor – även de med stark självkänsla – kan känna sig helt misslyckade i vissa situationer. Hur ofta har Du känt så?

aldrig   1   2   3   4   5   6   7   mycket ofta

36

11. När någonting har hänt, har Du i allmänhet upptäckt att Du..

över- eller under-   1   2   3   4   5   6   7   såg saker i dess
värderar betydelsen   rätta proportioner
av vad som hände

12. Hur ofta känner Du att det inte finns någon mening med Dina dagliga sysslor?

mycket ofta   1   2   3   4   5   6   7   mycket sällan
eller aldrig

13. Hur ofta har Du känslor som Du är osäker på att kunna behärska?

mycket ofta   1   2   3   4   5   6   7   mycket sällan
eller aldrig

11 ACKNOWLEDGEMENTS

There are so many people to whom I wish to express my sincere appreciation and gratitude for their support, inspiration and help during completion of this thesis. I sincerely hope that those of you who have been around and contributed in one way or another understand the value of your actions. My especial thanks are due to;

My main supervisor Professor Kerstin Sandelin, for introducing and guiding me through the scientific world. You have been there from the very beginning of my research, always enthusiastic, encouraging and willing to share your knowledge and experience in the field of breast cancer.

My co-supervisor Professor Ann Langius- Eklöf. With great knowledge and experience about sense of coherence and the scientific methods, you have been assisting me, as well as putting things into perspective to avoid being stuck with details. Always supportive and generous despite time constrains, with sharp and thoughtful comments you have the characteristics of a true academic.

My co-supervisor and dear friend Lena-Marie Petersson, I appreciate your involvement and presence in my research a lot. Meeting you, discussing our research, our new findings and how to proceed was always a highlight. Thank you for helping me to achieve this goal.

My co-supervisor and colleague Karl-Fredrik Sjölund. I appreciate your support both at work, and in research. Thank you for creating the conditions for research within the Multidisciplinary Pain Center.

My co-authors; Helena Sackey for taking time to discuss scientific matters and supporting me in my research, Camelia Rohani and Matteo Bottai for important statistical support and guiding me through the jungle of statistics.

My mentor and former colleague Karsten Ahlbeck, for your encouragement and support especially during the beginning of my research journey.

All the colleagues at the multicenter trial who participated in the initial planning, recruitment of patients and data collection: Leif Bergkvist, Li Bjelkebo, Lena Boman Engqvist, Yvonne Brandberg, Fuat Celebiuglo, Staffan Eriksson, Inga-Lill Fredriksson, Jan Frisell, Göran Liljegren, Helena Sackey and Viveca Åberg.

All dear and faithful friends, for all your support and sticking with me through this journey. I am so grateful to have you in my every-day life; you have become my extended family.

"If you change the way you look at things, the things you look at change"

Wayne Dyer

12 REFERENCES

1. Wilking N, Kasteng F. A review of breast cancer care and outcomes in 18 countries in Europe, Asia, and Latin America 2009. Available from: http://www.comparatorreports.se/A_review_of_breast_cancer_care_and_outcomes_2 6Oct2009.pdf.

2. Regional Cancer Center S. Report from National Breast Cancer Registry 2014. Available from: http://www.cancercentrum.se/globalassets/cancerdiagnoser/brost/kvalitetsregister/nati onell_rapport_2014-web.pdf.

3. Regional Cancer Center S, Stockholm and Gotland. National Care of Breast Cancer. 2014. Available from: http://www.cancercentrum.se/stockholm-gotland/cancerdiagnoser/brost/vardprogram/.

4. Swedish Breast Cancer Group. National Guidelines for Breast Cancer Treatment. 2013. Available from: http://www.swebcg.roc.se.

5. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22(8):1736-47.

6. National Board of Health and Welfare. Cause of Death Registry 2012. Available from: http://www.socialstyrelsen.se/register/dodsorsaksregistret.

7. National Board of Health and Welfare. Cancer in numbers 2013. Available from: https://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19108/2013-6-5.pdf.

8. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353(17):1784-92.

9. Compas BE, Luecken L. Psychological adjustment to breast cancer. Curr Dir Psychol Sci. 2002;11:111-4.

10. Schmidt JE, Andrykowski MA. The role of social and dispositional variables associated with emotional processing in adjustment to breast cancer: an internet-based study. Health Psychol. 2004;23(3):259-66.

11. Ramirez AJ, Craig TK, Watson JP, Fentiman IS, North WR, Rubens RD. Stress and relapse of breast cancer. BMJ. 1989;298(6669):291-3.

