CANCER DIAGNOSIS & PROGNOSIS *6*: 434-444 (2026)
doi: 10.21873/cdp.10543

Stressful Events in Life Due to Losses and Deficit Could Predict 25-year Outcome in Patients With Breast Cancer Symptoms

MATTI ESKELINEN[1], RIIKA KOSKELA[2], TUOMAS SELANDER[3], KAI KAARNIRANTA[4], PAULA OLLONEN[5] and MAARET ESKELINEN[1]

[1]Department of Surgery, Kuopio University Hospital (KUH) and School of Medicine, University of Eastern Finland (UEF), Kuopio, Finland;
[2]Department of Anaesthesiology, KUH and School of Medicine, UEF, Kuopio, Finland;
[3]Science Service Center, KUH, Kuopio, Finland;
[4]Department of Ophthalmology, KUH and School of Medicine, UEF, Kuopio, Finland;
[5]Department of Psychiatry, KUH and School of Medicine, UEF, Kuopio, Finland

Abstract

Background/Aim: Psychosocial stressful (PS) factors like losses and deficit could associate indirectly to breast carcinoma (BC) risk, but the long-term impact of losses, deficit and stressful (LDS) events on outcome of patients with BC symptoms is rarely reported.

Patients and Methods: A study cohort of 115 patients with BC symptoms completed the LDS inventory (LDSI). Associations between LDSI and long-term outcomes were examined.

Results: In the Cox model, the LDSI predicted the 25-year relapse-free survival (RFS) in patients with BC [hazard ratio (HR)=5.02, p=0.01] and the LDSI scale predicted 25-year overall survival (OS) in women with BC symptoms (HR=2.37, p=0.05). In the Kaplan-Meier survival analysis by the log-rank test, the 25-year relapse rate differed between low LDSI (<83) *versus* the high LDSI (≥83) in patients with BC symptoms (27.9% *versus* 54.5%, log-rank p-value=0. 098). Also, the low LDSI (<83) was a favourable predictor of the RFS [HR=5.02, 95% confidence interval (CI)=1.42-17.8, p=0.01] in patients with BC. The 25-year OS rate differed between low LDSI (<83) *versus* the high LDSI score (≥83) patients with BC symptoms (19.8% *versus* 36.8%, log-rank p-value=0.048). A similar figure was seen in BC as the LDSI predicted 25-year OS in female patients with BC (44.4% *versus* 71.4%, log-rank p-value=0.048).

Conclusion: This study found a significant long-term outcome effect for LDS events on both women with BC symptoms and patients with BC. These findings suggest that further research is needed to substantiate whether LDSI approach could be an important addition to PS events screening criteria for preventative or early BC care.

Keywords: Losses, deficit, stress, breast cancer, survival.

Matti Eskelinen, MD, PhD, School of Medicine, UEF, P.O. Box 1711, FI-70211 KYS, Finland. Tel: +358 17173311, Fax: +358 17172611, GSM: +358 400969444, e-mail: matti.eskelinen@kuh.fi

Received February 7, 2026 | Revised February 27, 2026 | Accepted March 3, 2026

Introduction

At present, there is few evidence for any biological assumption through which life events with psychosocial stress (PS) could predict the etiology or outcome in breast carcinoma (BC). Stressful experiences include physical stressors such as pathogens and toxins, and PS factors such as major life events, trauma, abuse, or factors related to the environment in the home, workplace, family, or at neighborhood (1, 2). Several PS mechanisms have been suggested, most of these hypotheses implicate neuroendocrine responses or hormonal status of patients (3-11). Neuroendocrine responses can impact immune, angiogenic, and inflammatory pathways that contribute to the incidence, progression and control of cancer. The responses are mainly regulated by the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) that release stress hormones: glucocorticoids and catecholamines (3, 5-7). Prolactin, growth hormone, and nerve growth factor are also linked to BC pathogenesis (11). It seems that BC-related PS responses can be found in many other psychosocial disorders also.

The studies focusing on stressful events in life due to losses and deficit are less studied than other adverse events and their role remains unclear in etiology and outcome of BC (13-26). Earlier reports have found some relationship of losses, deficit and stress (LDS) events with BC (14-16, 24, 25) including loss of a family member, divorce, job loss, physical, sexual, or psychological abuse. Hilakivi-Clarke *et al*. (9, 10) reported the effects of social isolation on BC and suggested deficit in social connections as risk factor for BC. The previously published results of the Kuopio Breast Cancer Study (KBCS) (18) support a weak association between LDS events in adulthood and the risk of BC. Furthermore, the same authors (19) reported that female patients with BC had higher mean score for loss and deficit in childhood than the non-BC patients. Patients with BC had also significantly more severe deficit in childhood than women without BC. The authors concluded that female patients with BC tended to have more LDS events than non-BC patients. However, the biological explanation for such an association is unclear and it might be that the LDS events impact indirectly on BC risk (18, 19). Unfortunately, the impact of LDS events on long-term outcome of patients with BC symptoms has not been reported.

Patients and Methods

Patients. The study cohort included 115 patients with BC symptoms diagnosed in Breast Cancer Diagnostic Unit (BCDU), Kuopio University Hospital (KUH), Finland (Table I). The Kuopio Breast Cancer Study (KBCS) (27-30) follows the protocol of the International Collaborative Study of Breast and Colorectal Cancer coordinated by the European Institute of Oncology and was initiated as a SEARCH program of the International Agency for Research on Cancer (31).

Losses, deficit and stressful events inventory (LDSI). The LDS events were evaluated over the whole lifespan, especially the previous ten years before admission. The LDS events and the context surrounding them were marked on the 'life line paper' during the interview. After the interviews, the LDS events were rated according to the degree of threat or stress they were likely to pose, and each LDS event was graded on a five-point scale, grade I (one point) indicating non-threatening event and grade V (five points) a severely threatening event. The defences used were also assessed on a five-point scale: grade I (one point) indicating very defensive, in denial and grade V (five points) non-defensive. The 'working through and actively confronting the LDS event' variable was also rated on a five-point scale: grade I (one point) indicating not resolved and grade V (five points) fully resolved. These measurements were put together in the final statement, one to two points on the scale meant little or mild loss or stress, and five meant very hard loss or stress. A detailed description of the LDSI protocol is shown in earlier reports (18, 19).

