Depressive Symptoms in Women with Breast Cancer:

What predicts depressive symptoms, and how do levels of depressive symptoms change from initiation of, during and after radiation therapy treatment?

Guro Lindviksmoen

Master's thesis
Department of Health Sciences
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This thesis was written as part of my master's degree at Department of Health Sciences, Faculty of Medicine, University of Oslo. In addition to giving new perspectives on health care and research, this education contributed in combining the knowledge and experience I have gained from working as a nurse with cancer patients clinically, and in a research study.

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Preface

This master's thesis consists of an article and a bibliography. The article discusses the research questions, and is modeled after the author guidelines of the journal Cancer Nursing. It is currently in the process of review, and does not represent the final version. The bibliography describes the previous research on the topic and background of the study more thorough, and in addition, it describes and discusses the initial analyses that were performed. Furthermore, the bibliography contains a discussion of the methods, including choice of research design, instrument, and data analysis approach. In order to avoid unnecessary redundancy, the article is placed at the beginning of the thesis, and will be referred to as "the article" later in the thesis.

Abstract

Background: Women with breast cancer undergoing radiation therapy (RT) are at increased risk for depressive symptoms. However, few previous studies evaluated for changes in - and predictors of depressive symptoms in these patients.

Purpose: To estimate the prevalence of depressive symptoms in Norwegian breast cancer patients, evaluate changes in depressive symptoms from the initiation of, during and after RT, and examine whether specific demographic, clinical, symptom, and psychological adjustment characteristics predicted levels of depressive symptoms.

Method: A total of 184 breast cancer patients completed the Center for Epidemiologic Studies - Depression Scale (CES-D) that evaluated depressive symptoms prior to and approximately 1, 2, 3, and 6 months after the initiation of RT, as well as measures of demographic, clinical, symptom, and psychological adjustment characteristics. Independent samples t-test, Analysis of Variance (ANOVA) and Hierarchical linear modeling (HLM) were used to examine change in depressive symptoms, and what predicted depressive symptoms.

Results: Approximately 1/4 of patients had clinically meaningful levels of depressive symptoms prior to RT, but the levels of depressive symptoms decreased over time. Women with less education, children living at home, a higher level of sleep disturbance, worry about disease outcome, who experienced less meaning in life, and less support from family and friends had higher levels of depressive symptoms prior to RT. In addition, women who received hormonal therapy during the study period, and women who were on sick leave or disability benefit had higher levels of depressive symptoms 6 months after initiation of RT.

Conclusion: This study showed that a substantial proportion of women with breast cancer experience depressive symptoms prior to, during, and after RT, and specific demographic, clinical, symptom, and psychological adjustment characteristics identified women at higher risk for depressive symptoms.

Sammendrag

Bakgrunn: Kvinner med brystkreft som gjennomgår strålebehandling har økt risiko for å utvikle depressive symptomer. Likevel har få studier undersøkt endringer i depressive symptomer, og hva som predikerer depressive symptomer hos disse pasientene.

Hensikt: Å estimere utbredelse av depressive symptomer hos norske brystkreftpasienter, undersøke hvordan depressive symptomer endres fra oppstart av, under og etter strålebehandling, og å undersøke om utvalgte demografiske, kliniske, symptomspesifikke og psykologiske variabler predikerer nivået av depressive symptomer.

Metode: Totalt 184 brystkreftpasienter fylte ut spørreskjemaet Center for Epidemiologic Studies – Depression Scale (CES-D), som estimerte nivå av depressive symptomer før, og 1, 2, 3 og 6 måneder etter oppstart av strålebehandling, i tillegg til ulike demografiske, kliniske, symptomspesifikke og psykologiske spørreskjema. ”Independent samples t-test”, ”Analysis of Variance” (ANOVA) og ”Hierarchical linear modeling” (HLM) ble brukt for å undersøke forskningsspørsmålene.

Resultater: Omtrent en fjerdedel av pasientene hadde et klinisk signifikant nivå av depressive symptomer før oppstart av strålebehandling, men nivåene sank over tid. Kvinner med lavere utdanning, hjemmeboende barn, søvnforstyrrelser, bekymring over utfallet av sykdommen, mindre følelse av mening i livet og mindre støtte fra familie og venner hadde høyere nivå av depressive symptomer før oppstart av strålebehandling. I tillegg hadde kvinner som fikk hormonbehandling i studieperioden, og kvinner som var sykemeldt eller uføretrygdet, høyere nivå av depressive symptomer 6 måneder etter oppstart av strålebehandling.

Konklusjon: Studien viste at en betydelig andel av kvinner med brystkreft som gjennomgår strålebehandling opplever depressive symptomer, og at utvalgte demografiske, kliniske, symptomspesifikke og psykologiske variabler predikerte depressive symptomer.

Article

Predictors of initial levels and trajectories of depressive symptoms in women with breast cancer undergoing radiation therapy

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ABSTRACT

BACKGROUND: Women with breast cancer undergoing radiation therapy (RT) are at increased risk for depressive symptoms. However, only 4 studies evaluated for changes in - and predictors of depressive symptoms in these patients.

OBJECTIVE: This study evaluated for changes in depressive symptoms from the initiation of and through 6 months following RT, and investigated whether specific demographic, clinical, symptom, and psychological adjustment characteristics predicted initial levels and trajectories of depressive symptoms.

METHODS: A total of 184 women with breast cancer completed the Center for Epidemiologic Studies - Depression Scale (CES-D) that evaluated depressive symptoms prior to and approximately 1, 2, 3, and 6 months after the initiation of RT. Hierarchical linear modeling (HLM) was used for these analyses.

RESULTS: Approximately 1/4 of patients had clinically meaningful levels of depressive symptoms prior to RT, but the trajectory of depressive symptoms improved over time. Women with less education, children living at home, a higher level of sleep disturbance, worry about disease outcome, less meaning in life, and less support from family and friends had higher levels of depressive symptoms prior to RT.

CONCLUSIONS: A substantial proportion of women experience depressive symptoms prior to, during, and after RT, and specific demographic, clinical, symptom and psychological adjustment characteristics identified women at higher risk for depressive symptoms.

IMPLICATIONS FOR PRACTICE: Nurses could use knowledge of the predictors to identify patients at risk for depressive symptoms, and in addition, to educate patients about how depressive symptoms may change during and following RT for breast cancer.

KEY WORDS: breast cancer; depressive symptoms; radiation therapy; hierarchical linear modeling; symptom trajectories

INTRODUCTION

Depending on specific disease characteristics, patients with breast cancer receive single or combination treatments. Many of these women will undergo radiation therapy (RT) following breast cancer surgery. While the occurrence of depressive symptoms is four times higher in cancer patients than in the general population,[1] patients with breast cancer report higher levels of depressive symptoms than most other cancer diagnoses.[1] Estimates of depressive symptoms in these women range from 15% to 30%,[2] but may vary between 1% to 50%.[3] Depression is associated with reduced quality of life (QOL),[1, 4] reduced adherence with treatment,[1, 2] and may decrease survival.[1, 2]

In a recent review,[5] Stiegelis and colleagues summarized findings from several studies that investigated psychological functioning in cancer patients who received RT. While results are inconsistent, depressive symptoms were more common during and at the completion of RT, than in the period prior to treatment. In addition, psychological functioning improved following the completion of RT. The authors suggested that these findings provide evidence that depressive symptoms may occur somewhat later in the process of adjustment to cancer and its treatment.

Most longitudinal studies of psychological distress in breast cancer patients use general measures (e.g., the General Health Questionnaire), not designed to measure depressive symptoms specifically. Only 4 longitudinal studies were found that evaluated depressive symptoms in breast cancer patients who underwent RT,[6-10] using either the Hospital Anxiety and Depression Scale (HADS)[11] or the Center for Epidemiologic Studies - Depression Scale (CES-D).[12] Consistent with Stiegelis and colleagues' review,[5] these studies reported higher levels of depressive symptoms during and immediately after RT, followed by a decrease over time.

The aforementioned studies have several limitations, making direct comparisons among them less meaningful. First, different instruments were used to measure depressive symptoms (i.e., HADS[6-8] and CES-D[9]). In addition, all studies used a dichotomous, case-based definition of depressive symptoms. As noted by Henselmans and colleagues,[13] this dichotomization of data limits one's ability to identify subtle differences in distress or depressive symptom profiles. Furthermore, the number and timing of assessments varied from a pre- and post-test design[7] to a 5 year follow-up.[6] In one study,[9] an assessment prior to RT was not done, which limits the possibility to evaluate changes during treatment. Finally, differences in inclusion and exclusion criteria across these studies resulted in more homogeneous[7] versus heterogeneous[6, 8, 9] samples.

In addition to understanding the trajectories of depressive symptoms during and after RT, it is important to determine patient characteristics associated with higher levels of depressive symptoms. In general, younger patients report higher rates of depressive symptoms,[1, 2, 14] which may be associated with a poorer prognosis.[14] In addition, younger women with breast cancer often require adjuvant treatment, which results in premature menopause and alterations in sexual functioning.[2, 14] Greater demands at work or from parenting may make cancer treatment more stressful for younger women.[15] In addition, previous psychiatric illness or depression,[1, 16] poorer socioeconomic status,[1, 4, 16] lower levels of social support,[1, 4] and a lower level of education[1, 16] are risk factors for depressive symptoms.

In terms of clinical characteristics, several studies on depressive symptoms suggest that patients with advanced disease are more likely to report depressive symptoms.[1, 4] In addition, poorer performance status,[1] more severe physical symptoms,[1, 4] and higher levels of disability and physical impairment[1, 4] are associated with higher rates of depressive symptoms. In general, more complex or toxic treatment regimens are predictors of depressive symptoms.[1] Patients who receive chemotherapy (CTX) have a higher risk of depressive symptoms, associated with the onset of premature menopause, as well as other

physical side effects of CTX.[2, 14, 16] Some studies indicate that receiving hormonal therapy increases depressive symptom rates, but the results are inconclusive, and further research is warranted on this matter.[2, 16] Both mastectomy and breast conservative treatment (BCT) are associated with a poorer body image, which may result in depressive symptoms. However, type of surgery is not associated with level of depressive symptoms.[4]

Despite the identification of several risk factors, it is challenging to identify a set of predictors that are consistently linked with depressive symptoms in breast cancer patients, due to the predictors' potential association with specific factors such as treatment type.[17] Most studies that aim to identify predictors of depressive symptoms are cross-sectional[3] and examine different populations of breast cancer patients.[17] Among the 4 studies of depressive symptoms in breast cancer patients receiving RT,[6-9] several predictors associated with demographic, clinical, and treatment characteristics were evaluated. Except for one study,[8] where fatigue was assessed, none of these studies evaluated the impact of physical symptoms on depressive symptoms. In addition, none of these studies examined the impact of physical functioning (e.g., comorbidities and performance status) on patients' levels of depressive symptoms.

The aforementioned limitations underscore the need for additional research on changes in depressive symptoms before, during and after RT in breast cancer patients. In order to provide information regarding the unique patterns of depressive symptoms, instruments specific for depressive symptoms (e.g., CES-D) can be used. Furthermore, newer methods of longitudinal data analysis (e.g., hierarchical linear modeling (HLM)) can be used to identify predictors of initial levels and trajectories of depressive symptoms while taking into account the variability that exists both among individuals and at different time points.[18, 19] Therefore, the purposes of this study were to evaluate how levels of depressive symptoms changed from prior to the initiation of RT to 6 months after enrollment and to investigate whether

specific demographic, clinical, symptom, and psychological adjustment characteristics predicted the initial levels and/or characteristics of the trajectories of depressive symptoms.

METHODS

PATIENTS AND SETTINGS

This study is part of a larger, longitudinal study of symptoms and QOL in oncology patients and their family caregivers. Patients (n=184) were included if they were adults (≥18 years of age); able to read, write and understand Norwegian; and were scheduled to receive curative RT for breast cancer or ductal carcinoma in situ (DCIS). Patients were excluded if they were to receive RT to the brain or had a disease that affected their cognitive ability. The majority of patients received a total of 50 Grey over a period of 5 weeks. Patients were recruited at the RT Department of Oslo University Hospital, Norwegian Radium Hospital (NRH). The study was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Directorate of Health, the privacy ombudsman at the hospital, and the institutional review board at NRH.

STUDY PROCEDURES

At the time of their first appointment in the RT Department (approximately 8 days prior to the start of RT), patients were introduced to a member of the research team and provided with information about the study. After obtaining written, informed consent, patients completed a number of self-report questionnaires to obtain information on demographic and clinical characteristics, important life changes, as well as several symptom specific- and QOL instruments, including the Karnofsky Performance Status (KPS) scale,[20, 21] the Self-administered Comorbidity Questionnaire (SCQ-19),[22] the CES-D,[12] the General Sleep Disturbance Scale (GSDS),[23] the Lee Fatigue Scale (LFS),[24] the Brief Pain Inventory (BPI),[25, 26] and the Multidimensional Quality of Life Scale - Cancer (MQOLS-CA).[27] Patients

completed these questionnaires again at approximately 1, 2, 3, and 6 months after enrollment.

INSTRUMENTS

Demographic characteristics

Patients provided information on marital status, living situation, level of education, and employment status. Study nurses completed information on age.

Clinical characteristics

Stage of disease and types of previous treatments were obtained from the medical record. Previous cancer treatments were categorized as surgery, CTX, RT, hormonal therapy, and immunotherapy. Based on the patients' TNM classification at the time of diagnosis, stage of disease was reclassified into 5 stages (0=DCIS to 4=advanced stage disease) using the TNM Classification of Malignant Tumors used by the Union for International Cancer Control (UICC) guidelines.[28, 29]

KPS score

Physical functioning was assessed using the KPS score, which can range from 0 (death) to 100 (the individual is able to carry on with normal activities).[20] As patients in the present study were outpatients, the 40- to 100-point range of the scale was used. The KPS scale is used extensively and has well-established validity and reliability.[21, 30]

SCQ-19

The SCQ-19 evaluated the number of, treatments for, and functional impact of health problems. It includes 16 common co-morbidities and 3 optional conditions. Using the SCQ-19, patients were asked to indicate whether they had the co-morbid condition (yes/no); if they had the condition, they were asked if they receive treatment for it (yes/no); and finally if it

limited their activities (yes/no). The total SCQ-19 score can range from 0 to 57 when the 3 optional items are used. A higher total score indicates a more severe co-morbidity profile.[22] The SCQ-19 is a clinical scale, with established validity and reliability for the assessment of co-morbidities in patients with chronic medical conditions.[22] In this study, the total number of co-morbidities (0 to 19) was used in the statistical analysis.

