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MODERATORS OF THE EFFECT OF PSYCHOSOCIAL INTERVENTIONS ON FATIGUE IN WOMEN WITH BREAST CANCER AND MEN WITH PROSTATE CANCER: INDIVIDUAL PATIENT DATA META-ANALYSES

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ABSTRACT

Objective: Psychosocial interventions can reduce cancer-related fatigue effectively. However, it is still unclear if intervention effects differ across subgroups of patients. These meta-analyses aimed at evaluating moderator effects of (1) sociodemographic characteristics, (2) clinical characteristics, (3) baseline levels of fatigue and other symptoms, and (4) intervention-related characteristics on the effect of psychosocial interventions on cancer-related fatigue in patients with non-metastatic breast and prostate cancer.

Methods: Data were retrieved from the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) consortium. Potential moderators were studied with meta-analyses of pooled individual patient data from 14 randomized controlled trials through linear mixed-effects models with interaction tests. The analyses were conducted separately in patients with breast (n=1,091) and prostate cancer (n=1,008).

Results: Statistically significant, small overall effects of psychosocial interventions on fatigue were found (breast cancer: β=-0.19 [95% confidence interval (95%CI)=-0.30;-0.08]; prostate cancer: β=-0.11 [95%CI=-0.21;-0.00]). In both patient groups, intervention effects did not differ significantly by sociodemographic or clinical characteristics, nor by baseline levels of fatigue or pain. For intervention-related moderators (only tested among women with breast cancer), statistically significant larger effects were found for cognitive behavioral therapy as intervention strategy (β=-0.27 [95%CI=-0.40;-0.15]), fatigue-specific interventions (β=-0.48 [95%CI=-0.79;-0.18]), and interventions that only targeted patients with clinically relevant fatigue (β=-0.85 [95%CI=-1.40;-0.30]).

Conclusions: Our findings did not provide evidence that any selected demographic or clinical characteristic, or baseline levels of fatigue or pain, moderated effects of psychosocial interventions on fatigue. A specific focus on decreasing fatigue seems beneficial for patients with breast cancer with clinically relevant fatigue.

Disclaimer: The views expressed are those of the authors and do not necessarily represent the officials of the U.S. National Cancer Institute.

1. BACKGROUND

Fatigue is one of the most commonly reported adverse effects of cancer and cancer treatment (1). Cancer-related fatigue is associated with a compromised quality of life and can persist for many years after treatment completion (1). Several interventions have been developed to manage cancer-related fatigue. Results of a recent meta-analysis indicated that psychosocial interventions (like cognitive behavioral therapy (CBT) and stress management) had statistically significant moderate effects on cancer-related fatigue, comparable with exercise interventions, but larger than pharmaceutical interventions (2).

It is still unclear what types of evidence-based psychosocial interventions work best on fatigue for which subgroups of patients with cancer (3). Therefore, characteristics that influence the direction or magnitude of the effect of such interventions on cancer-related fatigue (moderators of intervention effects) need to be identified (3). Thus far, meta-analyses on moderators of interventions of cancer-related fatigue have been based on pooled aggregate data of individual randomized controlled trials (RCTs) (2, 4-6). Inherent to the use of aggregate data is the loss of a large amount of valuable information about individual scores and characteristics, and an increased risk of ecological bias (7).

The use of individual patient data instead of aggregate data in meta-analyses allows for a more reliable and detailed examination of moderators of intervention effects (7). Collaboration with other researchers and sharing of data are needed to realize a meta-analysis based on individual patient data. Such an initiative was undertaken by the Predicting OptimaL cAncer RehabIlitation and Supportive care (POLARIS) consortium (8). This collaborative group has been established to share data of RCTs that evaluated the effects and moderators of exercise and psychosocial interventions for patients with cancer (8). Previous individual patient data meta-analyses from the POLARIS study examined the effects and moderators of exercise and psychosocial interventions on health-related quality of life (9-14).

This paper will specifically be focused on psychosocial interventions and will report on the first individual patient data meta-analyses to explore moderators of the effect of psychosocial interventions on cancer-related fatigue. Previous RCTs and meta-analyses of aggregate (study-level) data have reported more favorable outcomes of psychosocial interventions in patients with cancer in case of a younger or older age (contradictory findings), no cancer recurrence, treatment with chemotherapy, a longer intervention duration, and higher baseline levels of depression and distress (15,16). Potential moderators in the current study were selected based on this literature and categorized into sociodemographic, clinical and intervention-related factors, and baseline levels of symptoms (14).