Wirsching Psychosocial Risk Scale (WPRS). We used a modified WPRS for psychosocial risk assessment with

Table I. *The baseline data and mean sores of quality-of-life scales in three study groups.*

Variable	HSP (n=28)	BBD (n=53)	BC (n=34)	*p*-Value
Age, years	45.7	47.6	51.6	0.12
Height, cm	160.8	162.3	164.4	0.75
Body weight, kg	68.3	67.8	72.5	0.25
Age at menarche, years	13.4	13.4	13.4	0.99
Age at birth of I child, years	25	25	25.2	0.92
Age at menopause, years	50	48.9	47.9	0.53
No. of children	2.5	2.4	2.6	0.27
Parous*	23 (82%)	44 (83%)	31 (91%)	0.5
Breast feeding, months	3.9	3.4	3.6	0.77
Use of oral* contraceptives	18 (64%)	25 (47%)	13 (38%)	0.12
HRT*	14 (50%)	36 (68%)	27 (79%)	0.44
Premenopausal*	18 (64%)	28 (53%)	13 (38%)	0.1
Postmenopausal*	10 (36%)	25 (47%)	21 (62%)	0.12
History of previous BBD*	10 (36%)	22 (42%)	18 (53%)	0.37
Family history of BC*	5 (18%)	5 (9%)	1 (3%)	0.21
Use of alcohol*	13 (46%)	31 (58%)	21 (62%)	0.44
Smoking*	10 (36%)	21 (40%)	15 (44%)	0.8
BDI score	7.8	8.5	8.9	0.7
MADRS score	22.2	21.2	21.2	0.78
STAI score	39.2	41.3	40.1	0.29
FI score, 0-2 years	14.3	14.2	14.1	0.99
FI score, 2-6 years	12.5	11.8	9.8	0.43
SAI score	27.2	28.7	24	0.003
WPRS score	17.2	17.6	19.4	0.05
LDSI score	70.2	64.5	66.3	0.41
nLDSI score	11.2	9.4	10.3	0.47

Data represent mean values. *Data presented as n (%). BBD: Benign breast disease; BC: breast carcinoma; BDI: Beck Depression inventory; FI: Forsen inventory; HRT: hormonal replacement therapy; HSP: healthy study participants; MADRS: Montgomery-Asberg Depression Rating Scale; SAI: Sifneos Alexithymia inventory; STAI: State-trait Anxiety inventory; WPRS: Wirsching psychosocial risk scale ; LDSI: Losses; Deficit and Stress inventory; nLDSI: number of LDS incidents (nLDSI).

10 scales and a detailed description of the WPRS protocol is shown in earlier reports (32-34).

A detailed description of the classical psychosocial scales, Sifneos Alexithymia Inventory (SAI), Forsen Inventory (FI), Beck Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale (MADRS), Spielberger State-Trait Anxiety inventory (STAI) is provided in earlier reports (35-48).

Statistical analysis. Baseline group differences were analysed by two-sided chi-square and non-parametric Kruskall-Wallis tests. Scores are presented as mean values and standard deviation. Scores were compared between the two groups using Student's *t*-test. The relapse-free survival (RFS) was calculated from the time of diagnosis to the occurrence of the first relapse, contralateral BC, or metastatic disease. The overall survival (OS) was assessed as the time from the date of diagnosis to the date of last follow-up or death of the patient. The effect of the LDSI approach on the RFS and OS were calculated using the Kaplan-Meier survival analysis and the difference between the groups was assessed using the log-rank test. The *p*-values and the hazard ratios (HRs) with their 95% confidence intervals (CI) were calculated using the Cox proportional hazard models. Pearson's method was used to test for correlation between LDSI approach and the classical psychosocial scale levels. Data were analyzed using the IBM SPSS statistical software (IBM SPSS Statistics for Windows, version 26.0, IBM Corporation Armonk, NY, USA).

Results

BDI, MADRS, STAI, FI, SAI, WPRS and LDSI levels in BC and non-BC patients. Table I shows the baseline data and values of BDI, MADRS, STAI, FI, SAI, WPRS and LDSI scales in healthy study participants (HSP), benign breast disease (BBD) and breast carcinoma (BC) . The mean BDI, MADRS, STAI, FI scale (0-2 years), FI scale (2-6 years), LDSI and number of LDS events (nLDSI) values between female patients with BC and women without BC were quite similar (p=0.70, 0.78, 0.29, 0.99, 0.43, 0.41 and 0.47, respectively, Table I). The mean SAI levels were significantly higher in women without BC (HSP=27.2 and BBD= 28.7) *versus* women with BC (24.0, p=0.003, Table I), whereas the mean WPRS values in patients with BC were higher than in non-BC patients (BC=19.4 *versus* HSP=17.2 and BBD=17.6, p=0.05). However, there were no significant differences between the mean LDSI scores of losses (Table II) and deficits with stress (Table III) at adulthood among non-cancer women and female patients with BC using Student's *t*-test.

LDSI correlation to classical tests. The LDSI levels correlated with BDI *(r*=0.37, p<0.001; Figure 1), MADRS *(r*=0.51, p<0.001; Figure 2), STAI *(r=0.29, p*=0.002; Figure 3), and FI 0-2 years *(r*=0.50, p<0.001; Figure 4), FI 2-6 years *(r*=0.52, p<0.001), SAI (r=–0.52, p<0.001) and WPRS (r=0.34, p<0.001; Figure 5) (Table IV).