12. Sephton SE, Sapolsky RM, Kraemer HC, Spiegel D. Diurnal cortisol rhythm as a predictor of breast cancer survival. J Natl Cancer Inst. 2000;92(12):994-1000.

13. Antonovsky A. Health, stress and coping: new perspectives on mental and physical well-being. San Francisco, CA.: Jossey-Bass; 1979.

14. Antonovsky A. Unraveling the mystery of health : how people manage stress and stay well. San Francisco, CA.: Jossey-Bass; 1987.

15. Antonovsky A. A somewhat personal odyssey in studying the stress process. Stress Med. 1990;6:71-80.

16. Eriksson M, Lindstrom B. Validity of Antonovsky's sense of coherence scale: a systematic review. J Epidemiol Community Health. 2005;59(6):460-6.

17. Feldt T, Leskinen E, Kinnunen U, Mauno S. Longitudinal factor analysis models in the assessment of the stability of sence of coherence. Pers Individ Dif. 2000;28:239-57.

18. Feldt T, Lintula H, Suominen S, Koskenvuo M, Vahtera J, Kivimaki M. Structural validity and temporal stability of the 13-item sense of coherence scale: prospective evidence from the population-based HeSSup study. Qual Life Res. 2007;16(3):483-93.

19. Bruscia K, Shultis C, Dennery K, Dileo C. The sense of coherence in hospitalized cardiac and cancer patients. J Holist Nurs. 2008;26(4):286-94; discussion 95-6.

20. Gerasimcik-Pulko V, Pileckaite-Markoviene M, Bulotiene G, Ostapenko V. Relationship between sense of coherence and quality of life in early stage breast cancer patients. Acta Medica Lituanica. 2009;16:139-44.

21. Kenne Sarenmalm E, Browall M, Persson LO, Fall-Dickson J, Gaston-Johansson F. Relationship of sense of coherence to stressful events, coping strategies, health status, and quality of life in women with breast cancer. Psychooncology. 2013;22(1):20-7.

22. Antonovsky A. The structure and properties of the sense of coherence scale. Soc Sci Med. 1993;36(6):725-33.

23. Kivimaki M, Feldt T, Vahtera J, Nurmi JE. Sense of coherence and health: evidence from two cross-lagged longitudinal samples. Soc Sci Med. 2000;50(4):583-97.

24. Kouvonen AM, Vaananen A, Vahtera J, Heponiemi T, Koskinen A, Cox SJ, et al. Sense of coherence and psychiatric morbidity: a 19-year register-based prospective study. J Epidemiol Community Health. 2010;64(3):255-61.

25. Kouvonen AM, Vaananen A, Woods SA, Heponiemi T, Koskinen A, Toppinen-Tanner S. Sense of coherence and diabetes: a prospective occupational cohort study. BMC Public Health. 2008;8:46.

26. Suominen S, Helenius H, Blomberg H, Uutela A, Koskenvuo M. Sense of coherence as a predictor of subjective state of health: results of 4 years of follow-up of adults. J Psychosom Res. 2001;50(2):77-86.

27. Surtees PG, Wainwright NW, Luben R, Khaw KT, Day NE. Mastery, sense of coherence, and mortality: evidence of independent associations from the EPIC-Norfolk Prospective Cohort Study. Health Psychol. 2006;25(1):102-10.

28. Julkunen J, Ahlstrom R. Hostility, anger, and sense of coherence as predictors of health-related quality of life. Results of an ASCOT substudy. J Psychosom Res. 2006;61(1):33-9.

29. Karlsson I, Berglin E, Larsson PA. Sense of coherence: quality of life before and after coronary artery bypass surgery -a longitudinal study. J Adv Nurs. 2000;31(6):1383-92.

30. Eriksson M, Lindstrom B. Antonovsky's sense of coherence scale and the relation with health: a systematic review. J Epidemiol Community Health. 2006;60(5):376-81.

31. Wainwright NW, Surtees PG, Welch AA, Luben RN, Khaw KT, Bingham SA. Sense of coherence, lifestyle choices and mortality. J Epidemiol Community Health. 2008;62(9):829-31.

32. Eriksson M, Lindstrom B. Antonovsky's sense of coherence scale and its relation with quality of life: a systematic review. J Epidemiol Community Health. 2007;61(11):938-44.

33. Kenne Sarenmalm E, Ohlen J, Jonsson T, Gaston-Johansson F. Coping with recurrent breast cancer: predictors of distressing symptoms and health-related quality of life. J Pain Symptom Manage. 2007;34(1):24-39.

34. Gustavsson-Lilius M, Julkunen J, Keskivaara P, Hietanen P. Sense of coherence and distress in cancer patients and their partners. Psychooncology. 2007;16(12):1100-10.