We precluded heterogeneity in tumor type by conducting separate analyses for patients with breast cancer and prostate cancer. Specific knowledge on these two groups could add to the growing literature aimed at personalizing psychosocial interventions for patients with cancer. Comparison of patients with breast and prostate cancer made it possible to conduct separate analyses for men and women. We also chose to select patients with non-metastatic cancer, based on another meta-

analysis that demonstrated larger intervention effects on cancer-related fatigue in patients with non-metastatic compared to metastatic cancer (2). In this way, we aimed to study moderator effects in two relatively homogeneous groups of patients with cancer.

The aims of the current individual patient data meta-analyses were to examine the moderator effects of; (1) sociodemographic characteristics, (2) clinical characteristics, (3) baseline levels of fatigue and other symptoms (i.e., depression, anxiety, pain, and insomnia), and (4) intervention-related characteristics on the effect of psychosocial interventions on fatigue in patients with non-metastatic breast and prostate cancer. Psychosocial interventions could be fatigue-specific or more broadly focused.

2. METHODS

2.1 Protocol and registration

This section is written in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses of Individual Participant Data (PRISMA- IPD) (17). Before commencing in February 2013, the POLARIS study was registered in the International Prospective Register of Systemic Reviews (PROSPERO, reference no. CRD42013003805). This section provides a summary of the design and procedures of the POLARIS study. A more detailed description of the study protocol has been published (8).

2.2 Study procedure

Data were obtained from the POLARIS database which includes RCTs that: (i) evaluated the effects of physical activity and/or psychosocial interventions; (ii) included quality of life as primary or secondary outcome; (iii) were conducted among adult patients with cancer; and (iv) compared an intervention group with a waiting list, attention or usual care control group (8). All principal investigators (PIs) of eligible RCTs were invited to participate in the POLARIS consortium and to share data. This has resulted in PIs of 22 out of 61 eligible RCTs evaluating psychosocial interventions who have shared anonymized individual patient data (response rate 36%) (14). Outcomes of these RCTs were compared with RCTs of which individual patient data were not shared. This comparison showed no significant differences in effects on quality of life, which supported the representativeness of this sample for all eligible RCTs (14). The search strategy and data extraction have been described (14). Participating PIs signed a data sharing agreement statement, in which they agreed with the POLARIS policies. All individual RCTs had received approval from local ethics committees. After checking for completeness and correctness, shared databases were recoded and harmonized into the POLARIS database.

For the current study, we included RCTs that had examined the effects of (a) psychosocial interventions on (b) fatigue in (c) women with breast cancer or men with prostate cancer and (d) with non-metastatic disease. Exercise interventions were not included. Psychosocial interventions did not need to be fatigue-specific. This means that more broadly focused interventions were also eligible. The Cunningham criteria were used to classify all psychosocial interventions in five

categories in hierarchical order, from little to more active patient participation (18). These categories are providing information, emotional support, coping skills training, psychotherapy and, spiritual/existential therapy. Interventions needed to be at least a coping skills training, so interventions from the first two categories were excluded. This means that cognitive and/or behavioral methods must have been applied to change patients' cognitions or behaviors to improve their coping strategies (18). An overview from a review on psychosocial interventions in patients with cancer was used to specify the intervention strategies that were applied (19). The quality of the included studies was rated with the 'risk-of-bias' tool of the Cochrane Collaboration by two authors independently (20) and has been reported previously (14). This quality rating was based on the aspects random sequence generation, allocation concealment, incomplete outcome, and incomplete reporting.

2.3 Potential moderators

Potential moderators that were tested were based on previous, original RCTs or meta-analyses in patients with cancer (14). Patient characteristics were only included if individual data were available for at least 50% of patients, which was the case for age (continuous and groups of <50/50-70/≥70 years), married or living with a partner (yes/no), and education level (low/middle or high). Different cancer treatment types were also included as potential moderators (surgery, chemotherapy, radiotherapy and hormone therapy: yes/no), as well as continuous baseline levels of fatigue and other symptoms (depression, anxiety, pain, and insomnia). Fatigue was also tested as a dichotomous variable by dividing patients in a group with and without clinically relevant levels of fatigue at baseline. This division was based on the questionnaires for which a cut-off score was available (score ≤50 on Short Form-36 Item Health Survey vitality subscale (SF-36) (21), score ≥40 on European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 fatigue subscale (EORTC-QLQ) (22), and score ≥35 on Checklist Individual Strength, subscale Fatigue Severity (CIS-fatigue) (23)).

