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Reduced symptom burden with the support of an interactive app during neoadjuvant chemotherapy for breast cancer – A randomized controlled trial

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ABSTRACT

Objectives: Neoadjuvant chemotherapy causes distressing symptoms, which have to be managed by patients at home. Assessing and acting upon relevant patient-reported symptoms regularly with the support of mHealth such as apps, has shown to decrease symptom burden and improve health-related quality of life (HRQoL). There is a lack of apps for patients with breast cancer which are tested in rigorous trials and only a few include interactive components for immediate clinical management. The aim of this study was to evaluate whether the use of the interactive app Interaktor improves patients' levels of symptom burden and HRQoL during neoadjuvant chemotherapy for breast cancer.

Materials and methods: This randomized controlled trial included patients in an intervention group (n = 74) and a control group (n = 75), recruited at two university hospitals in Stockholm, Sweden. The intervention group used Interaktor for symptom reporting, self-care advice and support from health-care professionals during treatment, and the control group received standard care alone. Self-reported symptoms and HRQoL were assessed at two time points to determine differences between the groups.

Results: The intervention group rated statistically significant less symptom prevalence in nausea, vomiting, feeling sad, appetite loss and constipation. Overall symptom distress and physical symptom distress were rated statistically significant lower in the intervention group. Further, emotional functioning was rated statistically significant higher in the intervention group.

Conclusions: By using the Interaktor app in clinical practice, patients get individual support when managing treatment-related symptoms during neoadjuvant chemotherapy for breast cancer, leading to decreased symptom burden and improved emotional functioning.

1. Introduction

Neoadjuvant chemotherapy (NACT) is today an established and more commonly used treatment in early-stage and locally advanced breast cancer [1]. This treatment is considered effective and safe in reducing tumor size to facilitate breast-conserving surgery rather than mastectomy and potentially decrease morbidity associated with axillary surgery [2–5]. Patients who usually receive NACT are often those with more aggressive tumor characteristics [4,6].

It is well documented that both the illness itself and the chemotherapy are accompanied by disturbing physical and psychological symptoms [7,8]. Experienced symptoms can vary due to types and combinations of chemotherapies, dosages, and length of treatments as well as individual factors such as age, comorbidity, lack of social support and coping strategies [9–11]. The majority of the patients in Sweden receive their treatment as outpatients, which generally means self-management of symptoms at home during a long treatment period [10,12]. Studies show that patients may not

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receive adequate supportive care and have unmet care needs during chemotherapy, especially regarding treatment-related symptoms [13,14]. Uncontrolled symptoms can result in not only impaired well-being and health-related quality of life (HRQoL), but also poor treatment outcomes due to delay, reduction, or cancellation of chemotherapy as well as distressing visits to emergency departments and care that requires hospitalizations [10,12,15,16].

Assessing and acting upon relevant patient-reported symptoms regularly in oncological clinics, e.g. with the support of mHealth such as apps or web-based systems, has shown to decrease symptom burden and improve HRQoL, as well as increase survival [17–19]. Despite the large numbers of apps in health care, only a few include interactive components for immediate clinical management [20,21]. Furthermore, there is a lack of apps with evidence-based content for patients with breast cancer, which are tested in rigorous trials [22,23].

With the intention to support patients' symptom management in real time, we developed an interactive app (Interaktor) for early identification and management of symptoms and to facilitate interaction with health-care professionals [24]. The app is generic and has been shown to be both feasible and acceptable as well as to reduce symptom burden in patients with prostate cancer during radiotherapy, pancreatic cancer following surgery and among older people (>65 years old) receiving home-based health care [17,25–27].

The aim of this study was to evaluate whether the use of the interactive app Interaktor improves patients' levels of symptom burden and HRQoL during neoadjuvant chemotherapy for breast cancer.

2. Methods

2.1. Study design and sample

The study is a non-blinded, randomized controlled trial including patients with breast cancer undergoing NACT. The sample size was calculated from the results of a previous study on patients with prostate cancer [17] as there were no data in this population. With an effect size (Cohen's *d*) difference of 0.54 at the end of treatment in the primary outcome of symptom burden with 90% power at $P < .05$, 71 patients in each group were estimated in this study.

One hundred and fifty (150) patients newly diagnosed with breast cancer and planned for NACT, were consecutively screened for eligibility and consecutively included in the study at the oncological outpatient departments at two university hospitals in Stockholm, Sweden (Fig. 1). Inclusion criteria were patients with age over 18 years, diagnosed with non-metastatic breast cancer and able to read and understand Swedish. Exclusion criteria were patients with a documented cognitive dysfunction. Patients were equally randomized into an intervention group (IG) and a control group (CG). One patient in the IG was excluded after randomization due to a change of treatment to primary surgery instead of NACT. The final sample consisted of 74 patients who received the intervention in combination with standard care and 75 patients who received standard care alone. Sociodemographic and clinical characteristics are presented in Table 1.