35. Gustavsson-Lilius M, Julkunen J, Keskivaara P, Lipsanen J, Hietanen P. Predictors of distress in cancer patients and their partners: the role of optimism in the sense of coherence construct. Psychol Health. 2012;27(2):178-95.

36. Mendel B, Bergenius J, Langius A. The sense of coherence: a tool for evaluating patients with peripheral vestibular disorders. Clin Otolaryngol Allied Sci. 2001;26(1):19-24.

37. Forsberg C, Bjorvell H, Cedermark B. Well-being and its relation to coping ability in patients with colo-rectal and gastric cancer before and after surgery. Scand J Caring Sci. 1996;10(1):35-44.

38. Langius A, Bjorvell H, Antonovsky A. The sense of coherence concept and its relation to personality traits in Swedish samples. Scand J Caring Sci. 1992;6(3):165-71.

39. Langius-Eklof A, Samuelsson M. Sense of coherence and psychiatric morbidity in terms of anxiety and depression in patients with major depression before and after electric convulsive treatment. Scand J Caring Sci. 2009;23(2):375-9.

40. Schnyder U, Buchi S, Sensky T, Klaghofer R. Antonovsky's sense of coherence: trait or state? Psychother Psychosom. 2000;69(6):296-302.

41. Sjostrom H, Langius-Eklof A, Hjertberg R. Well-being and sense of coherence during pregnancy. Acta Obstet Gynecol Scand. 2004;83(12):1112-8.

42. Nilsson B, Holmgren L, Stegmayr B, Westman G. Sense of coherence--stability over time and relation to health, disease, and psychosocial changes in a general population: a longitudinal study. Scandinavian journal of public health. 2003;31(4):297-304.

43. Smith PM, Breslin FC, Beaton DE. Questioning the stability of sense of coherence--the impact of socio-economic status and working conditions in the Canadian population. Soc Psychiatry Psychiatr Epidemiol. 2003;38(9):475-84.

44. Carstens JA, Spangenberg JJ. Major depression: a breakdown in sense of coherence? Psychol Rep. 1997;80(3):1211-20.

45. Geyer S. Some conceptual considerations on the sense of coherence. Soc Sci Med. 1997;44(12):1771-9.

46. Buchi S, Sensky T, Allard S, Stoll T, Schnyder U, Klaghofer R, et al. Sense of coherence--a protective factor for depression in rheumatoid arthritis. J Rheumatol. 1998;25(5):869-75.

47. Richardson Gibson LM, Parker V. Inner resources as predictors of psychological well-being in middle-income african american breast cancer survivors. Cancer Control. 2003;10(5 Suppl):52-9.

48.   Hall-Lord ML, Steen B, Larsson G. Postoperative experiences of pain and distress in elderly patients. An explorative study. Aging (Milano). 1999;11(2):73-82.

49.   Kenne Sarenmalm E, Browall M, Gaston-Johansson F. Symptom burden clusters: a challenge for targeted symptom management. A longitudinal study examining symptom burden clusters in breast cancer. J Pain Symptom Manage. 2014;47(4):731-41.

50.   Boman L, Bjorvell H, Langius A, Cedermark B. Two models of care as evaluated by a group of women operated on for breast cancer with regard to their perceived well-being. Eur J Cancer Care (Engl). 1999;8(2):87-96.

51.   Rohani C, Abedi HA, Omranipour R, Langius-Eklof A. Health-related quality of life and the predictive role of sense of coherence, spirituality and religious coping in a sample of Iranian women with breast cancer: a prospective study with comparative design. Health and quality of life outcomes. 2015;13:40.

52.   Rohani C, Abedi HA, Sundberg K, Langius-Eklof A. Sense of coherence as a mediator of health-related quality of life dimensions in patients with breast cancer: a longitudinal study with prospective design. Health and quality of life outcomes. 2015;13:195.

53.   Shapiro SL, Lopez AM, Schwartz GE, Bootzin R, Figueredo AJ, Braden CJ, et al. Quality of life and breast cancer: relationship to psychosocial variables. J Clin Psychol. 2001;57(4):501-19.

54.   Persson L, Larsson G, Ohlsson O, Hallberg IR. Acute leukaemia or highly malignant lymphoma patients' quality of life over two years: a pilot study. Eur J Cancer Care (Engl). 2001;10(1):36-47.

55.   Poppius E, Virkkunen H, Hakama M, Tenkanen L. The sense of coherence and incidence of cancer-role of follow-up time and age at baseline. J Psychosom Res. 2006;61(2):205-11.