The potential intervention-related moderator 'timing of delivery of the intervention' was divided into during versus post cancer treatment. Data on this variable varied within included studies, so analysis of this potential intervention-related moderator was based on individual patient data. Women receiving hormone therapy for breast cancer were categorized as being post cancer treatment, as hormone therapy can continue for five years after completion of other types of cancer treatments. Men on androgen deprivation therapy for prostate cancer were categorized as being during cancer treatment.

Data on other potential intervention-related moderators did not vary within studies, so its analyses could only be based on aggregate data. We chose to distinguish CBT as potential moderator from the other intervention strategies because (i) CBT was tested in most of the available studies (7 of 12) and (ii) CBT was shown to be most effective in a recent meta-analysis compared to other strategies (1). By comparing CBT with the other intervention strategies, we aimed to build further on the existing literature. Other included intervention-specific characteristics were:

1. Selection of patients with clinically relevant levels of fatigue as part of the eligibility criteria (yes versus no)
2. Fatigue-specific intervention (i.e., specifically aimed at reducing fatigue) (yes versus no)
3. Intervention duration (<12 weeks versus ≥12 of weeks, median split drawn from the current study)
4. Number of sessions (<6 sessions versus ≥6 sessions, median split drawn from the current study)
5. Professional guidance (yes versus no)
6. Leading profession (psychologist versus other)
7. Delivery mode (individual versus couple or group)
8. Type of delivery (face-to-face versus telephone sessions)

2.4 Statistical analysis

All analyses were conducted separately for patients with breast and prostate cancer. Z-scores were used to pool outcomes of different measures of fatigue (calculated by subtracting the mean score at baseline from the individual score, divided by the mean standard deviation (SD) at baseline for each fatigue instrument). If more than one fatigue instrument was used, a fatigue-specific questionnaire was chosen. If this was not available, the fatigue scale of a cancer-specific quality of life questionnaire was used. In case more than one fatigue-specific or cancer-specific quality of life questionnaire were used in one study, we selected the questionnaire that was used most frequently in all included studies to increase power for subgroup analyses. The same procedure was used to pool outcomes of different instruments to measure four other symptoms that were explored as potential moderators (depression, anxiety, pain, and insomnia).

A one-step complete-case individual patient data meta-analysis was conducted to calculate the overall effect of psychosocial interventions on fatigue (measured at the end of the intervention) using linear mixed model analyses, adjusted for the baseline level of fatigue. The independent variables in the model were the allocated condition (psychosocial intervention or control group), and the baseline level of fatigue. We reported the regression coefficients and corresponding 95% CI that represent the between-group difference in z-scores, and correspond a Cohen's d effect size (0.2 to 0.5 was considered as small, 0.5 to 0.8 as moderate, ≥0.8 as large) (24).

Sociodemographic, treatment characteristics and pooled z-scores for baseline levels of anxiety, depression, pain and insomnia were tested as potential moderators by adding each patient characteristic and its interaction term with the intervention as independent variables into the model. To prevent ecological bias, all individual values were centered around the mean values at the study level. If there was a significant improvement of the model fit according to the likelihood ratio test (LRT) after adding the interaction term, a patient characteristic was considered to be a relevant moderator. Each potential moderator was tested in a separate model.

The same method was followed to test intervention characteristics as potential moderators, but individual values did not need to be centered because there was no variation in values within

studies. P-values below 0.05 were considered as statistically significant. All analyses were conducted with IBM SPSS Statistics 24.0.

3. RESULTS

3.1 Flow chart of patient inclusion

Authors of 22 psychosocial intervention studies had shared individual patient data in the POLARIS consortium. Eight of these 22 studies were not eligible because fatigue was not measured (k=4) (25-28), no patients with non-metastatic disease were included or status of metastases was unknown (k=2) (29,30), no patients with breast or prostate cancer were included (k=1) (31), or the tested intervention was not at least a coping skills training intervention (k=1) (32). Fourteen studies were eligible with a total of 2,497 patients, of which 112 patients with a tumor type other than breast or prostate cancer were excluded, as well as 252 patients with metastases at baseline and 34 patients with an unknown status regarding metastases. Finally, individual data of 2,099 patients from 14 studies were included in the analyses (Appendix, Figure A1) (33-46).