The 25-year RFS and OS. In the Cox model, the LDSI predicted the 25-year RFS in all women with BC symptoms (HR=2.37, p=0.05, Table V) and the RFS in female patients with BC (HR=5.02, p=0.01). In the Kaplan-Meier survival analysis by the log-rank test, the 25-year relapse level differed between low LDSI (<83) and high LDSI (≥83) in women with BC symptoms; though the difference was not statistically significant (27.9% *versus* 54.5%, log-rank p-value=0.098; Figure 6). Also, the low LDSI (<83) was a favourable predictor of the RFS (HR=5.02, 95% CI=1.42-17.8, p=0.01) in patients with BC. The 25-year OS rate differed between low LDSI (<83) and high LDSI score (≥83) in women with BC symptoms (19.8% *versus* 36.8%, log-rank p-value=0.048; Figure 7). A similar figure was seen in female patients with BC as the LDSI predicted 25-year OS in patients with BC (44.4% *versus* 71.4%, HR=2.59, 95% CI 0.90-7.40, p=0.076; Table VI).

Table II. *The scores of losses at adulthood among non-cancer patients and patients with breast cancer.*

Variable	Non-cancer	Cancer	p-Value*
Losses in adult relationship	2.42 (1.59)	2.44 (1.65)	0.949
Significance	2.14 (1.24)	2.35 (1.43)	0.444
Working	1.81 (0.98)	2.09 (1.22)	0.250
Losses in close relationship	2.11 (1.65)	2.18 (1.51)	0.807
Significance	1.85 (1.26)	2.06 (1.39)	0.457
Working	1.65 (1.01)	1.76 (0.96)	0.579
Loss of social status in adulthood	1.28 (0.88)	1.26 (0.86)	0.914
Significance	1.27 (0.87)	1.29 (0.97)	0.907
Working	1.16 (0.56)	1.09 (0.38)	0.423
Loss of health in adulthood	2.47 (1.68)	2.15 (1.48)	0.310
Significance	2.25 (1.47)	2.38 (1.48)	0.655
Working	1.74 (0.93)	1.65 (0.85)	0.602
Losses in adulthood (6-10 years)	1.49 (1.17)	1.41 (0.92)	0.691
Significance	1.48 (1.11)	1.50 (1.11)	0.935
Working	1.30 (0.75)	1.24 (0.61)	0.648
Losses in adulthood (2-6 years)	1.59 (1.23)	1.94 (1.39)	0.210
Significance	1.51 (0.98)	1.76 (1.11)	0.241
Working	1.37 (0.77)	1.62 (0.92)	0.174
Losses in adulthood (0-2 years)	1.90 (1.61)	1.47 (1.16)	0.111
Significance	1.58 (1.07)	1.38 (0.99)	0.342
Working	1.48 (0.91)	1.26 (0.67)	0.156

Data presented as mean (standard deviation). *Student's *t*-test.

Table III. *The scores of deficits and stress at adulthood among non-cancer patients and patients with breast cancer.*

Variable	Non-cancer	Cancer	p-Value*
Deficit in adulthood	1.95 (1.51)	1.97 (1.41)	0.946
Significance	2.01 (1.48)	2.12 (1.49)	0.701
Working	1.54 (0.90)	1.50 (0.86)	0.809
Severe illness of close relative	1.58 (1.28)	2.01 (1.44)	0.146
Significance	1.49 (1.06)	2.01 (1.44)	0.070
Working	1.37 (0.81)	1.59 (0.89)	0.225
Stress in adulthood (6-10 years)	2.41 (1.66)	2.12 (1.47)	0.357
Significance	2.33 (1.54)	2.18 (1.59)	0.627
Working	1.72 (0.96)	1.53 (0.79)	0.283
Stress in adulthood (2-6 years)	2.65 (1.67)	2.47 (1.54)	0.572
Significance	2.52 (1.52)	2.51 (1.62)	0.954
Working	1.91 (1.04)	1.85 (0.96)	0.811
Stress in adulthood (0-2 years)	2.68 (1.69)	2.24 (1.54)	0.176
Significance	2.53 (1.48)	2.26 (1.62)	0.409
Working	2.01 (1.19)	1.68 (0.98)	0.119

Data presented as mean (standard deviation). *Student's *t*-test.

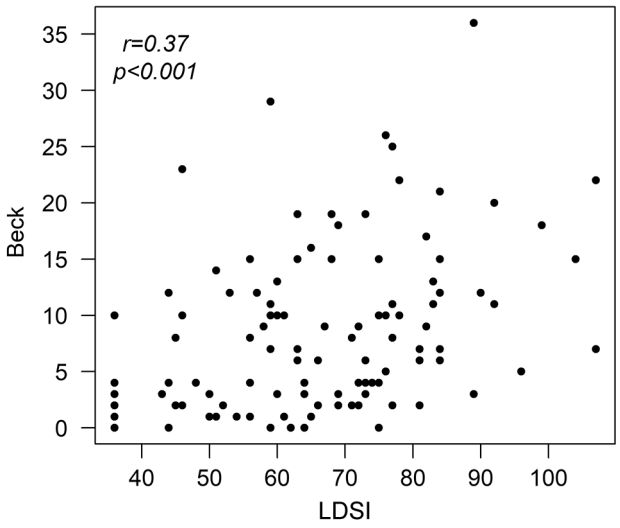

Figure 1. *Scatter plot of the losses, deficit and stress inventory (LDSI) score versus Beck Depression Inventory (BDI) score in patients with breast cancer symptoms (r=0.37, p<0.001).*

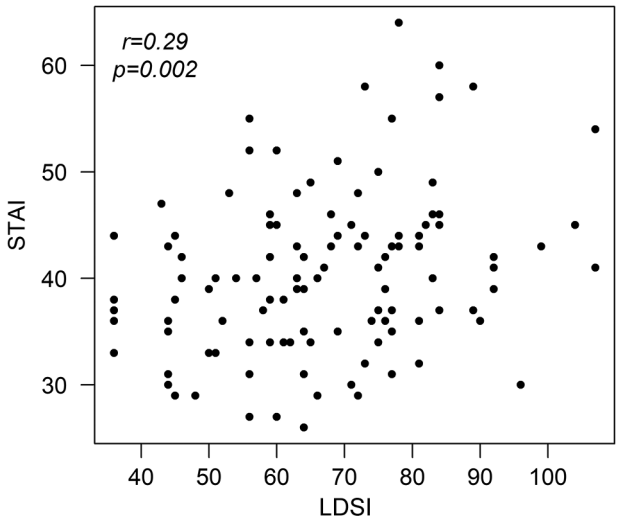

Figure 3. *Scatter plot of the losses, deficit and stress inventory (LDSI) score versus State-trait Anxiety Inventory (STAI) score in patients with breast cancer symptoms (r=0.29, p=0.002).*