CES-D

The 20-item CES-D assessed current depressive symptomatology. Patients rate how often they experienced symptoms over the past week. Item scores range from 0 to 3 and a total score can range from 0 to 60. A score of ≥16 suggests clinically meaningful depressive symptoms. While the CES-D was developed for use in the general population,[12] it has established validity and reliability for use in patients with breast cancer.[31] In this study, its Cronbach's alpha was 0.86.

GSDS

Sleep disturbance was assessed using GSDS, which consists of 21 items that evaluate various aspects of sleep disturbance. Each item is rated from 0 (never) to 7 (everyday) and describes the frequency of its occurrence during the past week. The 21 items are summed to yield a total score, that ranges from 0 (no disturbance) to 147 (extreme sleep disturbance). Higher total score indicates a higher level of sleep disturbance, and a GSDS total score of ≥43 indicates a significant level of sleep disturbance.[23] The GSDS was used with cancer patients,[32, 33] and has well-established validity and reliability.[23, 34] In this study, its Cronbach's alpha was 0.87.

LFS

Fatigue severity was assessed using the fatigue subscale from the LFS, which consists of 13 of the scale's 18 items. Each item was rated on a 0 to 10 numeric rating scale (NRS).

Patients were asked to rate each item based on how they feel “right now”. The fatigue subscale score was calculated as the mean of the 13 items, with higher scores indicating higher levels of fatigue severity.[24] The LFS has well-established validity and reliability with healthy individuals[24] as well as with cancer patients.[35] In this study, its Cronbach’s alpha was 0.96.

BPI

Pain was evaluated using the worst pain scale from the BPI that ranged from 0 (no pain) to 10 (excruciating pain).[25, 26] A descriptive NRS is a valid and reliable measure of pain intensity.[36]

MQOLS-CA

QOL was assessed using the MQOLS-CA, which consists of 33 items that evaluate five dimensions of QOL (i.e., psychological well-being, physical well-being, nutrition, symptom distress, interpersonal well-being). Patients rated each item using a 0 to 10 NRS. A total QOL score is calculated as the mean of the 33 items, where higher scores indicate better QOL.[27] The MQOLS-CA has well-established construct validity and test-retest reliability.[27, 37-39] Cronbach’s alpha for the total QOL score was 0.92.

In this study, specific items from the MQOLS-CA were chosen based on the review of the literature on predictors of depressive symptoms in breast cancer patients.[1, 4] These items were used to evaluate the impact of various psychological adjustment characteristics on initial levels as well as the trajectories of depressive symptoms. The items were “Are you worried about the outcome of your disease?” (0 = never worried, 10 = always worried), “Does life have meaning to you?” (0 = no meaning, 10 = much meaning), and “Do you receive enough emotional support from your family and friends?” (0 = not enough or too much support, 10 = right amount of support). These characteristics are not commonly assessed in breast cancer patients. However, when the MQOLS-CA scale was developed, they were

found to be important factors associated with psychological well-being, the most important construct in determining QOL.[27, 37]

Instruments were translated into Norwegian using a standard forward-backward translation procedure.[40] The CES-D was originally translated for use in an epidemiological study.[41] The SCQ-19 was used in two previous studies in Norway.[42, 43]

THEORETICAL FRAMEWORK

The Theory of Symptom Management (TSM), served as the theoretical framework for this study. It was first introduced by faculty members at the University of California, San Francisco (UCSF) School of Nursing in 1994,[44] and has undergone several revisions.[45] It consists of three essential components: symptom experience, symptom management strategies, and symptom status outcomes. This study focused on the symptom experience, defined as a simultaneous perception, evaluation, and response to a change in one's usual feeling.[45]

DATA ANALYSIS

Descriptive statistics and frequency distributions were generated on the sample characteristics and baseline symptom severity scores using SPSS version 19 (SPSS Inc., Chicago, Illinois). For each of the 5 assessments, a mean CES-D score was calculated for use in the subsequent statistical analyses.

HLM, based on full maximum likelihood estimation, was done using the software developed by Raudenbush and colleagues.[18, 19] Compared with other methods for analyzing change, HLM has two major advantages. First, it can accommodate unbalanced designs, which allows for the analysis of data when the number and spacing of assessments vary across respondents. Second, HLM has the ability to model individual change which helps to identify more complex patterns of change that often are overlooked by other methods.

With HLM, repeated measures of the outcome variable (i.e., depressive symptoms) are conceptualized as being nested within individuals, and the analysis of change in depressive symptom scores is at two levels: within persons (level 1) and between persons (level 2). At level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters plus error. At level 2, the person-specific change parameters are multivariate outcomes that vary across individuals. Level 2 outcomes can be modeled as a function of demographic or clinical characteristics that vary between individuals, plus an error associated with the individual. Combining level 1 with level 2 results in a mixed model with fixed and random effects.[18]

A HLM analysis was done to evaluate for changes over time in ratings of depressive symptoms. During stage 1, intra-individual variability in depressive symptoms over time was examined. Three level 1 models were compared to determine whether the patients' depressive symptoms did not change over time (i.e., no time effect), changed at a constant rate (i.e., linear time effect), or changed at a rate that accelerated or decelerated over time (i.e., quadratic effect). At this point, the level 2 model was constrained to be unconditional (i.e., no predictors) and likelihood ratio tests were used to determine the best model.

The second stage of the HLM analysis examined inter-individual differences in the trajectories of depressive symptoms by modeling the individual change parameters (i.e., intercept and linear slope) as a function of proposed predictors at level 2. Table 1 presents a list of the proposed predictors that was developed based on a review of the literature on depressive symptoms in women with breast cancer.[1, 2, 4, 14-16] To improve estimation efficiency and construct a model that is parsimonious, exploratory level 2 analyses were completed in which each potential predictor was assessed to determine whether it would result in a better model if it alone was added as a level 2 predictor. Predictors with a *t*-value of less than 2, which indicates a lack of significant effect, were dropped from subsequent model testing. All potential significant predictors from the exploratory analyses were entered into the model to

predict each individual change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other variables were retained in the final model. A *p*-value of < .05 indicates statistical significance.

Table 1 Potential Predictors of the Intercept (I) and Linear Coefficient (LC) for Depressive Symptoms using Baseline Characteristics

Characteristics	I	LC
Demographics		
Age		
Marital status		
Living situation		
Having children living at home	x	
Education level	x	
Employment status		
Clinical		
Karnofsky Performance Status Score	x	
Number of comorbidities	x	
Neoadjuvant CTX		
Type of breast cancer surgery		x
Type of lymph node surgery	x	
Symptom		
Worst pain		
Sleep disturbance	x	
Fatigue	x	
Psychological adjustment		
Worry about disease outcome	x	x
Sense of meaning in life	x	
Support from family and friends	x	

Note: Potential predictors that had a *t*-value of $\leq$ 2 in the exploratory analysis are indicated with an "x"

RESULTS

PATIENT CHARACTERISTICS AND SYMPTOM SEVERITY SCORES

A total of 245 patients were approached, 85% consented to participate, and 88% (n=184) of these patients completed the questionnaires prior to RT. As shown in Table 2, the majority of the sample was married or partnered (73.9%), had a secondary level of education (46.7%), a mean KPS score of 88.2 (SD 11.7), and had on average 1.8 comorbidities (SD 1.5). The most common comorbidities were neck/back pain (35.9%) and high blood pressure (22.3%).

Table 2 Demographic, Clinical, Symptom and Psychological Adjustment Characteristics of Patients (n=184) at Baseline

Characteristic		Mean (SD)	Range
Age (years)		57.9 (9.1)	27/81
		n	%
Ethnicity	White	182	98.9
	Asian	2	1.1
Marital status	Married/partnered	136	73.9
	Unmarried/divorced/widowed	48	26.1
Lives alone	Yes	33	17.9
	No	151	82.1
Children living at home	Yes	49	26.6
	No	135	73.4
Education level	Primary	36	19.6
	Secondary	86	46.7
	College/university	62	33.7
Employment status	Full/part time	15	8.2
	Sick leave/disability benefit	129	70.1
	Retired/other	40	21.7
Stage of disease	0	17	9.6
	1	69	39.0
	2	66	37.3
	3	25	14.1
Previous treatment	BCT	124	67.4
	Mastectomy	67	36.4
	SLNB	141	76.6
	ALND	93	50.5
	Chemotherapy	83	45.1
Reason for current treatment	Primary breast cancer	180	97.8
	Recurrence	4	2.2
Current treatment	RT breast	96	52.2
	RT breast and lymph nodes	88	47.8
	Hormonal therapy	103	56.0
	Immunotherapy	14	7.6
		Mean	SD
Clinical characteristics	KPS score	88.2	11.7
	Number of comorbidities	1.8	1.5
Symptom severity scores	Sleep disturbance	46.9	22.0
	Fatigue	2.7	2.2
	Worst pain	1.6	2.3
Psychological adjustment characteristics	Worry about disease outcome	4.3	2.9
	Sense of meaning in life	9.1	1.6
	Support from family and friends	8.9	2.0

Abbreviations: ALND, axillary lymph node dissection; BCT,breast conservative treatment; KPS, karnofsky performance scale; SLNB, sentinel lymph node biopsy

Seventy-eight percent of the patients who enrolled (n=184) completed all of the questionnaires. Except for age, no significant differences were found in any demographic or clinical characteristics between those who did and did not complete all of the questionnaires. Those patients who completed all of the questionnaires were significantly older (mean age 59.1 years [SD 8.8]; p = < .001) than those who did not (mean age 53.5 years [SD 8.7]).

INDIVIDUAL AND MEAN CHANGE IN DEPRESSIVE SYMPTOMS

The first stage of the HLM analyses examined how depressive symptoms changed from prior to RT to 6 months after enrollment. Two models were estimated in which the individual function of time was linear and quadratic. The linear model and slope was significant (p = .002). The quadratic component of the slope of the quadratic model was not significant (p = .860). The goodness-of-fit tests of the deviance between the linear and the quadratic models indicated that the quadratic model did not significantly improve the fit to the data over the linear model (p = .170).

Table 3 presents the estimates of the linear change model (unconditional model). Because the model had no covariates (i.e., unconditional), the intercept represents the estimated levels of depressive symptoms (10.468 on a 0 to 60 scale) prior to RT. The estimated linear rate of change in depressive symptoms for each assessment was -0.286 (p = .002).

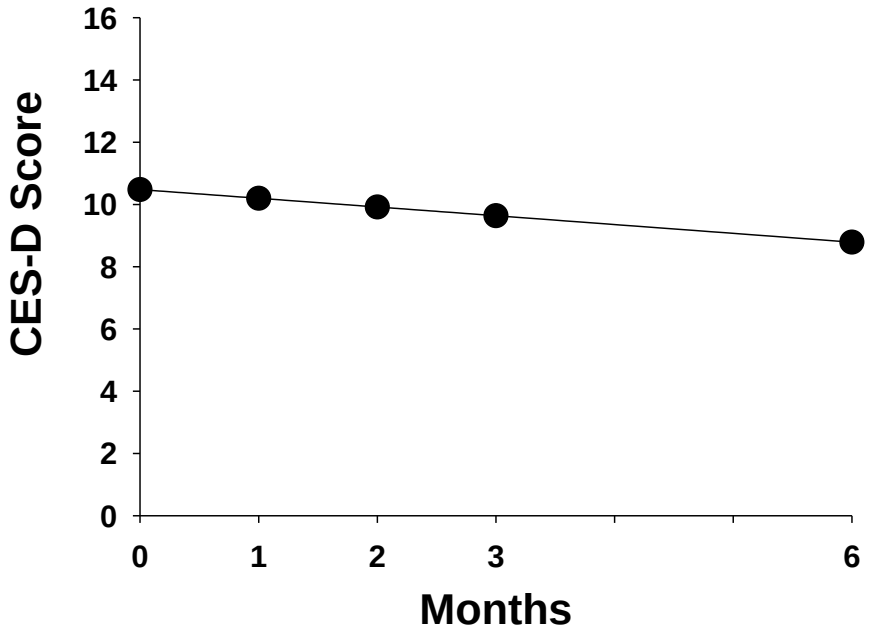
Table 3 Hierarchical Linear Modeling of Depressive symptoms

	Coefficient (SE)					
Variable	Unconditional Model			Final Model		
Depressive symptoms						
Fixed Effects						
Intercept:	10. 467950	(0.583)	***	11.395	(0.662)	***
Time [a] (linear rate of change)	-0.286	(0.092)	**	-0.836	(0.278)	**
Time invariant covariates						
Intercept:						
Children living at home				1.782	(0.760)	*
Education level				-1.214	(0.462)	**
Worry about disease outcome				0.809	(0.140)	***
Sense of meaning in life				-1.559	(0.240)	***
Support from family and friends				-0.776	(0.186)	***
Sleep disturbance at baseline				0.103	(0.016)	***
Linear:						
Worry about disease outcome x time				-0.071	(0.032)	*
Type of surgery x time				0.338	(0.164)	*
Variance component						
In Intercept		53.248	***		17.013	***
In linear rate		0.504	***		0.429	***
Goodness-of-fit deviance		5327.327 (6)			5127.523 (14)	
Model comparison (χ^2)					199.804 (8)	***

Note: [a] Time was coded zero at the visit prior to RT.
* $p < .05$; ** $p < .01$; *** $p < .001$

Figure 1 presents the trajectory for depressive symptoms, which decreased over the course of the 6 months to a CES-D score of 8.787. It should be noted that the mean scores depicted in the figures are estimated or predicted means based on the HLM analysis. Prior to RT and 6 months after initiation, 23.8% and 17.5% of the patients, respectively, scored above the cut-off of ≥16 on the CES-D.

Figure 1 Trajectory of depressive symptoms measured with the Center for Epidemiologic Studies – Depression scale from initiation of radiation therapy to 6 months after enrollment



INTER-INDIVIDUAL DIFFERENCES IN THE TRAJECTORIES OF DEPRESSIVE SYMPTOMS

The second stage of the HLM analyses tested whether the pattern of change in depressive symptoms over time varied based on specific demographic, clinical, symptom, and/or psychological adjustment characteristics that were found to influence levels of depressive symptoms in women with breast cancer.[1, 2, 4, 14-16] Exploratory analyses were done with the predictors listed in Table 1. To improve estimation efficiency and construct a model that was parsimonious, exploratory level 2 analyses were done in which each potential predictor with a *t*-value $\leq$ 2.0 was assessed to see if it would result in a better fitting model if it alone was added as a level 2 predictor. All of the significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final model.