56.   Surtees P, Wainwright N, Luben R, Khaw KT, Day N. Sense of coherence and mortality in men and women in the EPIC-Norfolk United Kingdom prospective cohort study. Am J Epidemiol. 2003;158(12):1202-9.

57.   Vilela LD, Allison PJ. An investigation of the role of sense of coherence in predicting survival among Brazilians with head and neck cancer. Oral Oncol. 2010;46(7):531-5.

58.   Geulayov G, Drory Y, Novikov I, Dankner R. Sense of coherence and 22-year all-cause mortality in adult men. J Psychosom Res. 2015;78(4):377-83.

59.   Lundman B, Forsberg KA, Jonsen E, Gustafson Y, Olofsson K, Strandberg G, et al. Sense of coherence (SOC) related to health and mortality among the very old: the Umea 85+ study. Arch Gerontol Geriatr. 2010;51(3):329-32.

60.   Poppius E, Tenkanen L, Hakama M, Kalimo R, Pitkanen T. The sense of coherence, occupation and all-cause mortality in the Helsinki Heart Study. Eur J Epidemiol. 2003;18(5):389-93.

61.   Super S, Verschuren WM, Zantinge EM, Wagemakers MA, Picavet HS. A weak sense of coherence is associated with a higher mortality risk. J Epidemiol Community Health. 2014;68(5):411-7.

62. Haukkala A, Konttinen H, Lehto E, Uutela A, Kawachi I, Laatikainen T. Sense of coherence, depressive symptoms, cardiovascular diseases, and all-cause mortality. Psychosom Med. 2013;75(4):429-35.

63. Sackey H, Johansson H, Sandelin K, Liljegren G, MacLean G, Frisell J, et al. Self-perceived, but not objective lymphoedema is associated with decreased long-term health-related quality of life after breast cancer surgery. Eur J Surg Oncol. 2015;41(4):577-84.

64. Sackey H, Magnuson A, Sandelin K, Liljegren G, Bergkvist L, Fulep Z, et al. Arm lymphoedema after axillary surgery in women with invasive breast cancer. Br J Surg. 2014;101(4):390-7.

65. National Board of Health and Welfare. National Cancer Registry 2012. Available from: http://www.socialstyrelsen.se/register/halsodataregister/cancerregistret.

66. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.

67. Wennman-Larsen A, Nilsson M, Saboonchi F, Olsson M, Alexanderson K, Fornander T, et al. Can breast cancer register data on recommended adjuvant treatment be used as a proxy for actually given treatment? Eur J Oncol Nurs. 2016;22:1-7.

68. Nunnally J, Bernstein I. Psychometric theory New York: McGraw-Hill; 1994.

69. Fleiss JL. Design and Analysis of Clinical Experiments. New York: John Wileys & Sons; 1986.

70. Wang J, Wang X. Structural equation modelling: Applications using Mplus. Chichester, West Sussex.: John Wiley & Sons Ltd; 2012.

71. Hu L, Bentler P. Fit indices in covariance structure modeling: Sensitivity to underparameterized model misspecification. Psychol Methods. 1998;3(4):424-53.

72. Munro B. Statistical Methods for Health Care Research. Philadelphia, PA.: Lippincott Williams & Wilkins; 2005.

73. Akaike H. Factor analysis and AIC. Psychometrika. 1987;52(3):317-32.

74. Geiser C, Eid M, Nussbeck FW, Courvoisier DS, Cole DA. Analyzing true change in longitudinal multitrait-multimethod studies: application of a multimethod change model to depression and anxiety in children. Dev Psychol. 2010;46(1):29-45.

75. Steyerberg EW, Borsboom GJ, van Houwelingen HC, Eijkemans MJ, Habbema JD. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. Stat Med. 2004;23(16):2567-86.

76. Polit D, Beck C. Nursing research: principles and methods. 7. ed. Philadelphia.: Lippincott Williams & Wilkins; 2004.

77. Polit D, Beck C. Nursing research: generating and assessing evidence for nursing practice. 9. ed. Philadelphia.: Wolters Kluwer Health/ Lippincott Williams & Wilkins; 2012.

78. Ding Y, Bao LP, Xu H, Hu Y, Rahm Hallberg I. Psychometric properties of the Chinese version of Sense of Coherence Scale in women with cervical cancer. Psychooncology. 2012;21:1205-14.

79.   Feldt T, Rasku A. The structure of Antonovsky's Orientation to Life Questionnaire. Pers Individ Dif. 1998;25:505-16.

80.   Gana K, Garnier S. Latent structure of the sense of coherence scale in a French sample. Pers Individ Dif. 2001;31:1079-90.