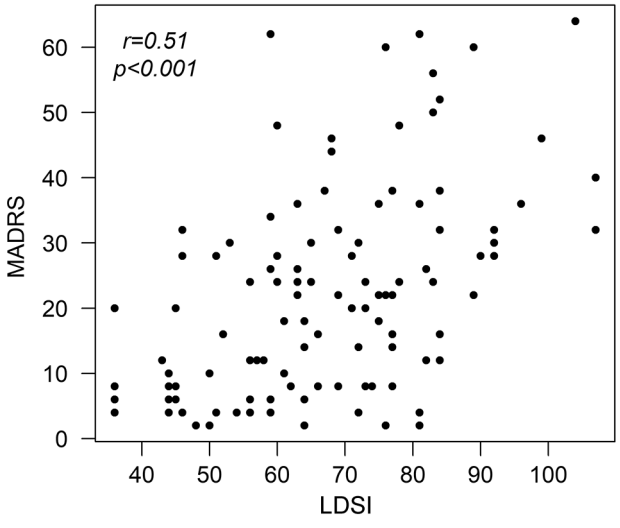

Figure 2. *Scatter plot of the losses, deficit and stress inventory (LDSI) score versus Montgomery-Asberg depression rating scale (MADRS) score in patients with breast cancer symptoms (r=0.51, p<0.001).*

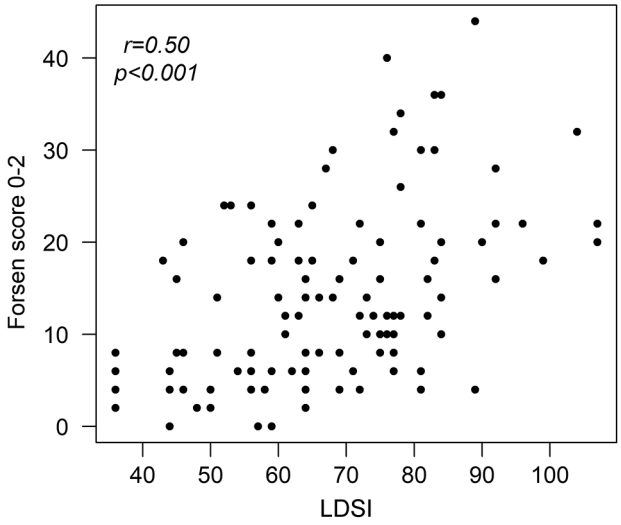

Figure 4. *Scatter plot of the losses, deficit and stress inventory (LDSI) score versus Forsen psychological risk inventory (FI, 0-2 years) score in patients with breast cancer symptoms (r=0.50, p<0.001).*

Discussion

BC is one of the main public health problems in women worldwide (49-52) and several PS factors for BC have been identified, while LDS events are less studied than other adverse events and their role remains unclear in etiology and outcome of BC (13-26). Earlier reports have found some relationship between the LDS events and BC, including loss of a family member, divorce, job loss, physical, sexual, or psychological abuse; (14-16, 24, 25,

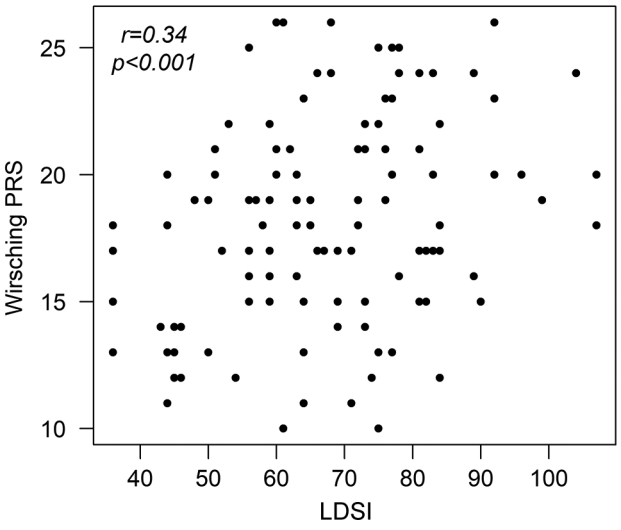

Figure 5. *Scatter plot of the losses, deficit and stress inventory (LDSI) score versus Wirsching's psychosocial risk scale (WPRS) score in patients with breast cancer symptoms (r=0.34, p<0.001).*

Table IV. *The LDSI levels and reported number of LDS events (nLDSI) versus the BDI, MADRS, STAI, FI 0-2 years, FI 2-6 years, SAI and WPRS in patients with BC symptoms. The r- values and p-values were calculated from the Pearson models.*

Scale	LDSI		nLDSI	
	r-Value	*p*-Value	r-Value	*p*-Value
BDI	0.37	<0.001	0.18	0.05
MADRS	0.51	<0.001	0.35	<0.001
STAI	0.29	0.002	0.07	0.46
FI 0-2 years	0.5	<0.001	0.29	0.002
FI 2-6 years	0.52	<0.001	0.38	<0.001
SAI	–0.32	<0.001	–0.06	0.543
WPRS	0.34	<0.001	0.15	0.121

BDI: Beck Depression inventory; FI: Forsen inventory; MADRS: Montgomery-Asberg Depression Rating Scale; SAI: Sifneos Alexithymia inventory; STAI: State-trait Anxiety inventory; WPRS: Wirsching psychosocial risk scale; LDSI: Losses; Deficit and Stress inventory; nLDSI: reported number of LDS incidents (nLDSI).

53, 54). Forsen (38) assessed the PS events and the findings indicated that female patients with BC had losses, and difficult life situations preceding BC diagnosis. The authors concluded that significant losses preceding BC diagnosis could enhance BC risk in women with BC symptoms (38).