The study was conducted after approval from the Regional Ethical Review Board of Stockholm, Sweden (Reg.no. 2013/1652–31/2).

2.2. Procedure and standard care

Eligible patients were identified through the medical appointment lists at the two clinics. During the patients' first visit at the oncology clinic, the patients received written information about the study from the assigned oncology contact nurse or physician. The patients were then contacted by the researcher and asked about participation. Patients who agreed to participate signed a written informed consent before filling in the baseline questionnaire. Subsequently, randomization was performed by sequentially drawn opaque sealed envelopes. The envelopes were shuffled by an independent individual prior to the randomization process.

Standard care included: visits with the physician at the oncology clinic before each chemotherapy treatment; a visit to an assigned contact nurse, in which the patients were informed about the treatment, related symptoms and how to manage them was scheduled; a phone number for contact with the nurse in case of questions regarding symptoms or concerns related to the treatment; recommendations to use an online eHealth system, offering different services for information, advice or contact with the healthcare [28].

2.3. The intervention with the Interaktor app

Interaktor is only used for research and the version for NACT was developed through literature reviews, discussions and consultations with the health-care professionals and clinical guidelines. Feasibility was tested in eight patients for optimization of the app before use in this RCT. The app includes various components: self-reporting of 14 common symptoms during chemotherapy such as fever, breathing difficulties, pain, numbness/tingling in hands and feet, nausea, vomiting, diarrhea, constipation, oral problems, depression, anxiety/worry, fatigue, insomnia and swelling/pain/redness in the arm (related to the peripherally inserted central catheter line for chemotherapy administration). The reported symptoms are immediately transferred via a secure server to a web interface where the health-care professionals can monitor patients' reports in real time. Further, a built-in risk assessment model for symptoms of concern sending alerts to contact nurses at the clinic by text message (SMS) leading them contacting the patient. There are two kinds of alerts: yellow and red. Yellow alerts are sent when symptoms are less severe and require a nurse to contact the patient during the day, and red alerts are sent in cases of greater severity and require contact within 1 h. In the app, the patient has continuous access to evidence-based self-care advice and relevant websites related to assessed symptoms and other areas of concern. If an alert is triggered, a notification suggests to the patient to read related self-care advice. Moreover, it is possible to monitor own reported symptom history over time in graphs. Illustrations of the app have been published in the study protocol and in a study on patients with prostate cancer [24,25].

The patients in the IG downloaded the app onto a smartphone or tablet and received an individual login as well as verbal and written information about how to use Interaktor. The patients reported symptoms daily on weekdays 8 a.m.–4 p.m. for approximately 18 weeks, starting on their first day of NACT and continuing until two weeks after end of NACT. A reminder message was sent to the patients if a daily report had not been submitted. In the event of an alert, the contact nurse contacted the patient to discuss the symptom and how it should be managed. The patients were instructed to contact the clinic according to standard procedure if emergency health-care attention outside these hours was needed.

2.4. Data collection

Primary endpoints, symptom burden and HRQoL, were collected at baseline and two weeks after end of NACT through self-reported questionnaires. Sociodemographic data was obtained from baseline questionnaires and clinical data was obtained from electronic medical records. Charlson Comorbidity Index was used to calculate