As shown in the final model in Table 3, the variables that predicted inter-individual differences in the intercept for depressive symptoms were: education level, having children living at home, level of sleep disturbance, worry about disease outcome, sense of meaning in life, and amount of support from family and friends. The variables that predicted inter-individual differences in the linear slope for depressive symptoms were: type of breast cancer surgery and worry about disease outcome.

To illustrate the effects of these predictors on patients' initial levels and trajectories of depressive symptoms, Figures 2 a and b and 3 a, b, c, and d display the adjusted change curves for depressive symptoms that were estimated based on differences in demographic characteristics (i.e., education level primary, secondary or college/university; 2a, children living at home or not; 2b), level of sleep disturbance (i.e., higher/lower levels of sleep disturbance calculated based on 1 SD above and below the mean GSDS total score; 3a), worry about disease outcome (i.e., less/more worry calculated based on 1 SD above and below the mean score of MQOLS-CA item 11; 3b), sense of meaning in life (i.e., low/high level of sense of meaning calculated based on 1 SD above and below the mean score of MQOLS-CA item 31; 3c) and amount of support from family and friends (i.e., low/high level of support calculated based on 1 SD above and below the mean score of MQOLS-CA item 32; 3d). Figures 2c and 3b display the adjusted change curves for depressive symptoms based on predictors of the linear slope parameters (i.e., type of breast cancer surgery, and worry about disease outcome; respectively).

Figure 2 Influence of education level (a), having children living at home (b), and type of breast cancer surgery (c) on inter-individual differences in the intercept and slope parameters of depressive symptoms

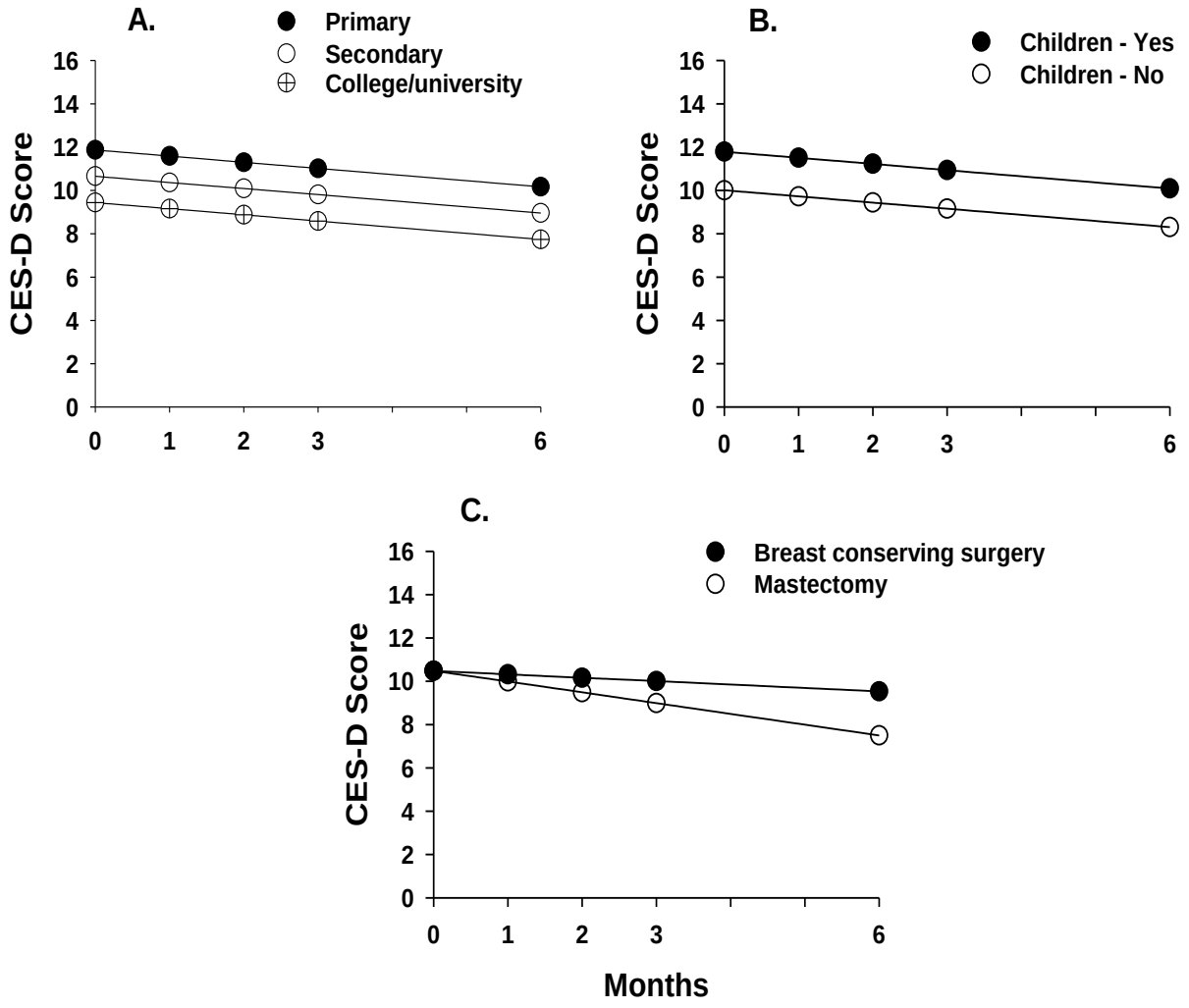
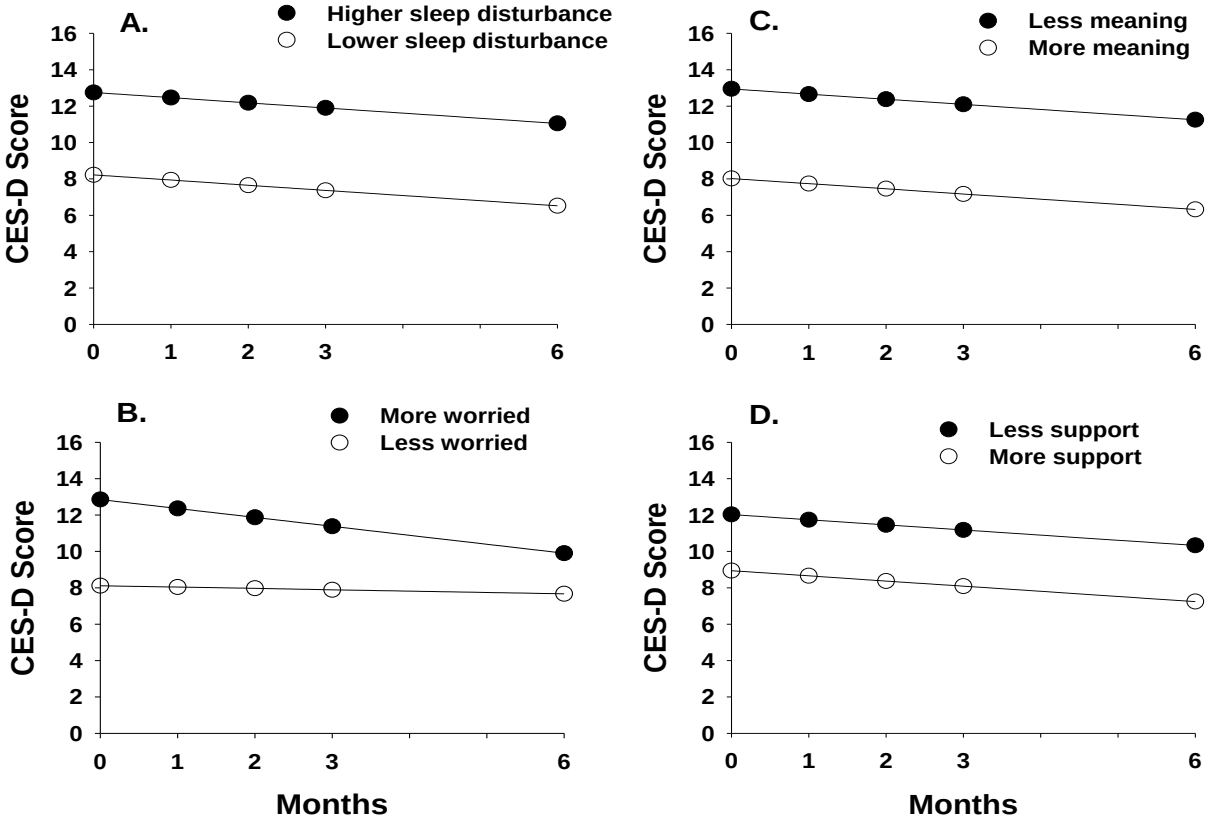


Figure 3 Influence of sleep disturbance (a), worry about disease outcome (b), sense of meaning in life (c), and amount of support from family and friends (d) on inter-individual differences in the intercept and slope parameters of depressive symptoms



DISCUSSION

This study is the first to use HLM to examine individual trajectories of depressive symptoms prior to and for 6 months following RT for breast cancer, and to investigate whether select demographic, clinical, symptom, and psychological adjustment characteristics predicted the initial levels and/or the trajectories of depressive symptoms over the study period. Consistent with previous research,[6-9] women with breast cancer experience higher levels of depressive symptoms prior to and during RT, which decline following the completion of RT.

Prior to RT, the mean CES-D score for this Norwegian sample of breast cancer patients was 10.5. This score, as well as the 6 month CES-D score of 8.8, are well below the cut-off of ≥16

that suggests clinically meaningful levels of depressive symptoms. The mean CES-D scores in this study are slightly lower than those of 12.9 to 9.9 reported in a study that assessed women with breast cancer at the end of RT and for 6 months following RT.[9] In addition, these CES-D scores are slightly lower than those reported in one,[3] but similar to those reported in another[15] study of breast cancer patients receiving a variety of cancer treatments. Furthermore, the mean CES-D scores are similar to those reported in a study of the general population in the United States.[12] Finally, the percentage of patients scoring above the cut-off of ≥16 in this study is similar to findings of a study of middle-aged and older people in the general population in Norway,[41] where 22.9% of women scored above the cut-off.

As this study is the first to use CES-D to assess depressive symptoms in Norwegian women with breast cancer, it is interesting that scores are generally lower than those reported by breast cancer patients in the United States.[3, 9, 15] A national health care and welfare system that provides patients with adequate care and enables them to receive sick leave benefits, as well as the higher socioeconomic standards in Norway, may decrease women's level of concerns regarding the impact of their disease on other aspects of their life which results in a decrease in levels of depressive symptoms. In addition, the sample in this study, as well as the Norwegian population, is relatively homogenous in terms of ethnicity, which has been associated with lower levels of depressive symptoms.[4, 17]

Level of sleep disturbance (Figure 3a) and worry about disease outcome (Figure 3b) were the two predictors that had the largest impact on initial levels of depressive symptoms. Consistent with previous research,[17] higher levels of sleep disturbance were associated with higher levels of depressive symptoms. Patients in this study reported a mean GSDS score of 46.9, above the cut-off of ≥43 indicating clinically meaningful levels of sleep disturbance, and slightly lower than the mean of 53.8 reported in a cross-sectional study of sleep disturbance in breast cancer patients prior to RT.[32]

While worry about disease outcome was not assessed in previous studies of patients with breast cancer receiving RT,[6-9] a number of studies have found that worry about cancer recurrence is common[15] and an important source of distress for these women.[15, 46] In addition, worry may be considered a proxy for anxiety,[27] a common symptom in breast cancer patients.[47] For example, in a study that assessed depressive symptoms and anxiety using categorical scoring of the HADS (i.e., normal, borderline, case) prior to and for 5 years following RT,[6] 9.4% of patients had co-existing anxiety and depression prior to RT, and 90% of anxious women reported no concurrent depression throughout the study. However, compared to women with anxiety scores in the normal range, borderline or case anxiety scores prior to RT significantly increased the risk for higher depression scores ($p < .001$). Findings from this study[6] are consistent with the current study in that worry about disease outcome, as a proxy for anxiety, predicted initial levels as well as the trajectory of depressive symptoms. As shown in Figure 3b, patients with higher levels of worry at the initiation of RT would have a steeper decrease in depressive symptoms over time. Some sources of worry (e.g., worry about side effects or impact of treatment) may naturally resolve during RT. Consistent with this hypothesis, the prevalence of anxiety is generally reported to be highest at the initiation of RT and decrease during and after RT.[5]

Consistent with previous research,[1, 4] lower levels of social support were associated with higher levels of depressive symptoms at the initiation of RT. In addition, the patients' sense of meaning in life predicted the initial level of depressive symptoms. This predictor was not assessed specifically in previous studies of patients with breast cancer receiving RT. However, meaning in life was found to be heightened through physical and emotional suffering and when facing mortality.[48] In addition, higher levels of psychological distress were reported by breast cancer patients who reported less meaning in life.[48]

An interesting finding is that having children living at home was associated with higher levels of depressive symptoms at the initiation of RT. This finding is consistent with a previous

study that assessed patterns of depressive symptoms after RT[10] and found that the group of patients who reported increasing levels of depressive symptoms had more children living at home. These authors suggested that this finding is consistent with previous research that found that younger breast cancer patients reported higher levels of psychological distress than older patients, if having children living at home is considered a correlate with age. However, in this study,[10] as well as in the current study, age was not associated with depressive symptoms.

Consistent with previous research,[4, 6] type of breast cancer surgery did not predict initial levels of depressive symptoms. However, in this study it did predict the trajectory of depressive symptoms. As shown in Figure 2c, patients who had a mastectomy were estimated to have a steeper decrease in depressive symptoms, compared to those who had BCT. Because this study is the first to examine this predictor among breast cancer patients who received RT, potential explanations for this finding are hypothetical. For example, psychological factors may influence the trajectory of depressive symptoms, in that women who had a mastectomy may be less concerned about disease recurrence.

Patients with a lower level of education reported higher levels of depressive symptoms at the initiation of RT, consistent with previous research on breast cancer patients in general,[1, 16] as well as a study investigating breast cancer patients who received RT.[6]

LIMITATIONS

Limitations of this study include the relatively small sample size, the inclusion of women with only curative treatment intent, and the relatively high level of physical functioning. Therefore, these findings cannot be generalized to breast cancer patients with advanced and metastatic disease, or women with impaired physical functioning. In addition, most women were white, married, and had a secondary level of education or higher, and therefore, these findings cannot be generalized to women from other ethnic groups or with different socioeconomic

status. Furthermore, considering the impact of worry about disease outcome on both initial levels and trajectories of depressive symptoms, having used a specific instrument to measure anxiety might have contributed more to the understanding of the relationship between these two symptoms.