Table V. *The LDSI levels versus the RFS for HSP (n=28), BBD (n=53) and BC (n=34) groups and groups combined (All). The p-values and HRs and their 95%CI were calculated from Cox proportional hazard models.*

Group	RFS (%)		HR	95% CI	*p*-Value
	LDSI<83	LDSI≥83			
All	27.9	54.5	2.37	0.98-5.72	0.05
HSP	13	33.3	2.95	0.49-17.7	0.24
BBD	16	50	3.17	0.40-25.4	0.28
BC	58.1	100	5.02	1.42-17.8	0.01

BBD: Benign breast disease; BC: breast carcinoma; CI: confidence interval; HR: hazard ratio; HSP: healthy study participants; LDSI: losses; deficit and stress inventory; RFS: relapse-free survival.

Chen *et al.* (53) reported that PS events enhanced the risk of BC in women with BC symptoms 3-fold and after adjustment for menopause and age, the risk for BC rose almost 4-fold in women with BC symptoms. The authors concluded that there is a significant association between severe PS events and risk of BC in women with BC symptoms.

Duijts *et al.* (13) conducted a meta-analysis to examine the association between the PS events and BC risk. They included the following PS events: death of spouse, death of relative or friend, personal or nonpersonal health difficulties, change in marital status, change in financial status and change in environmental status. The authors found a statistically significant effect of stressful life events (RR=1.77), death of spouse (RR=1.37) and death of a relative or friend (OR=1.35). Unfortunately, publication bias was detected in two PS variables; in the stressful life events and in the death of relative or friend categories. Therefore, only a modest association could be identified between death of spouse and risk of BC in women with BC symptoms.

Lillberg *et al.* (14) investigated retrospectively the PS events in BC by a self-administered questionnaire and found that the risk of BC was associated with the following life events: divorce (RR=2.2), death of spouse (RR=2.00), and death of a close relative or friend (RR=1.36). The authors suggest that major life events can play a significant role in the etiology of BC.

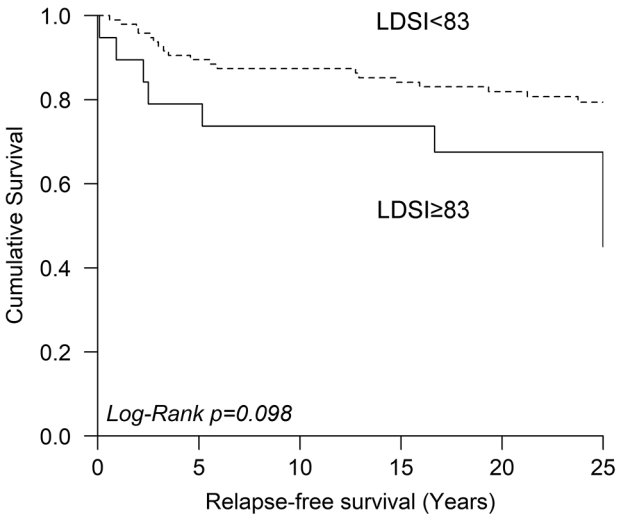

Figure 6. *The curves for relapse-free survival (RFS) in patients with breast cancer symptoms according to losses, deficit and stress inventory (LDSI). The effect of LDSI score on OS was not statistically significant (p=0.098, log-rank test).*

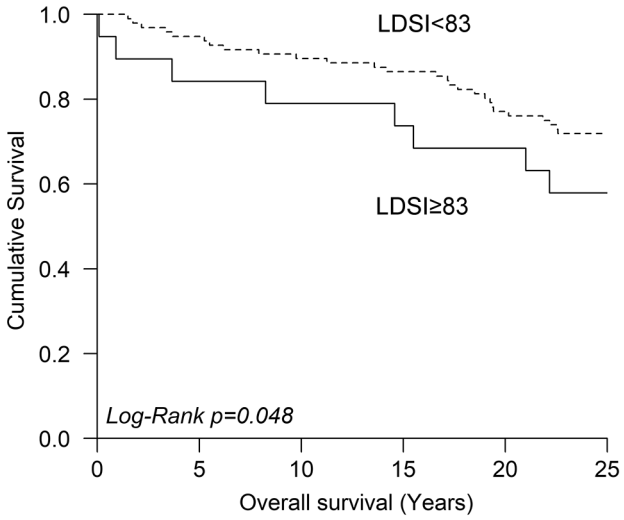

Figure 7. *The curves for overall survival (OS) in patients with breast cancer symptoms according to losses, deficit and stress inventory (LDSI). The LDSI score had a significant effect on OS (p=0.048, log-rank test).*

Kruk (15, 54) reported that women with a high number of PS events, four to six PS events, had over 5-fold increased risk for BC compared to women with low number of PS events. The authors found that the risk of BC is enhanced after high number of PS events and following death of a family member, personal injury or illness, imprisonment/trouble with the law, and retirement.

Chiriac *et al.* (23) performed a systematic review including all studies from 1966 to 2016 assessing the relationship between stress and the risk of BC. They found 17 retrospective, 20 limited prospective and 15 prospective studies for their review and the number of patients exceeded 29,000, for a total number of more than 700,000 women recruited from hospital, screening cohorts or population registers. They identified 26 'positive results' articles linking personal traits and stressful events to BC, 18 'negative results' articles that did not confirm their hypothesis and eight articles that could not be classified. They found heterogeneity and possible study bias factors such as: study design, information gathering, stress type, moment of exposure, individual susceptibility and personality. Authors concluded, that their qualitative analysis of articles revealed a possible association between stress and risk of BC, especially regarding stressful life events. However, without meta-analysis, their results are difficult to interpret and the role of chance is difficult to exclude.

Table VI. *The LDSI levels versus the OS for the HSP (n=28), BBD (n=53) and BC (n=34) groups and groups combined (All). The p-values and HRs and their 95% CI were calculated from the Cox proportional hazard models.*

Group	OS (%)		HR	95% CI	*p*-Value
	LDSI<83	LDSI≥83			
All	19.8	36.8	2.06	0.80-4.91	0.090
HSP	14.3	25.0	1.37	0.21-8.82	0.740
BBD	8.3	0.0	na	na	na
BC	44.4	71.4	2.59	0.90-7.40	0.076

BBD: Benign breast disease; BC: breast carcinoma; CI: confidence interval; HR: hazard ratio; HSP: healthy study participants; LDSI: losses; deficit and stress inventory; LS: losses and stress; OS: overall survival; RFS: relapse-free survival.