81.   Flannery RB, Perry JC, Penk WE, Flannery GJ. Validating Antonovsky´s Sense of Coherence Scale. J Clin Psychol. 1994;50(4):575-7.

82.   Holmefur M, Sundberg K, Wettergren L, Langius-Eklof A. Measurement properties of the 13-item sense of coherence scale using Rasch analysis. Qual Life Res. 2015;24(6):1455-63.

83.   Lerdal A, Fagermoen M, Bonsaksen T, Gay C, Kottorp A. Rasch analysis of the sense of coherence scale in a sample of people with morbid obesity - a cross-sectional study. BMC Psychology. 2014;2(1):1.

84.   Hittner JB. Factorial invariance of the 13-item Sense of Coherence scale across gender. J Health Psychol. 2007;12(2):273-80.

85.   McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338(3):171-9.

86.   Geyer S. Life events prior to manifestation of breast cancer: a limited prospective study covering eight years before diagnosis. J Psychosom Res. 1991;35(2-3):355-63.

87.   Geyer S. Life events, chronic difficulties and vulnerability factors preceding breast cancer. Soc Sci Med. 1993;37(12):1545-55.

88.   Winger JG, Adams RN, Mosher CE. Relations of meaning in life and sense of coherence to distress in cancer patients: a meta-analysis. Psychooncology. 2016;25(1):2-10.

89.   Onitilo AA, Nietert PJ, Egede LE. Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. Gen Hosp Psychiatry. 2006;28(5):396-402.

90.   Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med. 2010;40(11):1797-810.

91.   Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. Cancer. 2009;115(22):5349-61.

92.   Faller H, Bulzebruck H. Coping and survival in lung cancer: a 10-year follow-up. Am J Psychiatry. 2002;159(12):2105-7.

93.   Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jorgensen T. Depression as a prognostic factor for breast cancer mortality. Psychosomatics. 2003;44(1):24-30.

94.   Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. Lancet. 1999;354(9187):1331-6.

95.   Vodermaier A, Linden W, Rnic K, Young SN, Ng A, Ditsch N, et al. Prospective associations of depression with survival: a population-based cohort study in patients with newly diagnosed breast cancer. Breast Cancer Res Treat. 2014;143(2):373-84.

96. Giese-Davis J, Collie K, Rancourt KM, Neri E, Kraemer HC, Spiegel D. Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. J Clin Oncol. 2011;29(4):413-20.

97. Musselman DL, Miller AH, Porter MR, Manatunga A, Gao F, Penna S, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. Am J Psychiatry. 2001;158(8):1252-7.

98. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol. 2004;5(10):617-25.

99. Hyphantis T, Paika V, Almyroudi A, Kampletsas EO, Pavlidis N. Personality variables as predictors of early non-metastatic colorectal cancer patients' psychological distress and health-related quality of life: a one-year prospective study. J Psychosom Res. 2011;70(5):411-21.

100. Pillay B, Lee SJ, Katona L, De Bono S, Burney S, Avery S. A prospective study of the relationship between sense of coherence, depression, anxiety, and quality of life of haematopoietic stem cell transplant patients over time. Psychooncology. 2015;24(2):220-7.

101. Henje Blom EC, Serlachius E, Larsson JO, Theorell T, Ingvar M. Low Sense of Coherence (SOC) is a mirror of general anxiety and persistent depressive symptoms in adolescent girls - a cross-sectional study of a clinical and a non-clinical cohort. Health and quality of life outcomes. 2010;8:58.

102. Haynes R, Taylor D, Sackett D. Compliance in Health Care. Baltimore: John Hopkins University Press; 1979.

103. Cederfjall C, Langius-Eklof A, Lidman K, Wredling R. Self-reported adherence to antiretroviral treatment and degree of sense of coherence in a group of HIV-infected patients. AIDS Patient Care STDS. 2002;16(12):609-16.

104. Duvdevany I, Cohen M, Minsker-Valtzer A, Lorber M. Psychological correlates of adherence to self-care, disease activity and functioning in persons with systemic lupus erythematosus. Lupus. 2011;20(1):14-22.

105. Nabi H, Vahtera J, Singh-Manoux A, Pentti J, Oksanen T, Gimeno D, et al. Do psychological attributes matter for adherence to antihypertensive medication? The Finnish Public Sector Cohort Study. J Hypertens. 2008;26(11):2236-43.

106. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat. 2012;134(2):459-78.

"Om jag vill lyckas med att föra en människa mot ett bestämt mål, måste jag först finna henne där hon är och börja just där. Den som inte kan det lurar sig själv när hon tror att hon kan hjälpa andra."

Søren Kirkegaard