IMPLICATIONS FOR PRACTICE

In this study, 23.8% of women had CES-D scores that suggested clinically meaningful levels of depressive symptoms prior to RT. Women with a lower education level, children living at home, a higher level of sleep disturbance, higher level of worry about disease outcome, less sense of meaning in life, and a lower amount of support from family and friends had higher levels of depressive symptoms prior to RT. In addition, women who had a mastectomy, compared to those who had BCT, and women with a higher level of worry about disease outcome, compared to lower, had a steeper decrease in depressive symptoms throughout the study. An evaluation of depressive symptoms before RT, as well as knowledge of these predictors, may help clinicians identify women at higher risk for experiencing depressive symptoms, who may need targeted intervention. In addition, nurses can use this knowledge to educate patients about how depressive symptoms may change during and following RT for breast cancer.

IMPLICATIONS FOR RESEARCH

Additional longitudinal studies are needed to confirm these results. In addition, given their impact on depressive symptoms in this study, psychological adjustment characteristics that are not frequently evaluated need further examination. Finally, considering that a substantial number of patients had clinically meaningful levels of depressive symptoms prior to RT, future studies can develop and test the efficacy of pre-treatment interventions that are targeted at modifiable risk factors (e.g., anxiety, sleep disturbance).

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Abbreviations

ANOVA – Analysis of Variance

BCT – Breast Conservative Treatment

BSI - Brief Symptom Inventory

CES-D - Center for Epidemiologic Studies – Depression scale

CTX – Chemotherapy

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders

HADS – Hospital Anxiety and Depression Scale

HLM – Hierarchical Linear Modeling

MAR – Missing at random

NRH – Norwegian Radium Hospital

RSCL - Rotterdam Symptom Checklist

RT – Radiation therapy

TSM - The Theory of Symptom Management

QOL – Quality of Life

1 INTRODUCTION

The topic of this master's thesis is depressive symptoms in women with breast cancer who receive radiation therapy (RT). My interest in this topic is first and foremost due to experience from working with breast cancer patients as a nurse for several years. Furthermore, I have worked as a research nurse on a study of quality of life (QOL) and symptoms in cancer patients and their caregivers, the 2008_Cluster study, which made me interested in research in general, and in quantitative research methods in particular. Data material on breast cancer patients from the 2008_Cluster study is examined in this thesis.

There is a substantial amount of previous research on breast cancer patients' experience of depressive symptoms. In general, they are among the cancer patients that report the highest rates of depressive symptoms. Several characteristics that are associated with depressive symptoms in breast cancer patients have been identified, contributing to the understanding of depressive symptoms in these women in particular. However, there were only a few longitudinal studies that examined depressive symptoms in breast cancer patients undergoing RT specifically, and several limitations to these studies were acknowledged. Therefore, I found that there were still interesting research questions to examine. Hopefully, findings from this thesis can contribute further to clinicians' knowledge of how depressive symptoms can change through the RT treatment period, and what predicts depressive symptoms in these women.

1.1 Purpose

The aim of this thesis was to examine depressive symptoms in breast cancer patients who underwent RT, and it consisted of 3 research questions. The first was an estimation of the prevalence of depressive symptoms in Norwegian women with breast cancer who receive RT; the second was an evaluation of change in depressive symptoms over time in these

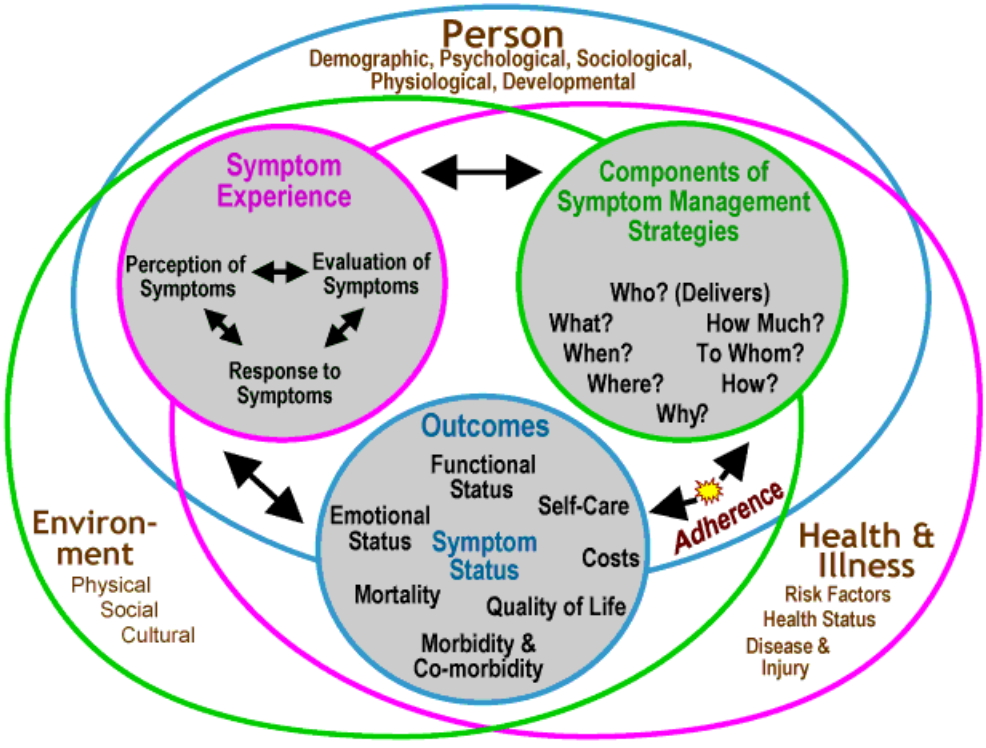
patients, and the third was further examination of predictors that are associated with depressive symptoms in these patients. While the research questions are discussed in the article as well as in the bibliography, the purpose of the bibliography also included a more thorough introduction of the topic of depressive symptoms in breast cancer patients, and the previous research on the topic. Furthermore, the purpose was a presentation and discussion of the initial analyses that were chosen to explore the data material, and to complement the analysis presented in the article. Finally, the bibliography discusses the research methods, including the study design, instrument, and data analysis approach, that were chosen.

2 BACKGROUND

2.1 Theoretical framework

The Theory of Symptom Management (TSM), shown in Figure 1, served as theoretical framework for this thesis. It was first introduced by faculty members at the University of California, San Francisco (UCSF) School of Nursing in 1994,[1] and has undergone several revisions.[2] A symptom is defined as "*a subjective experience reflecting changes in the biopsychosocial functioning, sensations, or cognition of an individual*"[2] (p.145). The TSM consists of three essential components; symptom experience, symptom management strategies and symptom status outcomes, the bidirectional arrows in Figure 1 are meant to indicate a simultaneous interaction among all three concepts.[2]

Figure 1 The Theory of Symptom Management model
Reprinted with permission M. Dodd et.al.[3]



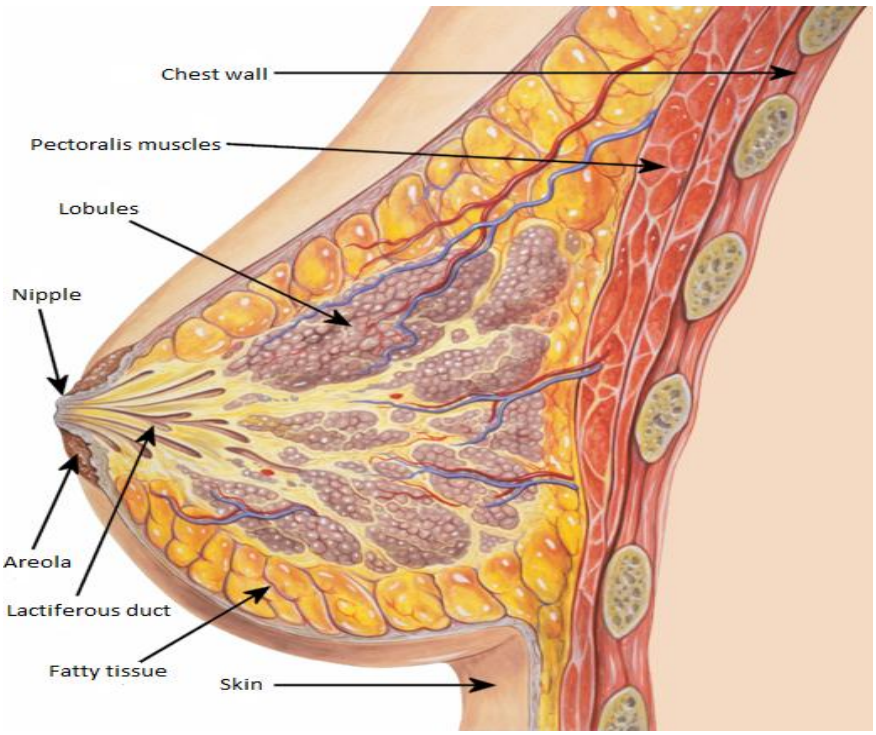
The concepts are framed within the dimensions of nursing science; person, environment and health/illness, to serve as a reminder of the contextual considerations for nursing research.[2] This thesis focused on the symptom experience, defined as a simultaneous perception, evaluation, and response to a change in one's usual feeling, and symptom status outcomes, which are clear and measurable outcomes to assess following an implementation (e.g., treatment), and includes change in symptom status (i.e., frequency, intensity, severity).[2] The ultimate goal of this research is to enhance the knowledge about the last component, symptom management strategies, which are efforts to avert, delay or minimize the symptom experience.[2] Application of the TSM can function as a contribution to better help patients that are experiencing symptoms in relation to their disease or treatment.

2.2 Breast cancer

Breast cancer is the most common malignancy among women worldwide,[4] about 1.1 million women are diagnosed with breast cancer every year.[5] Breast cancer usually originates from the cells of the lobules, the milk-producing glands, or the ducts, the passages that drain milk from the lobules to the nipple. Less commonly, breast cancer can originate from the stromal tissues, which include the fatty and fibrous connective tissues of the breast.[6] Breast cancer which is detected in the breast only, is categorized as local. Cancer cells can invade nearby healthy breast tissue and the underarm lymph nodes, which is categorized as locoregional disease. Local and locoregional breast cancer is treated with curative intent. Cancer cells can also spread lymphogenous or hematogenous to other parts of the body, categorized as distant metastasis, in which situation the disease is treated palliative.[7] The breast cancer's stage from 0 to 4 refers to the dispersion of the disease, and is dependent on the TNM-classification, which is a characterization of the patients' tumor (T), node (N) and metastasis (M).[6, 8] Breast cancer patients are treated with multiple treatment modalities, such as surgery, chemotherapy (CTX), RT, hormonal therapy and immunotherapy, each resulting in a unique set of symptoms,[9-11] such as depressive symptoms.

Figure 2 Anatomy of the breast

Adapted from P. J. Lynch, C. C. Jaffe.[12]



2.3 Radiation therapy

RT is an effective treatment modality used to cure cancer, as well as alleviate symptoms of the disease, and it is utilized alone, and in combination with other treatment modalities.[13] RT is ionizing radiation that initiates the process that leads to cancer cells' death. Normal cells have a higher tolerance for radiation than do cancer cells, and is therefore better able to repair the damage done by the radiation. By dividing the radiation into smaller doses that are given daily, this effect is magnified, and allows for time for normal tissue to repair between treatments.[13] Cancer patients receive RT as primary or adjuvant treatment, and about 45% of patients require RT.[14] Breast cancer patients receive curative, adjuvant RT for different reasons. Both patients who are operated with breast conservative treatment (BCT) (i.e., surgical removal of the tumor only), and those who are operated with a mastectomy (i.e., surgical removal of all breast tissue) where there is not a microscopically negative margin (i.e., close margin between tumor and normal tissue) receive RT towards the breast or chest

wall in order to reduce the risk of recurrence due to remaining cancer cells. In addition, a number of women in whom axillary lymph node metastases are diagnosed, receive RT towards this area.[15]

2.4 Depressive symptoms

The term depression has a variety of meanings, and is commonly used to describe emotions and behaviors, ranging from sadness, following for instance being diagnosed with cancer, to major depressive illness.[16] In literature on depression in medically ill patients, there are several definitions or conceptualizations, often associated with despair, hopelessness, lack of compliance, social isolation and premature mortality.[17] There are four different concepts frequently used; mood (i.e., predominant emotion), symptom, syndrome (i.e., groups of symptoms) and psychiatric illness.[18] The term depressive symptoms is often used to describe varying degrees of depressed feelings, or indicates that a patient experiences one or more symptoms associated with depression, without necessarily having a clinical diagnosis of depression.[17] Examples of symptoms associated with depression are depressed mood, insomnia, fatigue, feelings of worthlessness and diminished ability to think, all of which are symptoms which cancer patients often experience when diagnosed. However, the presence of depressive symptoms can be differentiated from clinical depression; when diagnosed with clinical depression, patients must have been experiencing several of the symptoms over a period lasting longer than two weeks.[16, 19, 20] Feelings of sadness, shock, anger and fear, all normal when receiving a cancer diagnose, typically resolve within a few weeks, all though these feelings often return.[20] In literature on depression in cancer patients, the terms depressive symptoms and depression are both used, while in this thesis, the term depressive symptoms is used.

2.4.1 Measuring depressive symptoms

Research show that depressive symptoms in cancer patients are under-recognized and thus under-treated,[16, 20] perhaps in part due to lack of a single screening tool to serve as a gold standard.[4, 20] Other barriers to diagnosing depressive symptoms is difficulty distinguishing between depressive symptoms and normal sadness, myth that all cancer patients are depressed, misconception that depressive symptoms are a normal part of the disease process, depressive symptoms often resemble physical symptoms of cancer or treatment, patients failure to disclose psychological symptoms, clinicians fear of exploring psychological symptoms, and lack of time.[20]

There is no common understanding on how to classify and measure depressive symptoms, and there are two major systems for measuring; criteria-based systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),[21] and self-report rating scales.[17] Rating scales commonly used with cancer patients include the Hospital Anxiety and Depression Scale (HADS),[22] the Rotterdam Symptom Checklist (RSCL),[23] the Beck Depression Inventory,[24, 25] the Brief Symptom Inventory (BSI) Depression Scale,[26, 27] the Zung Self-Rating Depression Scale,[28, 29] and the Center for Epidemiologic Studies - Depression Scale (CES-D).[30] While criteria-based systems often are used in structured interviews to assess for a clinical depression diagnosis, rating scales are primarily used as a screening tool, or as a means of quantifying the severity of depressive symptoms, and the definition of depression is reliant on a certain score on a rating scale.[17] Estimates based on screening tools are generally higher and more variable than those based on structured interviews.[4] High rates are associated with a decrease in specificity occurring when sensitivity increases.[30] In the current study, depressive symptoms are measured with the rating scale instrument CES-D.