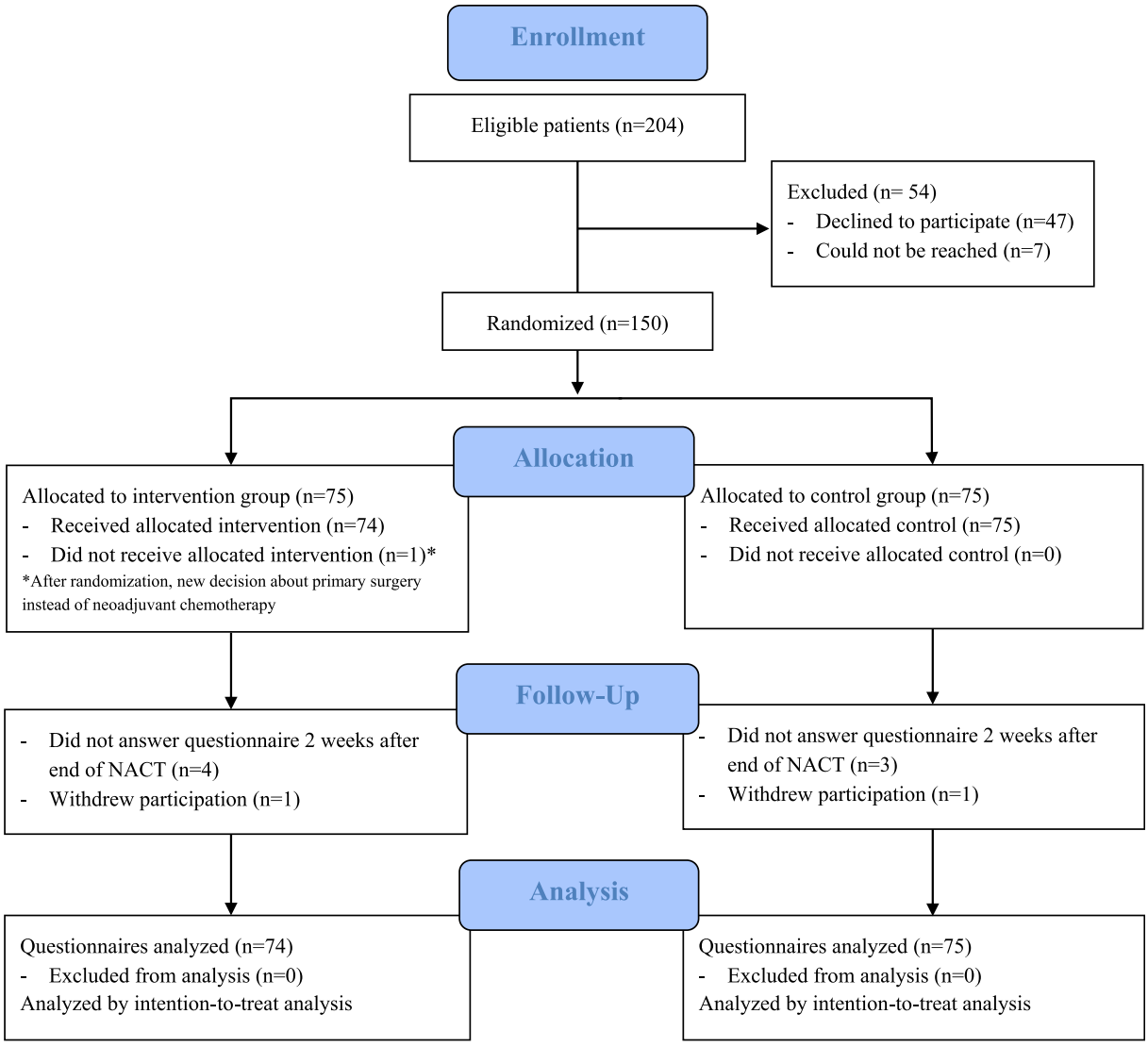

Fig. 1. CONSORT diagram of the study process.

comorbidity score [29]. Logged data of the patients' symptom reports and views on self-care advice were collected through app usage.

2.4.1. MSAS

The Memorial Symptom Assessment Scale (MSAS) was developed to measure the multidimensional experience of 32 common cancer-related symptoms in oncology patients [30]. Twenty-four symptoms assess prevalence (if a symptom is present or not), frequency (how often it is present), severity (how severe the symptom is perceived) and distress (how bothersome the symptom is perceived). Eight symptoms assess only prevalence, severity and distress. Each symptom is rated as being present or absent during the past week. If a symptom is present, frequency and severity are rated on a four-point rating scale and distress on a five-point rating scale. Higher scores indicate greater frequency, more severity and higher distress. The MSAS also features four subscales: Global Distress Index (MSAS-GDI), which measures overall symptom distress, includes the average of the frequency of four psychological symptoms (feeling sad, worrying, feeling irritable and feeling nervous) and the distress of six physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation and dry mouth). The Physical Symptom Subscale (MSAS-PHYS) includes the average of the frequency, severity and distress of 12 symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated and dizziness). The Psychological Symptom Subscale (MSAS-PSYCH) includes the average of the frequency, severity and distress of six symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable and difficulty concentrating). Total MSAS score (TMSAS) is the average of the symptom scores of all 32 items including frequency, severity and distress. The instrument is well-validated and reliable [30,31]. In this study all subscales in the MSAS had a Cronbach's alpha >0.80 at baseline and two weeks after treatment completion.

2.4.2. EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (version 3.0) measures HRQoL during the past week. The questionnaire includes 30 items divided into five functional scales (physical, role, emotional, cognitive and social function), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation and diarrhea), one global health status scale/

Table 1
Sociodemographic and clinical characteristics at baseline.