Fischer *et al.* (24) studied stressful life events that occurred prior to BC diagnosis and found that they were associated with increased BC risk (RR=1.63, 95% CI=1.00-

2.66). Conversely, non-stressful events did not have a significant impact on BC risk. Previous personal illness was directly related to increased BC risk, whether perceived as stressful (RR=2.84, 95%CI=1.96-4.11) or non-stressful (RR=3.47, 95% CI=1.34-8.94). Authors concluded that their study underscores the importance to pay attention to PS events when determining BC risk.

Bahri *et al.* (25) conducted a review and meta-analysis to investigate the relation between PS events and the risk of BC. Out of 168 publications, 11 documents met the inclusion criteria of their study and the results showed that history of the PS events slightly enhanced the risk of BC (RR=1.11, 95% CI=1.03-1.19). The authors concluded, that history of PS events could be associated with a moderate increase in the risk of BC.

Moayedi-Nia *et al*. (55) examined life-stress due to losses (death of a family member, divorce/separation) and socioeconomic events (job loss, major income reduction, or a move to a new city) as risk factors for lung cancer (LC) in a case-control study. They found that the high impact loss events enhanced significantly LC risk (RR=1.84, 95% CI=0.97-3.49).

In addition, the previously published results of the Kuopio Breast Cancer Study (KBCS) (26) showed association between the LDS events in adulthood and the risk of BC. Furthermore, the same authors (27) reported that patients with BC had higher mean score for deficit and loss at childhood than non-BC patients. Their results indicated that the women with BC tended to have more LDS events than non-BC women. However, the weakness of their BC study is that they had no data on the impact of LDS events on long-term outcome. At present, the relationship between PS events and BC has been widely studied; however, most existing research is characterized by a weak methodological structure and contradictory findings. However, the evidence is quite low for any biological assumption through which the PS factors could predict the etiology or outcome in patients with BC. Furthermore, the ability to adjust to repeated stress is also determined by the way a person perceives a situation. The determination of the role of stress in cancer has faced many difficulties such as the health habits or stage of cancer (1, 2). In addition, individuals who are stressed and depressed are more likely to have health behavior that puts them at higher risk, including worse sleep, excessive use of alcohol and drug abuse, worse nutrition, and less exercise – health habits that have immunological and endocrinological consequences (1, 2). Reducing the effect of the PS events through social support, including the presence of a social network or psychological intervention, has been shown to increase survival time and decrease the rate of metastasis (1, 2). Here, we report the characteristics of the PS events with the LDSI model in women with BC symptoms and their link with the long-term outcome. The LDS events should be identified by a doctor who is considering patients' potential risk of future BC. This study found significant long-term outcome effects for LDS events of both women with BC symptoms and patients with BC. In addition, we observed significant associations between BDI, MADRS, STAI, FI, SAI and WPRS scales and LDSI levels. These findings suggest that further research is needed to substantiate, whether LDSI could be an important addition to the PS events screening criteria for preventative or early breast cancer care. The results indicated that PS events detected with LDSI scale correlate with the 25-year RFS in women with BC symptoms and the RFS in women with BC. Also, low LDSI (<83) demonstrated as a favourable predictor of the RFS in women with BC. The 25-year OS rate differed between low LDSI (<83) and high LDSI score (≥83) women with BC symptoms. A similar figure was seen in BC as LDSI predicted 25-year OS in women with BC. The present data indicate that reducing the effect of the PS events at the prediagnostic phase could decrease the rate of relapse (RFS) and increase OS time.

Conclusion

The studies to date assessing PS events of women with BC have not considered LDSI *versus* outcome. The 25-year long follow-up time of women with BC symptoms permits us to assess the RFS and OS. The PS events observed with

the LDSI significantly correlate with the 25-year OS in women with BC and in women with BC symptoms. Therefore, the use of the LDSI observing PS events should be considered a useful tool in BCDU. Moreover, one can believe that all attempts aimed at suppressing the PS response, both pharmacologically and psychologically, have the potential to positively influence the outcome of women with BC symptoms.

Conflicts of Interest

The Authors report no conflicts of interest or financial ties regarding this study.

Authors' Contributions

All Authors contributed to the collection and analysis of data, drafting and revising the manuscript, and read and approved the final article.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

1 Reiche EMV, Nunes SOV, Morimoto HK: Stress, depression, the immune system, and cancer. Lancet Oncol 5(10): 617-625, 2004. DOI: 10.1016/S1470-2045(04)01597-9

2 Reiche EMV, Morimoto HK, Nunes SMV: Stress and depression-induced immune dysfunction: Implications for the development and progression of cancer. Int Rev Psychiatry 17(6): 515-527, 2005. DOI: 10.1080/02646830500382102

3 Mastorakos G, Pavlatou MG, Mizamtsidi M: The hypothalamic-pituitary-adrenal and the hypothalamic- pituitary-gonadal axes interplay. Pediatr Endocrinol Rev 3 Suppl 1: 172-181, 2006.

4 Powell ND, Tarr AJ, Sheridan JF: Psychosocial stress and inflammation in cancer. Brain Behav Immun 30 Suppl: S41-S47, 2013. DOI: 10.1016/j.bbi.2012.06.015

5 Toufexis D, Rivarola MA, Lara H, Viau V: Stress and the reproductive axis. J Neuroendocrinol 26(9): 573-586, 2014. DOI: 10.1111/jne.12179

6 Barel E, Abu-Shkara R, Colodner R, Masalha R, Mahagna L, Zemel OC, Cohen A: Gonadal hormones modulate the HPA-axis and the SNS in response to psychosocial stress. J Neurosci Res 96(8): 1388-1397, 2018. DOI: 10.1002/jnr.24259

7 Tollos I, Theodorakopoulou A, Christodoulou GN: [Stress and pathophysiological mechanisms for the development of psychosomatic disease]. Psychiatriki 32(2): 148-156, 2021. DOI: 10.22365/jpsych.2021.023