2.4.2 Prevalence of depressive symptoms

Cancer patients in general have an increased risk of experiencing depressive symptoms; the rates of depressive symptoms among cancer patients are estimated to be four times that of the general population.[20] At the same time, prevalence of depressive symptoms in cancer patients is likely to be underestimated.[4, 16, 20, 31] Depressive symptoms are more prevalent in women than men in the general population, but in cancer patients, the rates are similar.[20] Nevertheless, breast cancer patients consist almost exclusively of women, and are among the diagnostic groups that report the highest rates of depressive symptoms.[20] Most estimates of depressive symptoms in breast cancer patients range from 15% to 30%,[4] but vary within 1% to 50%.[32] Variable rates can be explained by different screening tools, various stages of cancer studied and heterogeneous samples, for instance in- and outpatients.[20] Prevalence of a clinical depression diagnosis is generally lower, but is also likely to be underestimated; it is estimated around 5% to 15% for breast cancer patients.[4]

2.4.3 Predictors of depressive symptoms

There are several risk factors for developing depressive symptoms in breast cancer patients. The risk is highest in the first year after diagnosis.[4] In general, younger breast cancer patients report higher rates of depressive symptoms.[4, 20, 33] A diagnosis of cancer may be more of a profound shock to a younger patient than an older one, in part due to social, vocational and economic factors.[33] Greater demands in the areas of work or parenting may also make cancer treatment more stressful for younger women.[34] It may also be associated with the fact that younger breast cancer patients overall tend to have a poorer prognosis, suggesting a more aggressive disease, than older patients.[33] Younger women often require adjuvant treatment, which leads to premature menopause and alterations in sexual functioning.[4, 33, 35] In addition, previous psychiatric illness or depression,[20, 35] poorer

socioeconomic status,[20, 31, 35] lower levels of social support,[20, 31] and a lower level of education[20, 35] are risk factors for depressive symptoms.

In terms of clinical characteristics, several studies found that disease stage and severity also predicts depressive symptoms; e.g., that patients with an advanced stage of disease report higher rates,[20, 31, 36] though one study found evidence was lacking for a strong association.[4] In addition, poorer performance status,[20] more severe physical symptoms,[20, 31] and higher levels of disability and physical impairment[20, 31] are all associated with depressive symptoms. Depending on disease characteristics, such as stage of disease, patients receive at least one type, and often a combination, of treatment modalities for breast cancer. In general, complex or toxic treatment regimens are predictors of depression.[20] Patients who receive CTX have a higher risk of depressive symptoms, associated with the onset of premature menopause, as well as other physical side effects of chemotherapy.[4, 33, 35] Some studies indicate that receiving hormonal therapy increase rates of depressive symptoms, but the results are inconclusive.[4, 35] Both mastectomy and BCT are associated with a lower body image, which may result in depressive symptoms. However, type of surgery does not seem to affect levels of depressive symptoms.[31]

2.4.4 Effects of depressive symptoms

In a global perspective, depressive symptoms have several negative consequences, and is one of the leading causes of disability, loss of productivity and premature death.[19] For cancer patients, depressive symptoms are frequently associated with a decrease in their QOL, as well as in overall perceived state of health.[36] They can increase length of hospital stay,[37] and influence acceptance of and adherence with adjuvant therapy,[20, 31] which may in turn affect disease outcome and mortality.[4, 20] They can also influence the severity and number of side effects of cancer treatment, in addition to increasing the burden of fatigue, anxiety and sleep disturbances,[4] all common symptoms in breast cancer patients.[22, 38, 39] There is also a strong association between depressive symptoms and pain.[4] Depressive symptoms in women with

breast cancer and estrogen deficiency is associated with significant cognitive and functional impairment.[4] In addition, depressive symptoms have a negative impact on patients' caregivers and families. In fact, untreated depressive symptoms in cancer patients may cause higher rates of depressive symptoms in family members.[4]

2.5 Depressive symptoms in patients undergoing radiation therapy

There are several studies investigating psychological functioning, including depressive symptoms, in cancer patients undergoing RT, summed up in a review by Stiegelis and colleagues.[14] While results are inconsistent, a general trend was that depressive symptoms were more common during and at completion of RT, than in the period prior to RT. Furthermore, psychological functioning improved following the completion of RT. The authors suggest that these findings provide evidence that depressive symptoms may occur somewhat later in the process of adjustment to cancer and its treatment.

Fifteen longitudinal studies were found that evaluated psychological distress in breast cancer patients in which some or all patients underwent RT.[11, 21, 32, 34, 40-51] Most found a pattern similar to that in Stiegelis and colleagues' review,[14] with a higher level of distress or depressive symptoms during and immediately after RT, followed by a decrease. However, most of these studies use general measures (e.g., the General Health Questionnaire) and not instruments specifically evaluating depressive symptoms (e.g., HADS and CES-D), resulting in differences in outcome measures, i.e., QOL, psychological distress and depressive symptoms. In addition, several of the studies examine heterogeneous samples, i.e., patients with different cancer diagnosis,[44] and patients receiving multiple treatment modalities.[21, 32, 34, 45-48]

Only 4 studies [40-43] evaluated depressive symptoms in breast cancer patients receiving RT specifically. Deshields and colleagues[43] evaluated depressive symptoms using CES-D at the end of RT and 6 months forward. Hopwood and colleagues[40] evaluated depressive symptoms using HADS prior to RT and 5 years forward. Kawase and colleagues[41] evaluated depressive symptoms using HADS prior to and after completion of RT. Noal and colleagues[42] also evaluated depressive symptoms using HADS prior to, during and at completion of RT, though it should be noted that this study focused on fatigue as a main outcome.

2.5.1 Limitations to previous research

The aforementioned studies have several limitations, making direct comparisons among them less meaningful. There are different instruments used to measure depressive symptoms (i.e., HADS[40-42] and CES-D[43]). In addition, all studies used a dichotomous, case-based definition of depressive symptoms. As noted by Henselmans and colleagues,[48] this dichotomization of data may have affected the ability to identify subtle differences in distress or depressive symptom profiles, because using a cut-off point may exaggerate small differences between respondents and create variability that is not representative of the sample. In addition, the number and timing of assessments varied from a pre- and post-test design[41] to a 5 year follow-up,[40] and assessment intervals varied from a few weeks to several months. For instance, one study[40] had no assessment between initiation of RT and 6 months after treatment. Another study[43] had no assessment prior to RT, which limits the possibility to evaluate changes during treatment. Finally, there were differences in inclusion and exclusion criteria, e.g., one study[41] only evaluated patients with stage 1 and 2 disease.

In addition to methodological limitations, there are also limitations regarding research on predictors of depressive symptoms in breast cancer patients. It is challenging to identify a set of predictors that are consistently linked with depressive symptoms in breast cancer patients, due to the predictors' potential association with specific factors such as treatment type.[52] The 4 studies of depressive symptoms in women undergoing RT have examined the impact of

several of the most commonly identified demographic, clinical and treatment predictors of depressive symptoms. However, except for one study[42] where fatigue is measured, they have not evaluated the impact of physical symptoms and physical functioning on depressive symptoms.

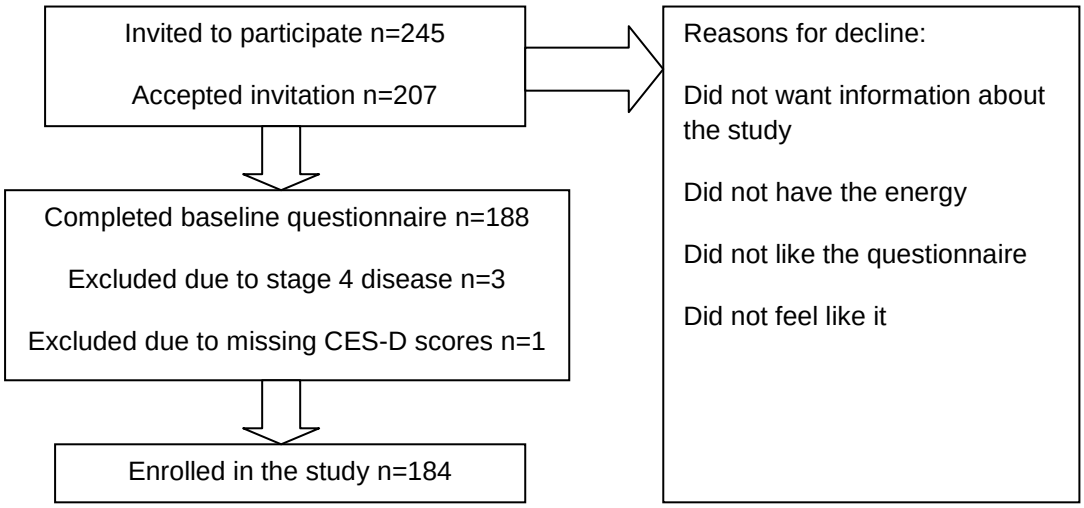
3 METHODS

3.1 Study design

This longitudinal, prospective, observational study of women with breast cancer undergoing RT was part of a larger study of symptoms and QOL in cancer patients and their caregivers at the Norwegian Radium Hospital (NRH), lasting from December 2008 to June 2011. The current study consists of 184 breast cancer patients who were scheduled to receive curative RT. The study was approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Directorate of Health, the privacy ombudsman at the hospital, and the institutional review board at NRH.

Patients are often vulnerable and in a dependent relationship to health care providers that may make them feel obligated to participate in research studies. All potential participants were therefore first asked by a hospital staff nurse if they were interested in receiving information about the study from study personnel, giving them the opportunity to decline information to someone not directly involved in the study. Patients that accepted the invitation received written and verbal information about the study objectives, methods and sources of funding, as well as potential benefits and discomfort. They were also informed specifically about their right to decline participation, and, if they accepted, their right to withdraw from the study without explanation at any time during the study period. Age was recorded for patients who declined, in order to examine potential differences that may have influenced results. Patients who declined were not asked specifically about the reason, but it was recorded where one was given, shown in Figure 3, and the most common reasons were that they didn’t like the questionnaire or didn’t have the energy.

Figure 3 Flowchart of all eligible patients



3.2 Measurement of depressive symptoms

The CES-D consists of 20 items that evaluate current depressive symptomatology. The items are selected from previously validated depression scales.[53] It is one of the most widely used self-report instruments to measure current depressive symptomatology and to identify possible cases of depressive disorders, both in the general population and in cancer patients.[18] The 20 CES-D items are symptoms associated with depression, and are distributed on six major components. The components of depressive symptomatology were identified from the clinical literature and factor analytic studies, and are: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. Patients rate how often they experienced symptoms over the past week, the responses are; rarely or none of the time (less than 1 day), some or little of the time (1-2 days), occasionally or a moderate amount of time (3-4 days) and most or all of the time (5-7 days). Each item scores from 0 to 3 on a scale of frequency or occurrence. The total score range from 0 to 60, where a score of $\geq$16 suggests

clinically meaningful levels of depressive symptoms. Some studies have found that a cut-off of ≥16 leads to cases of false positives.[17, 54] The established score norm for adults, based on a sample of 2514 healthy persons (59% women) between 18 to 65 years old, is 9.25.[53]

It is possible to create 4 CES-D subscales that are based on factor analysis; somatic, depressed affect, positive affect, and interpersonal problems.[53] Because symptoms of depression may be confounded with symptoms of disease or side effects of treatment, measures of depressive symptoms that include somatic items, as does the CES-D, may overestimate the prevalence of depressive symptoms.[43] Therefore, the CES-D may be a more valid measure of depressive symptoms if removing the somatic subscale items, but van Wilgen and colleagues[55] concluded evidence for this was not confirmed. However, the CES-D focuses primarily on cognitive and affective, rather than physical, components of depression,[37] and because the subscales are all dimensions of depression, Radloff[18] recommends the use of the total score.

The CES-D was developed for use in the general population, and has demonstrated acceptable test-retest stability, excellent concurrent validity, substantial evidence of construct validity and high internal consistency with a Cronbach's alpha coefficient of 0.85.[53] It has established validity and reliability in a sample of breast cancer patients, with a Cronbach's alpha of 0.89.[37] In the current study, Cronbach's alpha ranged between 0.85-0.90. The CES-D was originally translated into Norwegian for use in an epidemiological study.[56]

3.3 Data analyses

Descriptive statistics and frequency distributions were calculated for the sample characteristics, in addition to the CES-D scores on all 5 assessments. All analyses were performed using SPSS version 19. *P*-values were considered statistically significant at the < .05 level.

3.3.1 Missing data

Calculation of a CES-D total score is originally dependent on the patient answering all 20 items of the CES-D, referred to as the complete case approach.[57] In the current study, 60% of the patients answered all items on all assessments, leaving 40% of the sample with one or more missing total scores. These patients score on average 1.9 points higher than those with a complete set of total scores, a significant difference on the baseline assessment (p = .023), but not on the other assessments. One common method of handling missing data is by use of imputation, which is an estimation of the missing values based on valid values of other variables and/or cases in the sample.[57] There are several procedures of imputation, divided into single (e.g., item-mean, person-mean, worst/best value)[57] and multiple imputation (i.e., repeated draws from a model of the distribution of the variable with missing values, to create a number of complete datasets).[58] With both techniques, data must be missing at random (MAR),[57] which means that the chance of a missing value is not related to the unobserved response values.[59] In order to conduct the analyses with as many patients included as possible, total scores were calculated for patients' that had answered at least 80% of the items on a questionnaire using the single imputation procedure referred to as person-mean (i.e., missing items are substituted with the mean of the items that the patient have answered). This resulted in an increase in the proportion of total scores to 90%.