	Intervention group (n = 74)	Control group (n = 75)	*P*
Age at inclusion, years			.134[a]
Mean (SD)	48 (10.6)	50 (11.6)	
Marital status, n (%)			.333[b]
Married/Cohabiting	61 (82.4)	57 (76.0)	
Living alone	13 (17.6)	18 (24.0)	
Highest education level, n (%)			.469[b]
University	50 (67.6)	44 (58.7)	
Secondary school	18 (24.3)	25 (33.3)	
Primary school	6 (8.1)	6 (8.0)	
Occupation, n (%)			.107[b]
Working	57 (77.0)	48 (64.0)	
On sick leave	12 (16.2)	14 (18.7)	
Retired/Unemployed	5 (6.8)	13 (17.3)	
Menstruation status, n (%)			.545[c]
Premenopausal	45 (60.8)	41 (54.7)	
Postmenopausal	28 (37.8)	31 (41.3)	
Unknown	1 (1.4)	3 (4.0)	
Tumor characteristics, n (%)			.807[c]
Her2+ ER+ PR+	9 (12.2)	13 (17.3)	
Her2+ ER + PR-	7 (9.5)	8 (10.7)	
Her2+ ER- PR-	13 (17.6)	10 (13.3)	
Her2- ER + PR+	16 (21.6)	20 (26.7)	
Her2- ER + PR-	7 (9.5)	8 (10.7)	
Her2- ER- PR+	1 (1.4)	0	
Triple negative	21 (28.4)	16 (21.3)	
Proliferation rate (Ki-67), n (%)			.358[c]
≥20%	72 (97.3)	69 (92.0)	
<20%	2 (2.7)	5 (6.7)	
Missing	0	1 (1.3)	
Charlson comorbidity score*			.486[a]
Mean (SD)	0.9 (1.1)	1.0 (1.2)	
Type of chemotherapy, n(%)			.824[c]
Anthracyclines, Alkylators	3 (4.1)	1 (1.3)	
Anthracyclines, Alkylators, Taxanes	37 (50.0)	38 (50.7)	
Anthracyclines, Alkylators, Antimetabolites, Taxanes	9 (12.2)	13 (17.3)	
Antimetabolites, Alkylators	2 (2.7)	1 (1.3)	
Taxanes	11 (14.9)	14 (18.7)	
Taxanes, Alkylators	1 (1.4)	0 (0)	
Taxanes, T-DM1	2 (2.7)	2 (2.7)	
T-DM1	9 (12.2)	6 (8.0)	
Treatment duration, weeks			.493[a]
Mean (SD)	15 (2.6)	15 (4.8)	
Completion of planned cycles of NACT, n (%)			.830[b]
Yes	65 (87.8)	65 (86.7)	
No	9 (12.2)	10 (13.3)	
Reasons for early treatment discontinuation, n (%)			.370[c]
Adverse events/Symptoms	5 (55.6)	3 (30.0)	
Tumor progression/Generalized disease	4 (44.4)	7 (70.0)	

Abbreviations: NACT = Neoadjuvant chemotherapy.
*A higher value corresponds to greater comorbidity. Range between 0 and 37.
[a] Student's t-test.
[b] Chi-square test.
[c] Fischer's exact test.

quality of life and one item measuring financial impact. Each item has four response alternatives except for two items, which have seven response alternatives. Higher scores indicate better functioning in the functional scales and global health status scale and more symptoms in the symptom scales. This instrument is well validated with good reliability [32]. In this study the EORTC QLQ-C30 scales had a Cronbach's alpha >0.72 at baseline and two weeks after treatment completion, except for nausea and vomiting, which was 0.47 at baseline and 0.61 after treatment completion.

2.5. Data analysis

Statistical analyses were performed using IBM Statistical Package for Social Sciences version 24, Windows version. An intention-to-treat analysis approach was used for the analyses with missing values being replaced using the baseline observation carried forward method (BOCF) [33,34]. Analyses according to both BOCF and complete cases are presented in Tables 3 and 4. A statistical significance level of $P < .05$ was applied in all analyses. Effect size was calculated using Cohen's *d* [35]. Between-group analyses were performed using Chi-square and Fisher's exact tests for categorical variables and Student's t-test for continuous variables. Analysis of covariance (ANCOVA) was used to assess group differences in scores of MSAS and EORTC QLQ-C30 adjusted for baseline values. Descriptive statistics was used for analyzing the logged data.

3. Results

3.1. Baseline assessment

There were no statistically significant differences between the IG and the CG in sociodemographic and clinical characteristics at

Table 2
The Memorial Symptom Assessment Scale (MSAS): Symptom prevalence reported in the intervention group (IG) and control group (CG) before and after NACT.