8 Wang C, Shen Y, Ni J, Hu W, Yang Y: Effect of chronic stress on tumorigenesis and development. Cell Mol Life Sci 79(9): 485, 2022. DOI: 10.1007/s00018-022-04455-3

9 Hilakivi-Clarke L, de Oliveira Andrade F: Social isolation and breast cancer. Endocrinology 164(10): bqad126, 2023. DOI: 10.1210/endocr/bqad126

10 Andrade FO, Jin L, Clarke R, Wood I, Dutton M, Anjorin C, Rubin G, Gao A, Sengupta S, FitzGerald K, Hilakivi-Clarke L: Social isolation activates dormant mammary tumors, and modifies inflammatory and mitochondrial metabolic pathways in the rat mammary gland. Cells 12(6): 961, 2023. DOI: 10.3390/cells12060961

11 Reznik E, Torjani A: Mechanisms of stress-attributed breast cancer incidence and progression. Cancer Causes Control 35(11): 1413-1432, 2024. DOI: 10.1007/s10552-024-01884-2

12 Hilakivi-Clarke L, Rowland J, Clarke R, Lippman ME: Psychosocial factors in the development and progression of breast cancer. Breast Cancer Res Treat 29(2): 141-160, 1994. DOI: 10.1007/BF00665676

13 Duijts SF, Zeegers MP, Borne BV: The association between stressful life events and breast cancer risk: A meta-analysis. Int J Cancer 107(6): 1023-1029, 2003. DOI: 10.1002/ijc.11504

14 Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M: Stressful life events and risk of breast cancer in 10,808 women: a cohort study. Am J Epidemiol 157(5): 415-423, 2003. DOI: 10.1093/aje/kwg002

15 Kruk J, Aboul-Enein HY: Psychological stress and the risk of breast cancer: a case-control study. Cancer Detect Prev 28(6): 399-408, 2004. DOI: 10.1016/j.cdp.2004.07.009

16 Falagas ME, Zarkadoulia EA, Ioannidou EN, Peppas G, Christodoulou C, Rafailidis PI: The effect of psychosocial factors on breast cancer outcome: a systematic review. Breast Cancer Res 9(4): R44, 2007. DOI: 10.1186/bcr1744

17 Fuller-Thomson E, Brennenstuhl S: Making a link between childhood physical abuse and cancer: results from a regional representative survey. Cancer 115(14): 3341-3350, 2009. DOI: 10.1002/cncr.24372

18 Eskelinen M, Ollonen P: Life stress and losses and deficit in adulthood as breast cancer risk factor: a prospective case-control study in Kuopio, Finland. In Vivo 24(6): 899-904, 2010.

19 Eskelinen M, Ollonen P: Life stress due to losses and deficit in childhood and adolescence as breast cancer risk factor: a

prospective case-control study in Kuopio, Finland. Anticancer Res 30(10): 4303-4308, 2010.
20 Brown MJ, Thacker LR, Cohen SA: Association between adverse childhood experiences and diagnosis of cancer. PLoS One 8(6): e65524, 2013. DOI: 10.1371/journal.pone.0065524
21 Hyland ME, Alkhalaf AM, Whalley B: Beating and insulting children as a risk for adult cancer, cardiac disease and asthma. J Behav Med 36(6): 632-640, 2013. DOI: 10.1007/s10865-012-9457-6
22 Bellis MA, Hughes K, Leckenby N, Hardcastle KA, Perkins C, Lowey H: Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: a national survey. J Public Health (Oxf) 37(3): 445-454, 2015. DOI: 10.1093/pubmed/fdu065
23 Chiriac VF, Baban A, Dumitrascu DL: Psychological stress and breast cancer incidence: a systematic review. Clujul Med 91(1): 18-26, 2018. DOI: 10.15386/cjmed-924
24 Fischer A, Ziogas A, Anton-Culver H: Perception matters: Stressful life events increase breast cancer risk. J Psychosom Res 110: 46-53, 2018. DOI: 10.1016/j.jpsychores.2018.03.010
25 Bahri N, Fathi Najafi T, Homaei Shandiz F, Tohidinik HR, Khajavi A: The relation between stressful life events and breast cancer: a systematic review and meta-analysis of cohort studies. Breast Cancer Res Treat 176(1): 53-61, 2019. DOI: 10.1007/s10549-019-05231-x
26 Bowen DJ, Fernandez Poole S, White M, Lyn R, Flores DA, Haile HG, Williams DR: The role of stress in breast cancer incidence: risk factors, interventions, and directions for the future. Int J Environ Res Public Health 18(4): 1871, 2021. DOI: 10.3390/ijerph18041871
27 Ollonen P, Lehtonen J, Eskelinen M: Stressful and adverse life experiences in patients with breast symptoms; a prospective case–control study in Kuopio, Finland. Anticancer Res 25(1B): 531-536, 2005.
28 Ollonen P, Lehtonen J, Eskelinen M: Anxiety, depression and the history of psychiatric symptoms in patients with breast disease: a prospective case–control study in Kuopio, Finland. Anticancer Res 25(3C): 2527-2533, 2005.
29 Ollonen P, Lehtonen J, Eskelinen M: Coping and defending as risk factors for breast cancer in patients with breast disease: a prospective case–control study in Kuopio, Finland. Anticancer Res 25(6C): 4623-4630, 2005.
30 Ollonen P, Eskelinen M: Idealization as risk factor for breast cancer in patients with breast disease: a prospective case–control study in Kuopio, Finland. Anticancer Res 27(3B): 1625-1630, 2007.
31 Boyle P: SEARCH programme of the international agency for research on cancer. Eur J Cancer 26(5): 547-549, 1990. DOI: 10.1016/0277-5379(90)90069-6
32 Wirsching M, Stierlin H, Hoffmann F, Weber G, Wirsching B: Psychological identification of breast cancer patients before biopsy. J Psychosom Res 26(1): 1-10, 1982. DOI: 10.1016/0022-3999(82)90057-5
33 Wirsching M, Hoffmann F, Stierlin H, Weber G, Wirsching B: Prebioptic psychological characteristics of breast cancer patients. Psychother Psychosom 43(2): 69-76, 1985. DOI: 10.1159/000287862
34 Eskelinen M, Ollonen P: Psychosocial risk scale (PRS) for breast cancer in patients with breast disease: a prospective case-control study in Kuopio, Finland. Anticancer Res 29(11): 4765-4770, 2009.
35 Sifneos PE: Alexithymia: past and present. Am J Psychiatry 153(7 Suppl): 137-142, 1996. DOI: 10.1176/ajp.153.7.137
36 Eskelinen M, Ollonen P: Sifneos alexithymia questionnaire in assessment of general alexithymia in patients with breast disease and breast cancer: a prospective case-control study in Finland. Anticancer Res 31(9): 3101-3106, 2011.
37 Eskelinen M, Koskela R, Selander T, Kaarniranta K, Ollonen P, Eskelinen M: An investigation of alexithymia personality features *versus* outcome: a prospective 25-year follow-up study in women with breast cancer symptoms. Anticancer Res 45(11): 5085-5094, 2025. DOI: 10.21873/anticanres.17849
38 Forsén A: Psychosocial stress as a risk for breast cancer. Psychother Psychosom 55(2-4): 176-185, 1991. DOI: 10.1159/000288427
39 Eskelinen M, Ollonen P: Forsen psychological risk inventory for breast cancer patients: a prospective case-control study with special reference to the use of psychiatric medications. Anticancer Res 31(2): 739-744, 2011.
40 Eskelinen M, Koskela R, Selander T, Kaarniranta K, Ollonen P, Eskelinen M: Psychological stress *versus* outcome in patients with breast disease and breast cancer: a prospective 25-year follow-up study in patients with breast cancer symptoms. Anticancer Res 45(9): 3817-3826, 2025. DOI: 10.21873/anticanres.17741
41 Eskelinen M, Ollonen P: Beck Depression Inventory (BDI) in patients with breast disease and breast cancer: a prospective case–control study. In Vivo 25(1): 111-116, 2011.
42 Eskelinen M, Korhonen R, Selander T, Ollonen P: The relation of hopelessness/helplessness *versus* Beck Depression Inventory (BDI) in healthy individuals and in patients with benign breast disease and breast cancer: a prospective case-control study in Finland. Anticancer Res 35(2): 941-947, 2015.
43 Eskelinen M, Korhonen R, Selander T, Ollonen P: Beck depression inventory as a predictor of long-term outcome among patients admitted to the breast cancer diagnosis unit: a 25-year cohort study in Finland. Anticancer Res 37(2): 819-824, 2017. DOI: 10.21873/anticanres.11383
44 Eskelinen M, Ollonen P: Montgomery-Asberg depression rating scale (MADRS) in healthy study subjects, in patients with breast disease and breast cancer: a prospective case–control study. Anticancer Res 31(3): 1065-1069, 2011.
45 Eskelinen M, Korhonen R, Selander T, Ollonen P: Agreement between hopelessness/helplessness *versus* Montgomery-Asberg depression rating scale (MADRS) in healthy individuals and in patients with benign breast disease and