3.3.2 Initial analyses

In the initial analyses, Independent samples t-test and Analysis of Variance (ANOVA) were used to test for differences in depressive symptoms scores between patients with different demographic, clinical and treatment characteristics, on the baseline and 6 month assessments. The two assessments were chosen because they were done at times when side effects of RT were expected to have little impact on the CES-D scores, and they were expected to yield the largest difference in CES-D scores. In addition, the 6 month

assessment was chosen in order to examine potential differences in levels of depressive symptoms between patients who received different treatments (i.e., hormonal therapy, immunotherapy, radiation target). The tests use t and F statistic, respectively, to test whether differences in mean scores between the groups are significant.[60] Results are presented as mean (SD), and significance of the tests are presented with degrees of freedom, t or F ratio, and *p*-value. Both tests assume normally distributed data, but are used even though the distribution, shown in Figure 4 and 5, is somewhat skewed in this sample, since the tests are reasonably tolerant of violations of this assumption, especially with larger samples (i.e., >30).[60]

Figure 4 Distribution curve of CES-D score at baseline

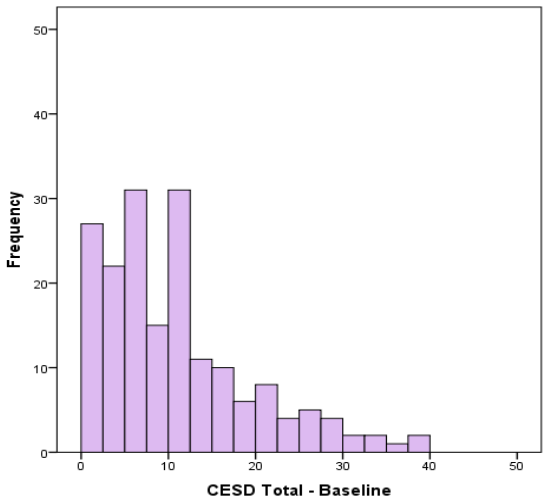
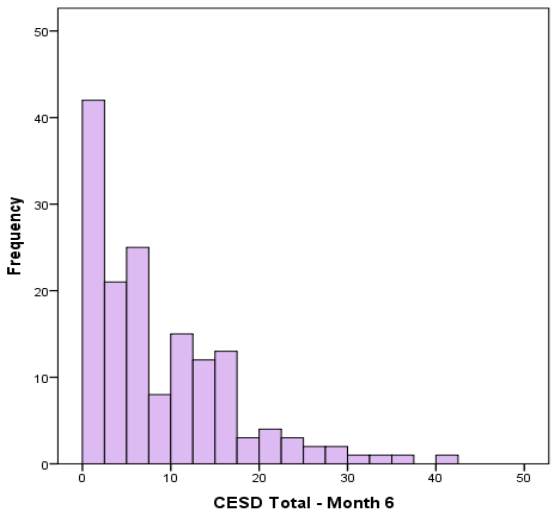


Figure 5 Distribution curve of CES-D score at 6 months



When variables with 3 or more response categories had significant between-group differences ($p < .05$), post hoc analyses were performed. The Tukey HSD method was used to correct *p*-values for multiple testing and to reduce the risk of making type 1 errors (i.e., falsely rejecting the null-hypothesis).[60]

3.3.3 Analysis of change over time

Hierarchical Linear Modeling (HLM) was used to examine intra-individual (i.e., within subjects) and inter-individual (i.e., between subjects) change in depressive symptoms scores over time, as well as possible predictors of depressive symptoms. A correlation matrix was constructed in preparation for the HLM analysis, that revealed that a number of variables were significantly correlated with each other, which resulted in removal of several potential predictor variables. Based on previous research, the initial analyses and the correlation matrix, 17 potential predictor variables were chosen for the HLM analysis. The HLM analysis showed that several demographic, clinical, symptom, and psychological adjustment characteristics predicted the initial levels and trajectories of depressive symptoms, these results are presented and discussed in the article.

4 RESULTS

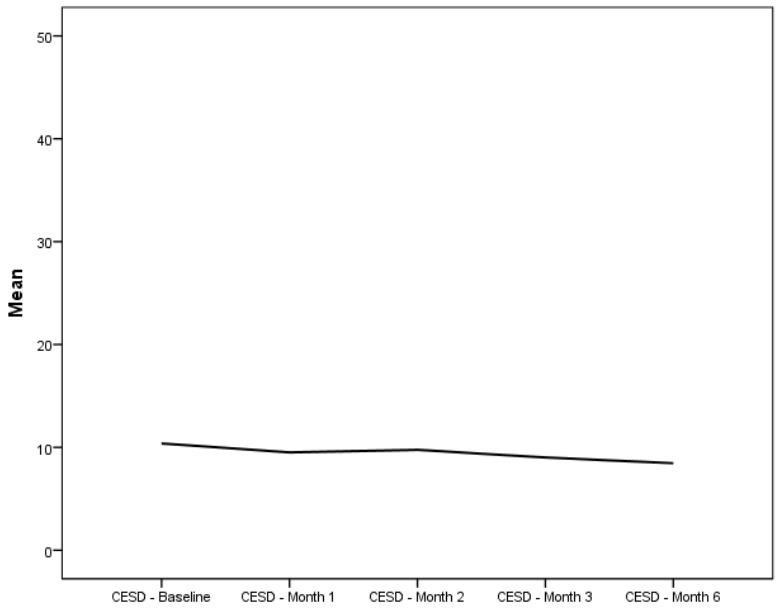
4.1 Levels of depressive symptoms

Consistent with previous research,[40-43] these women with breast cancer experienced higher levels of depressive symptoms prior to and during RT, which declined following the completion of RT. The mean score, shown in Table 1, ranged between 10.63 and 8.51, with the highest score on the baseline assessment, and the lowest score on the last assessment. The mean score is well below the cut-off of ≥16 suggesting clinically meaningful depressive symptoms on all 5 assessments. However, it is noteworthy that on each assessment, a substantial portion of the sample scored above the cut-off. When examining the dichotomous version of the scale, patients with a CES-D score ≥16 at the baseline assessment scored significantly higher on the last assessment (mean 16.79) than patients with a score below the cut-off at baseline (mean 6.17) ($t(38.3) = 5.793$, $p = <0.001$), indicating that some of the patients with initial elevated levels of depressive symptoms continued to have elevated levels.

Table 1 CES-D Total and subscale scores on all assessments

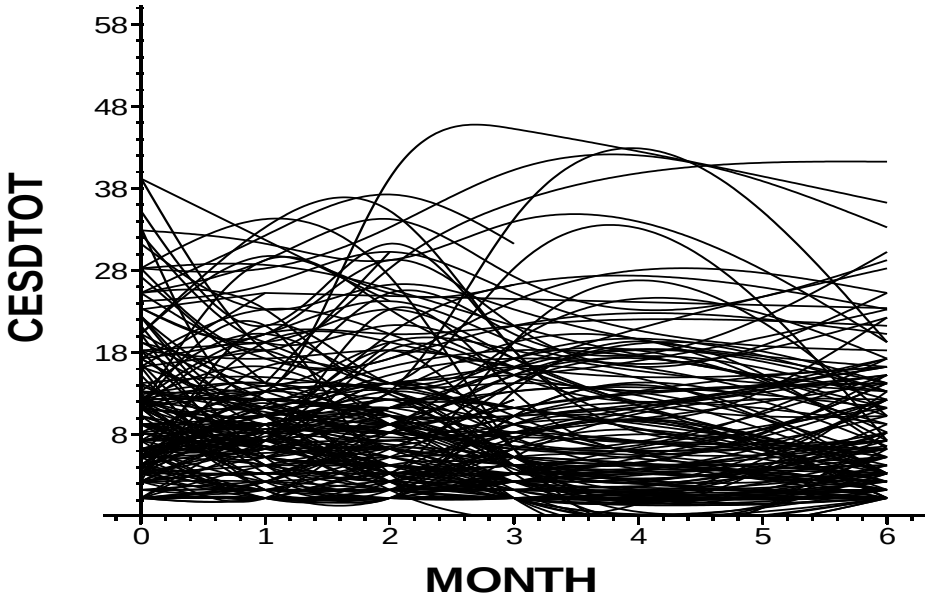
	Baseline (n=181)	1 month (n=171)	2 months (n=167)	3 months (n=161)	6 months (n=154)
Mean [SD]	10.63 [8.54]	9.91 [7.83]	9.97 [8.81]	9.39 [8.85]	8.51 [8.21]
Range	39	34	39	45	41
Score ≥ 16 in %	23.8	19.9	19.8	22.4	17.5
	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]
Somatic	4.29 [3.70]	4.35 [3.38]	4.35 [3.54]	3.78 [3.47]	3.52 [3.43]
Depressed affect	2.94 [3.70]	2.58 [3.38]	2.86 [3.73]	2.73 [3.57]	2.45 [3.36]
Positive affect	8.75 [3.12]	9.12 [3.07]	9.35 [2.94]	9.24 [3.11]	9.52 [2.84]
Interpersonal problems	0.18 [0.66]	0.12 [0.62]	0.14 [0.63]	0.11 [0.53]	0.08 [0.37]

Figure 6 Timeline of mean CES-D total score on all assessments



The decrease in mean CES-D score from baseline and throughout the study, shown in Figure 6, is significant (β = 1.82, t = -3.161, *p* = .002). However, while the mean score depicted in Figure 6 was relatively stable and decreasing, there was a large amount of intra-individual variability in CES-D scores among these women, shown in Figure 7.

Figure 7 Timeline of individual CES-D total scores on all assessments



The CES-D subscale scores, shown in Table 1, also changed throughout the study. The Somatic subscale (β = 0.61, t = -2.48, *p* = .014) and Interpersonal problems subscale (β = 0.11, t = 2.17, *p* = .032) decreased significantly, while the Depressed affect subscale decreased, but not significantly (β = 0.34, t = -1.28, *p* = .202). The Positive affect subscale, which includes 4 positively formulated items, had the opposite pattern, and increased (β = 0.73, t = 2.71, *p* = .008).

4.2 Predictors of depressive symptoms

The Independent samples t-test analysis and the ANOVA were chosen to examine differences in CES-D scores between patients with different demographic, clinical and treatment characteristics, on the baseline and 6 month assessments, shown in Tables 2 and 3. There were differences in depressive symptoms scores between several of the groups where one would expect this based on previous research. However, on the baseline assessment, there was a statistically significant difference only in two comparisons. Patients with a primary level of education had higher levels of depressive symptoms compared to those with college/university education (F (2, 173) = 7.115, *p* = .001). Patients with a secondary level of education did not differ significantly from either of the other groups. In addition, patients who had children living at home had higher levels of depressive symptoms compared to those who had not (t (179) = - 2.331, *p* = .027).

Table 2 Demographic and Clinical differences in CES-D scores prior to Radiation Therapy

Characteristic	Mean	SD	*P*-value
Marital status			0.961
Unmarried/divorced/widowed	10.68	8.57	
Married/partnered	10.61	8.56	
Children living at home			**0.027**
No	9.78	8.10	
Yes	12.96	9.35	
Education level			**0.001**
Primary *	14.60	10.09	
Secondary	10.87	8.12	
College/university *	8.05	7.23	
Employment status			0.334
Full-/part time	7.72	6.44	
Sick leave/disability benefit	10.71	8.45	
Retired/other	11.54	9.35	
Stage of disease			0.153
0	7.01	7.21	
1	9.83	8.06	
2	11.85	8.24	
3	11.18	9.82	
Received previous CTX			0.254
No	9.97	8.21	
Yes	11.43	8.90	
Type of breast surgery			0.161
Mastectomy or mastectomy + BCT	11.82	9.20	
BCT	9.96	8.10	
Type of lymph node surgery			0.098
ALND or ALND + SLNB	11.67	8.99	
SLNB	9.57	7.96	

Abbreviations: ALND, axillary lymph node dissection; BCT, breast conservative treatment; SLNB, sentinel lymph node biopsy
Note: Statistically significant numbers are in bold font. Significant differences marked *

On the last assessment, the difference between the education level groups was still significant (F (2, 148) = 4.644, *p* = .011). However, in this ANOVA comparison, Levene's test was significant (*p* = < 0.001), indicating that the test had violated the assumption of homogeneity of variances, which means that the variability of scores for each of the groups is similar.[60] When checking the Robust tests of Equality of Means, the difference between the groups were both significant (Brown-Forsythe *p* = .035) and borderline significant (Welch *p* = .065). However, as the difference in mean score between the groups was relatively large, the Brown-Forsythe *p*-value was chosen and the result was considered significant. In addition, patients who received hormonal therapy during the study period had higher levels of depressive symptoms compared to those who did not (t (152) = - 2.334, *p* = .021), and patients who were on sick leave or disability benefit had higher levels of depressive symptoms compared to those who were working (F (2, 149) = 5.953, *p* = .003). Patients who were retired did not differ significantly from either of the other groups.

Table 3 Demographic and Clinical differences in CES-D scores after 6 months

Characteristic	Mean	SD	*P*-value
Marital status			0.177
Unmarried/divorced/widowed	10.08	7.58	
Married/partnered	8.01	8.42	
Children living at home			0.099
No	7.75	7.13	
Yes	10.92	10.74	
Education level			**0.035**
Primary *	12.34	12.07	
Secondary	8.16	7.06	
College/university *	6.81	6.29	
Employment status			**0.003**
Full-/part time *	5.83	6.58	
Sick leave/disability benefit *	10.90	9.39	
Retired/other	9.16	7.60	
Stage of disease			0.311
0	5.24	6.93	
1	7.93	8.63	
2	9.72	7.65	
3	7.76	9.38	
Hormonal therapy treatment			**0.021**
No	6.78	7.29	
Yes	9.85	8.67	
Immunotherapy treatment			0.888
No	8.48	8.23	
Yes	8.83	8.32	
Radiation target			0.144
Breast only	7.58	8.18	
Breast and axillary lymph nodes	9.52	8.19	

Note: Statistically significant numbers are in bold font. Significant differences marked *

5 DISCUSSION

5.1 Levels of depressive symptoms

The mean CES-D total score that ranged between 10.63 to 8.51, as well as the number of patients who scored above the cut-off of $\geq$16, are slightly lower than the results from Deshields and colleagues[43] study of depressive symptoms in patients undergoing RT using CES-D; they found a mean score between 12.9 to 9.9, with 23% to 30% of patients scoring above cut-off. It should be noted that this study did not assess depressive symptoms prior to RT. Reasons for these differences may include a higher percentage of patients with higher stage disease, a larger proportion of married women, and of women who were on sick leave in the current study. In addition, CES-D scores in the current study were slightly lower than those reported in one,[32] but similar to those reported in another[34] study of breast cancer patients receiving different treatments.