Symptom n (%)	Before NACT			2 weeks after end of NACT					
				Complete cases			ITT with BOCF		
	IG (n = 74)	CG (n = 75)	*P*	IG (n = 69)	CG (n = 71)	*P*	IG (n = 74)	CG (n = 75)	*P*
Difficulty concentrating	42 (56.8)	35 (46.7)	.218	45 (65.2)	37 (52.1)	.116	49 (66.2)	39 (52.0)	.078
Pain	43 (58.1)	42 (56.0)	.795	43 (62.3)	48 (67.6)	.512	45 (60.8)	50 (66.7)	.457
Lack of energy	33 (44.6)	31 (41.3)	.688	57 (82.6)	59 (83.1)	.939	59 (79.7)	61 (81.3)	.805
Cough	16 (21.6)	14 (18.7)	.653	23 (33.3)	25 (35.2)	.815	23 (31.1)	25 (33.3)	.769
Feeling nervous	49 (66.2)	47 (62.7)	.651	22 (31.9)	30 (42.3)	.204	26 (35.8)	34 (45.3)	.204
Dry mouth	15 (20.3)	15 (20.0)	.967	40 (58.0)	43 (60.6)	.755	40 (54.1)	44 (58.7)	.570
Nausea	16 (21.6)	13 (17.3)	.509	17 (24.6)	29 (40.8)	**.041**	18 (24.3)	30 (40.0)	**.041**
Feeling drowsy	12 (16.2)	16 (21.3)	.424	32 (46.4)	34 (47.9)	.858	33 (44.6)	34 (45.3)	.928
Numbness/Tingling in hands and feet	15 (20.3)	12 (16.0)	.499	40 (58.0)	37 (52.1)	.486	41 (55.4)	37 (49.3)	.458
Difficulty sleeping	53 (71.6)	42 (56.0)	**.047**	45 (65.2)	47 (66.2)	.903	48 (64.9)	50 (66.7)	.817
Feeling bloated	8 (10.8)	6 (8.0)	.557	26 (37.7)	33 (46.5)	.292	27 (36.5)	33 (44.0)	.350
Problems with urination	2 (2.7)	2 (2.7)	.989	3 (4.3)	7 (9.9)	.206	3 (4.1)	7 (9.3)	.198
Vomiting	4 (5.4)	3 (4.0)	.685	2 (2.9)	12 (16.9)	**.006**	4 (5.4)	12 (16.0)	**.037**
Shortness of breath	18 (24.3)	19 (25.3)	.887	44 (63.8)	53 (74.6)	.163	46 (62.2)	55 (73.3)	.145
Diarrhea	9 (12.2)	13 (17.3)	.374	22 (31.9)	35 (49.3)	**.036**	24 (32.4)	36 (48.0)	.053
Feeling sad	41 (55.4)	45 (60.0)	.570	33 (47.8)	52 (73.2)	**.002**	37 (50.0)	55 (73.3)	**.003**
Sweats	0 (27.0)	20 (26.7)	.960	30 (43.5)	40 (56.3)	.128	31 (41.9)	42 (56.0)	.085
Worrying	60 (81.1)	57 (76.0)	.450	40 (58.0)	50 (70.4)	.124	45 (60.8)	53 (70.7)	.205
Problems with sexual interest or activity	24 (31.1)	20 (26.7)	.552	39 (56.5)	42 (59.2)	.752	41 (55.4)	43 (57.3)	.812
Itching	5 (6.8)	7 (9.3)	.563	14 (20.3)	20 (28.2)	.277	15 (20.3)	20 (26.7)	.357
Lack of appetite	24 (32.4)	19 (25.3)	.339	26 (37.7)	36 (50.7)	.121	27 (36.5)	37 (49.3)	.113
Dizziness	17 (23.0)	14 (18.7)	.517	16 (23.2)	28 (39.4)	**.038**	17 (23.0)	28 (37.3)	.056
Difficulty swallowing	0 (0)	4 (5.3)	**.044**	10 (14.5)	15 (21.1)	.306	10 (13.5)	15 (20.0)	.289
Feeling irritable	28 (37.8)	22 (29.3)	.272	39 (56.5)	48 (67.6)	.176	40 (54.1)	50 (66.7)	.115
Mouth sores	3 (4.1)	2 (2.7)	.638	27 (39.1)	27 (38.0)	.893	27 (36.5)	27 (36.0)	.951
Changes in the way food tastes	6 (8.1)	3 (4.0)	.293	43 (62.3)	43 (60.6)	.831	43 (58.1)	44 (58.7)	.945
Weight loss	6 (8.1)	8 (10.7)	.593	17 (24.6)	18 (25.4)	.922	17 (23.0)	19 (25.3)	.736
Hair loss	2 (2.7)	2 (2.7)	.989	21 (30.4)	29 (40.8)	.199	21 (28.4)	29 (38.7)	.184
Constipation	11 (14.9)	6 (8.0)	.188	14 (20.3)	25 (35.2)	**.049**	15 (20.3)	25 (33.3)	.072
Swelling of arms and legs	3 (4.1)	2 (2.7)	.638	16 (23.2)	18 (25.4)	.765	17 (23.0)	18 (24.0)	.882
I don't look like myself	20 (27.0)	19 (25.3)	.814	36 (52.2)	38 (53.5)	.873	37 (50.0)	40 (53.3)	.684
Changes in skin	4 (5.4)	5 (6.7)	.747	29 (42.0)	25 (35.2)	.407	30 (40.5)	26 (34.7)	.459

Abbreviations: NACT = Neoadjuvant chemotherapy, ITT = Intention-to-treat, BOCF = Baseline observation carried forward, *P* values were determined by Chi-square test, Prevalence = If a symptom is present.