breast cancer: a prospective case-control study in Finland. Anticancer Res 35(4): 2215-2221, 2015.
46 Eskelinen M, Selander T, Ollonen P, Korhonen R: Moderate/severe depression (MADRS) can affect the quality of life and outcome among patients admitted to breast cancer diagnosis unit. Anticancer Res 37(5): 2641-2647, 2017. DOI: 10.21873/anticanres.11611
47 Eskelinen M, Ollonen P: Assessment of general anxiety in patients with breast disease and breast cancer using the Spielberger STAI self-evaluation test: a prospective case–control study in Finland. Anticancer Res 31(5): 1801-1806, 2011.
48 Eskelinen M, Koskela R, Selander T, Kaarniranta K, Ollonen P, Eskelinen M: The impact of State-trait Anxiety Inventory (STAI) self-evaluation *versus* 25-year outcome: a prospective follow-up study in patients with breast cancer symptoms. Anticancer Res 45(5): 2161-2169, 2025. DOI: 10.21873/anticanres.17590
49 Luengo-Fernandez R, Leal J, Gray A, Sullivan R: Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol 14(12): 1165-1174, 2013. DOI: 10.1016/S1470-2045(13)70442-X
50 GBD 2023 Cancer Collaborators: The global, regional, and national burden of cancer, 1990-2023, with forecasts to 2050: a systematic analysis for the Global Burden of Disease Study 2023. Lancet 406(10512): 1565-1586, 2025. DOI: 10.1016/S0140-6736(25)01635-6
51 Iwakura M, Nagashima K, Shimizu K, Tanihara S, Terata K, Yamazaki T, Jung S, Kimura T, Terauchi M, Nomura K: Resignation in working women with breast and gynecologic cancers. JAMA Netw Open 8(8): e2528844, 2025. DOI: 10.1001/jamanetworkopen.2025.28844
52 Vancoppenolle J, Franzen N, Azarang L, Juslin T, Krini M, Lubbers T, Mattson J, Mayeur D, Menezes R, Schmitt J, Scotte F, Seoane López O, Skaali T, Ubels J, Schlander M, Retel V, van Harten WH, OECI Working Group Health Economics: Financial toxicity and socioeconomic impact of cancer in Europe. ESMO Open 10(6): 105293, 2025. DOI: 10.1016/j.esmoop.2025.105293
53 Chen CC, David AS, Nunnerley H, Michell M, Dawson JL, Berry H, Dobbs J, Fahy T: Adverse life events and breast cancer: case-control study. BMJ 311(7019): 1527-1530, 1995. DOI: 10.1136/bmj.311.7019.1527
54 Kruk J: Self-reported psychological stress and the risk of breast cancer: A case-control study. Stress 15(2): 162-171, 2012. DOI: 10.3109/10253890.2011.606340
55 Moayedi-Nia S, Dutczak H, Richardson L, Siemiatycki J, Koushik A: Stressful life events, perceived degree of stress, and the risk of lung cancer. Prev Med Rep 59: 103250, 2025. DOI: 10.1016/j.pmedr.2025.103250