Among the studies of depressive symptoms in breast cancer patients undergoing RT using HADS, the number of patients who scored above the HADS cut-off indicating depression, were both higher (41.9% to 32.6%)[41] and lower (15.3% to 11.9%).[40] These studies also found a decrease in depressive symptoms scores, though significant only in one.[41] It should be noted that these studies used a case-based definition of depressive symptoms (i.e., cut-off score), the former used a dichotomous definition (i.e., normal, depressed), while the latter used a categorical version (i.e., normal, borderline, case). As previously mentioned, this may have affected the ability to identify subtle differences in depressive symptom profiles. Setting a cut-off limit can be difficult, as a low cut-off score often increases the sensitivity, but decreases specificity, and vice versa.[30] In addition, one of the studies[40] found that patients who were depressed at baseline reported repeated high scores, though only 13% rated as cases on all assessments. In contrast, Deshields and colleagues[43] found that while 23% to

30% scored above the clinically relevant cut-off score, only 6% of the patients were above cut-off on all assessments. This is consistent with the large intra-individual variability in CES-D scores in the current study, depicted in Figure 7, and is also supporting results reported in a number of studies that evaluate depressive symptoms in breast cancer patients using newer methods of statistical analysis that enables the examination of this variability.[32, 46-50] Furthermore, it underlines the need for further analysis of the change in levels of depressive symptoms over time.

5.2 Demographic predictors of depressive symptoms

Employment status was not a predictor of depressive symptoms prior to RT, where most of the women were not working. However, it was a predictor at the last assessment, where the proportion of women who had returned to work was larger (38.6%). More precisely, the difference was significant between those who were working and those who were on sick leave or disability benefit. This may be associated with the level of physical and psychological functioning of the women, those who were capable of returning to work may have had a higher level of physical and psychological functioning compared to those who were not. One other study of women with breast cancer undergoing RT[50] examined this and found no significant differences between groups, but a similar result was found in a study of patients with oral cancer.[61]

An interesting finding is the significant difference in depressive symptoms scores prior to RT between those with children living at home and those without. This is consistent with a previous study that assessed patterns of depressive symptoms after RT[50] and found that the group of patients who reported increasing levels of depressive symptoms had more children living at home. These authors suggested that this finding is consistent with previous research that found that younger breast cancer patients reported higher levels of psychological

distress than older patients, if having children living at home is considered a correlate with age. However, in this study,[50] age was not associated with depressive symptoms.

In contrast to previous research suggesting that poor social support predicts depressive symptoms,[20, 31] marital status was not a significant predictor of depressive symptoms in the current study. It should be noted that in this sample, a large proportion of patients were married or partnered. Evidence of this correlation was also lacking in another study of breast cancer patients undergoing RT.[43]

Consistent with previous research on breast cancer patients in general,[20, 35] as well as one of the studies investigating patients undergoing RT,[40] education level was a significant predictor of depressive symptoms, in that patients with a primary level of education reported higher levels than those with a college/university education.

5.3 Clinical predictors of depressive symptoms

Another interesting finding, in light of the inconsistent results in previous research, is that women who received hormonal therapy reported higher levels of depressive symptoms than those who did not. This is consistent with two other studies on breast cancer patients receiving RT.[40, 43] In contrast, another study[41] found that patients who did not receive hormonal therapy reported higher levels of depressive symptoms before RT, and lower levels after RT, compared to those who did receive hormonal therapy, meaning that the latter had more consistent scores. It should be noted that the number of patients who received hormonal therapy in this study was relatively small (33.1%) compared to the current study (55.7%), and they only assessed depressive symptoms prior to and after completion of RT, limiting the time of follow-up to a few weeks. Furthermore, a comparison of these two groups before initiation of RT might be of less value, due to the probable short duration of hormonal therapy treatment.[62] In the current study, there were significant differences between patients who did and did not receive hormonal therapy in terms of stage of disease (p = <0.001) and

previous CTX treatment (p = <0.001) Patients who received hormonal therapy had a mean stage of disease of 2, and 61.2% had received previous CTX, while patients who did not receive hormonal therapy had a mean stage of disease of 1, and only 24.7% had received previous CTX. These differences in disease severity and previous treatment may have contributed to the difference in levels of depressive symptoms. In addition, considering the physical and psychological side effects of hormonal therapy, it is not unlikely that this treatment does affect the levels of depressive symptoms, but this warrants further research.

In contrast to previous research on breast cancer patients in general, suggesting that patients with more advanced disease report higher levels of depressive symptoms,[20, 31, 36] stage of disease did not predict depressive symptoms in the current study. In addition, previous treatment with CTX did not predict depressive symptoms, also contrasting previous research on women with breast cancer in general.[4, 33, 35] However, similar results were found in all but one[40] of the studies investigating breast cancer patients undergoing RT. Furthermore, type of breast cancer surgery, as well as type of lymph node surgery, did not predict depressive symptoms, consistent with previous research.[31] Finally, neither immunotherapy treatment nor RT target predicted depressive symptoms.

These findings on demographic and clinical predictors of depressive symptoms have contributed with valuable information, considering the lack of previous research on employment status and having children living at home, and the inconsistent results on the effects of hormonal therapy on levels of depressive symptoms. In addition, the findings interestingly contradicted previous studies suggesting that stage of disease and previous CTX are important predictors of depressive symptoms, but supported that education level is a strong predictor of depressive symptoms, and that type of surgery is not. Finally, the findings suggests that receiving immunotherapy treatment, and additional RT towards axillary lymph nodes, does not impact the levels of depressive symptoms.

5.4 Study design

In this study, depressive symptoms were measured in a longitudinal design. Most studies of depressive symptoms in breast cancer patients are cross-sectional.[32] The advantages of cross-sectional studies are that they are cost-effective in terms of time and economy, and easy to administer.[63] However, because the objective in this study was to measure depressive symptoms prior to the initiation of, during, and after RT, and because depressive symptoms often are characterized by change,[17] they were measured in a longitudinal design.

Furthermore, there was a relatively large number of patients that declined participation in the study. In addition, missing data increased throughout the study, as is often the case in longitudinal research studies because of attrition (e.g., loss of subjects).[63] However, considering the fact that the sample size is relatively large compared to previous studies, the sample is considered large enough to draw conclusions that are likely to be representative of the population.

Finally, information about the patients' disease and previous treatment was collected from medical records by study personnel. Different study personnel collected this data, with the possible disadvantage that records may have been interpreted differently, so in order to ensure continuity, medical records were reviewed for control after the study period by one person.

5.5 Measurement of depressive symptoms

A self-administered questionnaire was chosen to measure the outcome in this study. While it is recognized that the best way to identify depressive symptoms is through a structured interview, the challenge is that it is time-consuming and requires skills, and questionnaires may be less expensive.[16] Brief questionnaires may in fact be preferable in cancer patients, especially for those with poor performance status.[20] However, questionnaires may fail

because patients' misunderstand them, get offended by the questions, or dislike how they look.[64] Another concern with self-administered questionnaires is the variability in the environment where patients answer the questionnaires. Answering them in private, for instance at home, is considered an advantage, although patients may be interjected by friends and family, creating biased answers.[64] In addition, while patients in the current study were provided with a phone number to reach study personnel, the opportunity to ask for assistance in for instance interpretation of questions was limited.

The CES-D was chosen to measure depressive symptoms in this study, among several instruments that measure depressive symptoms that are established as valid and reliable. While the CES-D has been used in previous research on the general population in Norway,[56] it does not have an established reference value in the normal population, as does other instruments (e.g., HADS).[65] However, as previously mentioned, it is widely used both in general populations and in cancer patients,[18] and is therefore suitable for comparison to other samples.

Regarding the discussion whether or not to include somatic items in an instrument measuring depressive symptoms, it is worth noting that the somatic subscale score was significantly lower on the last assessment compared to the first, suggesting a decrease in physical symptoms, whether caused by disease, treatment or depressive symptoms. However, the depressed affect and interpersonal problems subscales also decreased towards the end of the study, revealing a positive trend in general. Furthermore, the number of patients who scored above the CES-D cut-off of $\geq$16 is consistent with previous research on depressive symptoms in women with breast cancer, indicating that 15% to 30% of breast cancer patients report depressive symptoms,[4] as well as reports of depressive symptoms in patients undergoing RT.[40-43] This suggests that the construction of the instrument did not contribute to an over-estimation of depressive symptoms in this sample, and support the results of a previous study.[55]

5.6 Data analyses and methodological reflections

5.6.1 Missing data

In this study, CES-D total scores were calculated where patients had answered at least 80% of the items on a questionnaire, using the person-mean imputation procedure. The procedure was chosen instead of no imputation, imputation by another single imputation method, or multiple imputation. The advantage of person-mean imputation is that because it does not substitute a constant value, it does not reduce the measure's variability and is less likely to reduce the correlation, while the disadvantage is that this technique can inflate the reliability estimates as the number of missing items increases.[57] However, the common requirement that patients must answer at least 80% of the items on a questionnaire, secures that this technique provides good estimates of the reliability of measures.[57] While multiple imputation is frequently recognized as a strong imputation method, it requires a substantial sample size, and it is a more complicated procedure with multiple steps, which increases the potential for computational mistakes.[66] In addition, it produces different estimates every time, which can result in researchers getting different results with the same data.[67] However, while the different imputation procedures may lead to different results, using no form of imputation, and hence discarding all data that is incomplete may reduce power, lead to bias, and influence the results.[57] In a study of imputation of missing data on the CES-D, using person-mean imputation did not significantly alter the conclusions regarding factors that were associated with variations in CES-D scores.[57]

5.6.2 Initial analyses

Longitudinal design involve repeated time-ordered observations of an individual or group of individuals, and the goals for analysis of longitudinal data should ideally include study of: intra-individual change; inter-individual differences in intra-individual change; the relationship between intra- and inter-individual changes; and the variables that influence intra- and inter-

individual change.[68] While the initial analyses using Independent samples t-test and ANOVA contributed with valuable information on predictors of depressive symptoms in this sample of women with breast cancer, especially on predictors of depressive symptoms on the last assessment, these analyses do have limitations. First, when a 5% significance level test is used for each test, then the probability of type 1 error sometimes is considerably greater than 5%, which can lead to false-positive conclusions. If the risk of type 1 error is controlled using procedures such as a Tukey HSD correction, then power is compromised (i.e., group differences may not be detected when they exist). Performing separate tests at each time point also ignores trends over time, and does not allow for direct comparison between different groups over time.[59] A Multiple linear regression analysis could also have been used to examine correlations between depressive symptoms scores and patient characteristics. This would have enabled the use of several continuous variables that the Independent samples t-test and ANOVA are not able to use, such as age. While Multiple linear regression would likely have contributed with valuable information about predictors of depressive symptoms in this sample of women with breast cancer, this analysis would also not be suitable to examine change over time. Therefore, a statistical analysis that can incorporate both was ideal for this data.

5.6.3 Analysis of change over time

The HLM analysis was used to examine change in depressive symptoms over time, as well as predictors of depressive symptoms, as described in the article. It was chosen among a number of statistical methods that can be used to examine change over time. One common method is the Repeated measures ANOVA, that is used to assess whether different groups show different response curves over time (treatment x time interaction effect).[59] Time and group are the independent variables in the Repeated measures ANOVA model; effects of variables are evaluated at the group level (between subjects), and the F statistic is used to test the significance for each effect (i.e., time effect, group effect, and interaction effect).[69] While the Repeated measures ANOVA focus on the “between subjects” effects, the HLM

focuses first on modeling individual change patterns within individual subjects (i.e., intra-individual variability), and subsequently on analyzing individual variations in the variables that describe the change patterns. Another difference is that in HLM, change is considered a continuous process rather than a series of discrete changes.[68]

When comparing the Repeated measures ANOVA with the HLM, the HLM has several advantages. First, the Repeated measures ANOVA requires that several assumptions are met; normal distribution, homogeneity of variances, and sphericity (i.e., all differences between pairs of repeated scores are equally variable),[68] all though corrections (e.g., the Greenhouse-Geisser, the Huynh-Feldt) can be made to meet this assumption.[59] In addition, patients must be assessed at the same time points, and there must be equal time spacing between assessments.[69] If these assumptions are not met, the repeated measures ANOVA is not robust in a longitudinal design.[69] Furthermore, as long as data is missing at random, the HLM is able to accommodate missing data better, as it uses all available data on each subject.[59] Because the Repeated measures ANOVA requires no missing data, and has assumptions regarding assessment time points, these analyses are vulnerable to large effects from missing values. For example, researchers may drop subjects with even 1 missing assessment from the analyses, which can introduce sample bias, as the group of people with complete data may not be representative of the entire sample.[59] Thus, the HLM can make better use of the data. Finally, because the HLM can model time effects more flexibly, and allow the examination of different patterns of change with varying complexity to select the best fitting pattern, it can more accurately depict change over time.[59]

5.6.4 Representativity

The current study have several strengths and limitations that need to be addressed. The instrument that measured the outcome is a valid and reliable instrument that is tested for use among breast cancer patients, and in addition, it was used in a previous study in the Norwegian population. A limitation to this study is the inclusion of women with curative

treatment intent only, since findings cannot be generalized to breast cancer patients with advanced and metastatic disease. In addition, most women were white, married, and had a secondary level of education or higher, and therefore, findings cannot be generalized to women from other ethnic groups or with different socioeconomic status.

5.7 Theoretical framework

The TSM (Figure 1) was chosen as theoretical framework for this study. As previously mentioned, the TSM consists of three components; symptom experience, symptom management strategies and symptom status outcomes, and this study focused on the symptom experience and symptom status outcomes. The TSM model contributed to the understanding of depressive symptoms within the dimensions of nursing science (i.e., person, environment and health/illness). Depressive symptoms, as described in previous chapters, involves the patient (person), its immediate surroundings and society (environment), as well as affects the patients' perception of health and illness both physically (e.g., side effects) and psychologically (e.g., QOL). This study involved several of the factors that lie within the "Person"-factor, as it measured demographic, physiological, sociological and psychological characteristics, and the model contributed to the understanding of depression as a symptom that is affected by these different factors. The model was also applicable in the conceptualization of depression as a symptom, as the study captured the patients' perception of symptoms, and, through several data analysis approaches, evaluated depressive symptoms in a larger context. This contributed in understanding the patients' experience of depressive symptoms. Hopefully, findings from this study can contribute to enhancement of the last component of the TSM model, symptom management strategies. The symptom management strategies is the component where nurses should concentrate their efforts, and where they have the ability to make a large impact, for instance in creating interventions that relieve patients' symptoms.