Table 3
The Memorial Symptom Assessment Scale (MSAS) subscales: Symptom burden reported in the intervention group (IG) and control group (CG) at two weeks after end of NACT.

Subscale	Before NACT			2 weeks after end of NACT						
	Mean (SD)			Adjusted mean from ANCOVA Complete cases			Adjusted mean from ANCOVA ITT with BOCF			
	IG (n = 74)	CG (n = 75)	P^a	IG (n = 69)	CG (n = 71)	P^b	IG (n = 74)	CG (n = 75)	P^b	ES
MSAS-GDI	0.83 (0.68)	0.75 (0.59)	.473	0.88	1.17	**.005**	0.88	1.16	**.004**	.34
MSAS-PHYS	0.37 (0.45)	0.30 (0.34)	.324	0.77	0.98	**.032**	0.75	0.94	**.031**	.27
MSAS-PSYCH	1.27 (0.94)	1.16 (0.88)	.471	1.03	1.27	.052	1.07	1.29	.050	.18
TMSAS	0.48 (0.43)	0.43 (0.35)	.393	0.80	0.98	**.030**	0.79	0.96	**.028**	.26

Abbreviations: NACT = Neoadjuvant chemotherapy, ES = Effect size (Cohen's *d*) 2 weeks after end of NACT, ANCOVA = Analysis of covariance, ITT = Intention-to-treat, BOCF = Baseline Observation Carried Forward.
Higher scores indicate higher symptom distress.
P^a values were determined by Student's t-test.
P^b values were determined by ANCOVA adjusted for baseline values.

baseline (Table 1), or in the MSAS subscales and the EORTC QLQ-C30 (Tables 3 and 4). In the MSAS, the IG rated statistically significant higher prevalence of difficulty sleeping ($P = .047$) and lower prevalence of difficulty swallowing ($P = .044$) than the CG (Table 2).

3.2. MSAS between groups after NACT

Analyses according to BOCF showed that the IG reported statistically significant lower prevalence in nausea ($P = .041$), vomiting ($P = .037$), and feeling sad ($P = .003$) two weeks after end of treatment compared with the CG (Table 2). In the subscale MSAS-GDI, the IG rated statistically significant less overall symptom distress than the CG after treatment completion ($P = .004$). In the MSAS-PHYS, the IG rated statistically significant lower levels of physical symptom distress in comparison with the CG ($P = .031$). The IG rated statistically significant lower scores in the total MSAS than the CG ($P = .033$). Effect size ranged between 0.26 and 0.34 (Table 3).

3.3. EORTC QLQ-C30 between groups after NACT

Analyses according to BOCF showed that the two groups differed in one out of five functional scales after treatment. The IG rated statistically significant higher emotional functioning ($P = .008$) than

Table 4
The EORTC QLQ-C30: Health-related quality of life reported in the intervention group (IG) and control group (CG) at two weeks after end of NACT.

EORTC-QLQ-C30 Questionnaire	Before NACT			2 weeks after end of NACT						
	Mean (SD)			Adjusted mean from ANCOVA Complete cases			Adjusted mean from ANCOVA ITT with BOCF			
	IG (n = 74)	CG (n = 75)	P^a	IG (n = 69)	CG (n = 71)	P^b	IG (n = 74)	CG (n = 75)	P^b	ES
Functional scales										
Physical functioning	94.41 (10.47)	94.84 (9.90)	.797	83.66	77.85	.057	83.74	78.75	.091	.23
Role functioning	63.51 (34.09)	71.11 (33.60)	.173	51.95	47.87	.447	51.93	47.76	.416	.04
Emotional functioning	59.23 (25.83)	60.78 (26.87)	.721	72.58	63.03	**.012**	71.69	62.15	**.008**	.30
Cognitive functioning	72.07 (27.74)	77.11 (27.23)	.265	71.47	71.85	.919	70.84	71.22	.914	.13
Social functioning	71.62 (29.03)	74.22 (29.29)	.587	61.79	53.10	.059	61.69	53.36	.059	.23
Symptom scales										
Fatigue	30.78 (24.09)	29.33 (25.55)	.723	48.83	57.09	.052	47.70	55.53	.058	.27
Nausea and vomiting	8.33 (17.50)	5.11 (10.24)	.174	4.36	12.43	**.002**	5.48	12.59	**.007**	.40
Pain	25.00 (25.02)	21.33 (22.02)	.344	25.45	33.48	.091	24.95	33.16	.071	.23
Dyspnea	16.67 (25.43)	16.89 (27.05)	.959	35.27	42.72	.146	34.73	42.18	.130	.24
Insomnia	46.40 (33.02)	40.00 (40.64)	.293	34.78	40.85	.258	36.04	42.66	.199	.11
Appetite loss	19.82 (28.63)	17.33 (28.14)	.594	19.16	30.68	**.030**	19.59	30.90	**.027**	.35
Constipation	8.11 (18.14)	5.33 (16.48)	.330	8.96	21.81	**.004**	9.19	20.71	**.007**	.43
Diarrhea	4.96 (11.94)	8.44 (19.83)	.195	17.37	26.32	.075	16.22	25.33	.057	.35
Financial difficulties	13.06 (23.93)	18.67 (31.59)	.224	22.33	27.59	.279	23.55	27.65	.383	.23
Global health status/QoL	65.65 (24.36)	67.33 (23.76)	.671	58.21	54.82	.315	58.71	54.98	.248	.14