6 CONCLUSION

The topic of this thesis was depressive symptoms in women with breast cancer undergoing RT, and there were 3 research questions. The first was an estimation of the prevalence of depressive symptoms in Norwegian women with breast cancer who receive RT, the second was an evaluation of change in depressive symptoms over time, and the third was further examination of predictors that are associated with depressive symptoms. While there is a substantial amount of previous research on depressive symptoms in women with breast cancer, this study has contributed with valuable knowledge about this topic. The results support recent research suggesting that depressive symptoms in women with breast cancer changes in a variety of patterns, and is characterized by both intra- and inter-individual variability. Furthermore, it has contributed to the previous knowledge on predictors of depressive symptoms in women with breast cancer. While several previously identified characteristics, such as age, marital status, and previous chemotherapy treatment, did not predict depressive symptoms in this sample of breast cancer patients, other characteristics, such as education level, employment status, having children living at home, and receiving hormonal therapy, did. In addition to examining demographic and clinical characteristics that have previously been identified as predictors, this is the first study of depressive symptoms in breast cancer patients undergoing RT to use symptom-specific instruments, as well as instruments measuring physical functioning and psychological adjustment characteristics, to examine predictors that have been suggested in previous research on breast cancer patients in general. The results described in the article suggests that these are important predictors of depressive symptoms. This is important information that can be utilized clinically; nurses may for instance use this information on predictors to identify vulnerable groups who may need intervention to reduce the risk for depressive symptoms during and after RT. In addition, nurses can use this knowledge to educate patients about how depressive symptoms may change during and following RT for breast cancer.

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8 APPENDIX

Appendix 1: Information for informed consent

Appendix 2: Recommendation from The National Committee for Medical and Health Research Ethics (Tilrådning fra REK, ref:154-08158d 6.2008.547)

Appendix 3: The Center for Epidemiologic Studies – Depression scale

Appendix 1: Information for informed consent

RIKSHOSPITALET

Kreftklinikken
RADIUMHOSPITALET

Forespørsel om deltakelse i forskningsprosjektet

"Symptomgrupper hos kreftpasienter og deres pårørende"

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en studie for å kartlegge i hvor stor grad mennesker som mottar behandling for kreft opplever symptomer og ubehag. Denne studien ønsker å kartlegge omfanget av symptomer, og samtidig se på hvordan disse symptomene opptrer sammen. Ved å få mer kunnskap om dette, håper vi å kunne bedre behandlingen av symptomer. Studien gjennomføres av Senter for Pasientmedvirkning og Sykepleieforskning ved Rikshospitalet, og i samarbeid med Kreftklinikken på Radiumhospitalet.

Hva innebærer studien?
Alle som deltar i studien vil bli bedt om å fylle ut spørreskjema for å kartlegge tilstedeværelsen og opplevelsen av ulike symptomer som smerter, søvnforstyrrelser, angst, depresjon, fatigue (tretthet). Du vil også bli spurt om eventuelle andre sykdommer, livskvalitet, helsetilstand og funksjonsstatus. Det vil ta i underkant av en time å fylle ut alle skjemaene. For å kartlegge dine symptomer ønsker vi å følge deg gjennom strålebehandlingen, totalt sett over et halvt år. Det innebærer at du fyller ut spørreskjema første gang før strålebehandlingen starter. Du vil så bli tilsendt spørreskjema hjemme, 4 og 8 uker etter at behandlingen har startet. For å se hvordan du har det over tid vil du også bli tilsendt spørreskjema etter 3 og 6 måneder hjemme. Dersom du trenger hjelp til å svare på noen av spørsmålene vil undertegnede være tilgjengelig på avdelingen eller på telefon.

I tillegg ønsker vi å ta blodprøver for genetiske analyser en gang av alle som deltar i studien. Disse prøvene vil, så langt det lar seg gjøre, bli tatt i forbindelse med rutinemessige blodprøver og vil derfor ikke medføre noen tilleggsbelastning.

Mulige fordeler og ulemper
Studien medfører ingen kostnader og det er ingen risiko forbundet med studien. Du vil kanskje oppleve det som slitsomt eller belastende å svare på noen av spørsmålene. Vi vil bistå med dette dersom du ønsker det, og du kan bruke så lang tid du selv ønsker på utfyllingen av skjemaene. Blodprøvene vil bli tatt av kyndig helsepersonell.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene av deg vil bli behandlet uten navn og eller andre direkte gjenkjennende opplysninger. En kode, som vil være unik for hver deltager i studien, knytter deltagerne til dataene. Listen som sammenkobler koden og personnummer, oppbevares innelåst i et skap, fysisk atskilt fra svarene på spørreskjemaene. Kodeboken vil bli slettet når studien er avsluttet. Vi regner med at studien i sin helhet vil avsluttes i 2015, og kodeboken vil slettes senest 20 år etter at studien er avsluttet, men sannsynligvis før. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg.

Blodprøvene vil bli oppbevart i en forsknings Biobank, og det vil bli gjort genetiske analyser for å undersøke om det kan være genetiske forskjeller som gjør at man reagerer ulikt på sykdom. På grunn av et tett forskningssamarbeid med University of California (UCSF) i USA og deres gode rutiner for

genetiske analyser, kan det hende at blodprøvene vil bli sendt dit for analysering. Rutinene for ivaretakelse av personvern kan være dårligere ivaretatt i USA, men prøvene vil være avidentifiserte før de sendes, og blodet vil bli destruert (kastet) umiddelbart etter at analysene er utført. Det resterende blodprøvematerialet vil destrueres senest 20 år etter at studien er avsluttet, og senest innen 2035, og vil bli oppbevart i Norge. Interessante funn i forbindelse med denne studien kan gi grobunn for videre forskning i fremtiden, og blodprøvene kan da bli benyttet til utvidede undersøkelser eller nye studier. For at blodprøvene skal kunne benyttes til eventuelle nye studier, må det innhentes tillatelser hos samtlige formelle instanser på nytt.

Som en del av studien ønsker vi å hente informasjon om din kreftdiagnose, tidligere og nåværende behandling, tilleggsykdommer og medisiner du står på fra din medisinske journal på sykehuset. Du vil ha rett til innsyn i hvilke opplysninger som er registrert, samt til å kreve retting av feilaktige opplysninger.

Studien er anbefalt av Regional Etisk Komite (REK) Sør-Norge, Sosial og Helsedirektoratet, Protokollutvalget ved Kreftklinikken og Personvernombudet ved Rikshospitalet. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke deg fra studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Du kan kreve at allerede innsamlede data blir slettet, og at blodprøvene destrueres. Data som allerede har rukket å bli analysert og publisert kan ikke trekkes tilbake.

Dersom du sier ja til å delta i studien, kommer vi til å kontakte deg for videre registrering av dine symptomer inntil seks måneder. Vi setter pris på om du følger opp denne registreringen.

Dersom du vil være med i studien vil vi også spørre deg om å få kontakte din nærmeste pårørende, over 18 år. Dette er for å øke forståelsen av hvordan kreftsykdom påvirker helsen og livskvalitet til pårørende. Dette er **ikke** en forutsetning for å delta i studien. Hvis du syntes det er i orden at din nærmeste kontaktes, krysser du av for dette på et eget skjema.

Dersom du sier nei til å delta i studien, ber vi om at vi kan registrere alder, kjønn og kreftdiagnose på deg. Grunnen til at vi ønsker dette, er fordi det er viktige opplysninger for å kunne beskrive utvalget vi forsker på, best mulig. Disse opplysningen vil på ingen måte kunne føres tilbake til deg.

Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte stipendiat Kristin Hofsø (kristin.hofso@rr-research.no, tlf 99 54 45 09) eller prosjektleder Tone Rustøen (tone.rustoen@rr-research.no, tlf 41 45 48 70).

Med Vennlig hilsen

Tone Rustøen	**Kristin Bjordal**	**Kristin Hofsø**
(sykepleier og professor)	**(seksjonsoverlege)**	**(sykepleier og stipendiat)**

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien.

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert , rolle i stuudien, dato)

Appendix 2: Recommendation from The National Committee for Medical and Health Research Ethics

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

Professor Tone Rustøen
Rikshospitalet
Senter for Pasientmedvirkning og
Sykepleieforskning
Forskningsveien 2b
0027 Oslo

Dato: 02.05.08
Deres ref.:
Vår ref.: 154-08158d 6.2008.547

Regional komité for medisinsk og hesefagligl forskningsetikk Sør-Øst D (REK Sør-Øst D)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 85 05 93
Telefaks: 22 85 05 90
E-post: i.m.middelthon@medisin.uio.no
Nettadresse: www.etikkom.no

Vedr. svar på merknader for forskningsprosjektet "Symptomgrupper hos polikliniske kreftpasienter i aktiv behandling, og symptomer og omsorgsbelastning hos pårørende til mennesker som har kreft"
Søknad om opprettelse av forskningsbiobank

Komiteen behandlet svar på merknader 16.04.08. Prosjektet er vurdert etter lov om behandling av etikk og redelighet i forskning av 30. juni 2006, jfr. Kunnskapsdepartementets forskrift av 8. juni 2007 og retningslinjer av 27. juni 2007 for de regionale komiteer for medisinsk og helsefaglig forskningsetikk.

Komiteen har følgende merknader til informasjonsskrivene:

1. Komiteen ber om at tidsangivelsen for utfyllingen av skjemaene gjøres mer realistiske og med tanke på at det er syke mennesker som skal svare.
2. Komiteen ber om at forespørselen vedrørende måling av frafallsfrekvens tas ut av informasjonsskrivene.

Komiteen har følgende merknader til søknad om opprettelse av forskningsbiobank:

3. Komiteen har ingen innvendinger mot opprettelse av forskningsbiobank og videresender søknaden om opprettelse av denne sammen med kopi av dette vedtaket til Helsedirektoratet for endelig godkjenning.

Vedtak:
Komiteen godkjenner at prosjektet gjennomføres under forutsetning av at de merknadene som er anført ovenfor blir innarbeidet før prosjektet settes i gang.

Vedtaket var enstemmig

Komiteenes vedtak etter Forskningsetikklovens § 4 kan påklages (jfr. forvaltningsloven § 28) til Den nasjonale forskningsetiske komité for medisin og helsefag. Klagen skal sendes

REK Sør-Øst D(jfr. forvaltningsloven § 32). Klagefristen er tre uker fra den dagen du mottar dette brevet (jfr. forvaltningsloven § 29).

Med vennlig hilsen

Stein A. Evensen (sign.)
Professor dr.med.
Leder

Ingrid Middelthon
Komitésekretær

Kopi:
- Seksjon for sosialmedisin, Rikshopspitalet v/ Roy Nystad 0027 Oslo
- Sosial- og helsedirektoratet

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

Professor Tone Rustøen
Rikshospitalet
Senter for Pasientmedvirkning og
Sykepleieforskning
Forskningsveien 2b
0027 Oslo

Dato: 30.07.08
Deres ref.:
Vår ref.: 154-08158d 6.2008.547

Regional komité for medisinsk og hesefagligl forskningsetikk Sør-Øst D (REK Sør-Øst D)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 85 05 93
Telefaks: 22 85 05 90
E-post: i.m.middelthon@medisin.uio.no
Nettadresse: www.etikkom.no

Vedr. endringsmelding for studien "Symptomgrupper hos polikliniske kreftpasienter i aktiv behandling, og symptomer og omsorgsbelastning hos pårørende til mennesker som har kreft."

Vi viser til endringsmelding av 09.07.08 med følgende vedlegg: EORTC-spørreskjema, revidert informasjonsskriv til pasienter som får strålebehandling, revidert informasjonsskriv til pasienter som får cellegift, følgebrev til spørreskjemapakke for pasienter og følgebrev til spørreskjemapakke for pårørende. I tillegg vises det til e-post av 23.07.08.

Komiteen behandlet endringsmelding og forespørsel i e-post 30.07.08. Prosjektet er vurdert etter lov om behandling av etikk og redelighet i forskning av 30. juni 2006, jfr. Kunnskapsdepartementets forskrift av 8. juni 2007 og retningslinjer av 27. juni 2007 for de regionale komiteer for medisinsk og helsefaglig forskningsetikk.

Komiteen har ingen innvendinger til de ønskede tiltak/endringer.

Vedtak:
Prosjektet godkjennes slik det nå foreligger.

Med vennlig hilsen

Stein A. Evensen (sign.)
Professor dr.med.
Leder

Ingrid Middelthon
Komitésekretær

Kopi:
- Seksjon for sosialmedisin, Rikshopspitalet v/ Roy Nystad 0027 Oslo

Appendix 3: The Center for Epidemiologic Studies – Depression scale

Draft

Reg. nr.: ☐☐☐

DEPRESJON (CES-D)

Vennligst sett ett kryss i den ruten som markerer hvor ofte du har følt det slik i løpet av den siste uken.

	Aldri eller nesten aldri (Mindre enn 1 dag i uken)	**Litt av tiden** (1-2 dager i uken)	**En del av tiden** (3-4 dager i uken)	**Hele eller nesten hele tiden** (5-7 dager i uken)
1. Jeg var plaget av ting som vanligvis ikke plager meg	☐	☐	☐	☐
2. Jeg hadde dårlig appetitt	☐	☐	☐	☐
3. Jeg var nedstemt og kunne ikke riste det av meg, til tross for støtte fra familie og venner	☐	☐	☐	☐
4. Jeg følte meg like mye verdt som andre	☐	☐	☐	☐
5. Jeg hadde problemer med å konsentrere meg om det jeg holdt på med	☐	☐	☐	☐
6. Jeg følte meg deprimert	☐	☐	☐	☐
7. Jeg følte at alt var et ork	☐	☐	☐	☐
8. Jeg så lyst på framtiden	☐	☐	☐	☐
9. Jeg tenkte at livet mitt hadde vært mislykket	☐	☐	☐	☐
10. Jeg følte meg engstelig	☐	☐	☐	☐
11. Jeg sov urolig	☐	☐	☐	☐
12. Jeg følte meg lykkelig	☐	☐	☐	☐
13. Jeg var mer taus enn vanlig	☐	☐	☐	☐
14. Jeg følte meg ensom	☐	☐	☐	☐
15. Folk var uvennlige	☐	☐	☐	☐
16. Jeg satte pris på livet	☐	☐	☐	☐
17. Jeg gråt	☐	☐	☐	☐
18. Jeg følte meg trist	☐	☐	☐	☐
19. Jeg følte at folk mislikte meg	☐	☐	☐	☐
20. Jeg var initiativløs	☐	☐	☐	☐

SNU ARKET!