Abbreviations: NACT = Neoadjuvant chemotherapy, IG = Intervention group, CG = Control group, ES = Effect size (Cohen's *d*) 2 weeks after end of NACT, ANCOVA = Analysis of covariance, ITT = Intention-to-treat, BOCF = Baseline observation carried forward.
Higher scores indicate better functioning in the functional scales and global health scale.
Higher scores indicate more symptoms in the symptom scales.
P^a values were determined by Student's t-test.
P^b values were determined by ANCOVA adjusted for baseline values.

the CG. Further, the IG rated statistically significant lower levels in three symptom scales, nausea and vomiting ($P = .007$), appetite loss ($P = .027$), and constipation ($P = .007$), in comparison with the CG. Effect size ranged between 0.30 and 0.43 (Table 4).

3.4. Symptoms reported and self-care advice viewed in the Interaktor app

During the study period the patients in the IG reported a total number of 15,386 symptoms. Each patient reported on average two prevalent symptoms per day. Fatigue was the most commonly reported symptom (n = 3591), followed by oral problems (n = 1847). The distribution of all reported symptoms is shown in Fig. 2. The most common self-care advice viewed were related to oral problems (n = 196), nausea (n = 126) and pain (n = 114) (Table 5).

4. Discussion

The main findings were that patients using the Interaktor app reported significantly less symptom prevalence and symptom burden than the control group after NACT. Reporting and managing symptoms regularly during treatment with the support of the app had positive effects on several symptoms following chemotherapy. Symptom relief was highest in those symptoms known to be most directly related to treatment, such as gastrointestinal and emotional symptoms [8,36]. Our results of symptom relief are in contrast with the results in a study by Ruland et al. (2013), in which patients with breast cancer received symptom support via a web-based application and significant differences was observed solely in the MSAS-GDI scale [37]. The authors discuss some limitations that may have diluted their results such as a long time since diagnosis and the fact that 23% of the intervention group never logged onto the web-application. Our results showed emotional improvement when using a digital self-management tool like Interaktor, which is in line with the work by Kondylakis et al. (2020) [38]. In the present study emotional functioning (tension, worry, irritability and depression) was the only functional scale of the EORTC QLQ-C30 that was affected. An explanation could be, that symptoms are more relevant to assess during the ongoing treatment, since they occur rather instant in relation to the treatment [39,40]. Functional impairments are more prominent post-treatment, as consequences of remaining symptom burden [41,42]. Although the intervention resulted in few effects on HRQoL, it is important to recognize the clinical benefits reduced symptom burden has for the patients. A recent study of patients with advanced lung cancer showed that by reporting symptoms via a web-based system, symptoms were detected and managed early [43]. Furthermore, it was found that real-time follow-up of symptoms may improve survival duration and explained this by early detection of cancer relapse. Other clinical benefits of early identification of symptoms were shown in a study among patients with different cancer diagnoses receiving outpatient-based chemotherapy [44]. The patients remained on chemotherapy longer, had fewer visits to the emergency room and less hospital admission.

The logged data from using the app showed that nausea, a treatment-related symptom, which also showed to significantly differ between the intervention group and the control group, had the most viewed self-care advice. The various components of Interaktor, allowing for daily reflection over symptoms by reporting and viewing patterns in the graphs and having access to self-care advice, may have led to greater awareness among patients concerning how to manage their own health. The different app features may also have helped the patients in planning daily activities according to symptom patterns. Further, patients got attention from the health-care professionals when contacted if alerts were generated. Symptoms were thus identified early and discussed and managed in an effective and supportive way.

It is well known that patients during chemotherapy have varying needs due to individual impact of the treatment, which lead to unique experiences [7,10,41]. It is therefore recommended that assessing symptoms and providing support during treatment should be performed according to the patients' individual needs

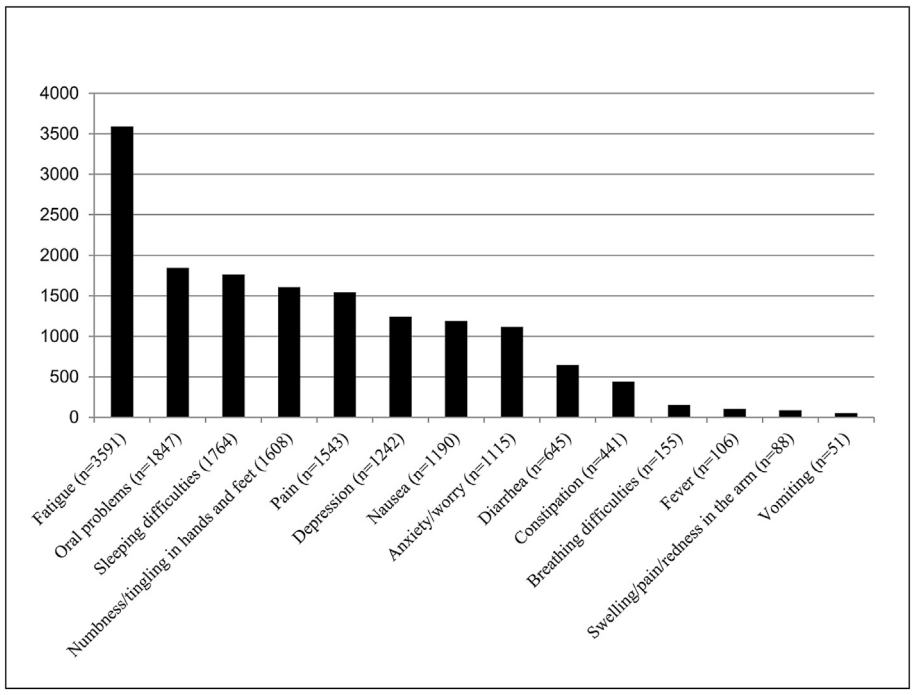

Fig. 2. Distribution over reported symptoms in the app during the study period (n = 15,386).

Table 5
Self-care advice viewed by the patients using the app (n = 74).

Self-care advice (n = patients)	Views *n*
Oral problems (n = 55)	196
Nausea (n = 49)	126
Pain (n = 47)	114
Fever (n = 42)	70
Swelling/pain/redness in the arm (n = 38)	68
Diarrhea (n = 30)	53
Breathing difficulties (n = 28)	52
Nutrition (n = 33)	51
Hair/skin/mucous (n = 32)	51
Numbness/tingling in hands and feet (n = 28)	49
Anxiety/worry (n = 26)	46
Depression (n = 23)	45
Sleeping difficulties (n = 25)	41
Constipation (n = 26)	40
Fatigue (n = 27)	35
Smoking (n = 18)	21
Vomiting (n = 13)	17

[10]. Self-care management of symptoms has in studies shown to not only minimize symptoms during treatment but also helps to cope with the treatment leading to a better experience of the care [45,46], and achieves a faster return to daily activities and work [47]. It can also be argued that having support in managing symptoms during treatment is advantageous for compliance with further treatments [48].

The adherence to using the app in our study was high despite the long treatment period (submitted for publication). Earlier studies in cohorts using Interaktor show the same high adherence (around 80%), and that the patients perceived the app as easy to use and that it facilitated interaction with health-care professionals and made the patients feel secure and taken care of [25,26].

4.1. Strengths and limitations

The strong study design and low dropout rate (6%) support the rigor of this intervention. The study result did not reach a medium effect size, and it is a limitation that the power was calculated in another population of patients. However, according to Osoba et al. (1998), a mean change of 10 points or more in the EORTC-scales is good and considered as an established level showing a clinical change [49]. Using BOCF for imputation of missing data is a well-known conservative method, which can lead to under- or over-estimating the results [33]. A strength is that the results from the complete cases analyses showed similar results. A lower mean age of the patients receiving NACT compared to the mean age of the overall population of patients diagnosed with breast cancer in Sweden may limit the generalizability of the results. However, our previous studies in samples with older age, patients with prostate and pancreatic cancer, have shown high acceptability, feasibility and clinical significance [25–27,50]. It is possible that including the influence of objective data and cost benefits would strengthen study results and should be considered in further studies.

5. Conclusions

We conclude that by using the Interaktor app, patients get individual support when managing treatment-related symptoms during neoadjuvant chemotherapy for breast cancer, leading to decreased symptom burden and improved emotional functioning. These promising results contribute to existing research of the value of using mHealth for routine collection of patient-reported symptoms and symptom management in clinical practice. Additional studies of user experience and health-care costs are needed before in-clinic implementation of Interaktor.

Author contributions

Conception and design: Ann Langius-Eklöf, Kay Sundberg, Yvonne Wengström. Provision of study material or patients: Ann Langius-Eklöf, Kay Sundberg, Yvonne Wengström. Collection and assembly of data. Maria Fjell, Marie Nilsson. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors.

Declaration of competing interest

The authors of this manuscript declare no conflict of interests.

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