3.2 Study characteristics

Ten of the 14 studies included patients with breast cancer (33-42), two studies only included patients with prostate cancer (43,44), and the other two studies included patients with both tumor types (45,46). Most studies were conducted in the United States (k=4) (37,38,40,44) and the Netherlands (k=4) (34,36,42,45). Sample sizes ranged from 30 (36,40) to 734 (43). Patients with clinically relevant levels of fatigue were only selected in one of the 14 studies (36). Five different self-report questionnaires were used to measure fatigue, with the SF-36 vitality subscale as most frequently used questionnaires in five studies (34,39,40,43,44). A usual care (33,35,38-40,42-46) or waiting list control condition was used as control group (34,36,37,41) (Table 1).

3.3 Patient characteristics

The sample of women with breast cancer consisted of 1,091 patients with a mean age of 53 years (SD=9.7). The majority of these patients was married or living with a partner (n=714, 76%) and had a low or middle education level (n=437, 62%). Almost all patients were treated with surgery (n=1,087, 99.7%). The majority of patients had also received radiotherapy (n=894, 82%), chemotherapy (n=715, 66%) and/or hormone therapy (n=595, 60%) (Table 2).

The sample of men with prostate cancer included 1,008 patients with a mean age of 62 years (SD=8). The majority of these patients was married or living with a partner (n=836, 87%) and had a high education level (n=506, 53%). Half of patients were treated with surgery (n=495, 50%) and less than half were treated with radiotherapy (n=431, 44%) and/or hormone therapy (n=301, 30%) (Table 2).

Mean levels of fatigue and other symptoms are shown for each different questionnaire in Table A1 and A2 (Appendix). Examining the subsample of patients in which a questionnaire with validated cut-off score for fatigue was used, 27% of patients with breast cancer (n=299) and 41% of patients with prostate cancer (n=421) reported clinically relevant levels of fatigue at baseline.

3.4 Intervention characteristics

Two of the 14 studies tested an intervention that was specifically aimed at treating cancer-related fatigue (36,45). The intervention was provided post cancer treatment in 7 of 14 studies (34-36,38,41,42). The duration of the interventions ranged from four days (35) to 30 weeks (45), with a mean duration of 12 weeks. The most commonly applied intervention strategy (7 of 14 studies) was CBT (34,36,39,41-43,45,46). Other intervention strategies were dyadic therapy (40,44), problem solving therapy (33), expressive writing (35), social cognitive therapy (37), and coping skills intervention (38). Two interventions were self-guided (35,42), of which one was an e-health intervention (42). The other interventions were professionally guided and had a mean of seven sessions (range 3 (46) to 13 (36)) and were mostly guided by a psychologist (k=5) (36,39,41,45,46), delivered individually (k=5) (33,36,43,45,46) and face-to-face (k=10) (33,34,36,37,39-41,44-46) (Table 1).

3.5 Overall intervention effect

Compared to control conditions, psychosocial interventions had statistically significant, small overall effects on fatigue in patients with breast cancer (β=-0.19 [95% confidence interval (95%CI)=-0.30;-0.08]) and prostate cancer (β=-0.11 [95%CI=-0.21;-0.00]).

3.6 Potential moderators based on individual patient data

Age (continuous and categorical (<50/50-70/≥70 years)), being married and/or living with a partner, education level, type of cancer treatment, and baseline levels of fatigue (continuous and dichotomous) and pain did not significantly moderate the intervention effect on fatigue, neither in women with breast cancer nor in men with prostate cancer. Baseline levels of depression, anxiety, and insomnia were only tested as moderators in women with breast cancer and were also not statistically significant (Table 3).

3.7 Potential intervention-related moderators in patients with breast cancer

Given the small number of studies among patients with prostate cancer (k=4), all intervention-related moderators were only explored for studies among patients with breast cancer (k=12). Effects on fatigue were significantly larger (p= 0.02) when CBT was used as a intervention strategy compared with other intervention strategies like expressive writing and social cognitive therapy (respectively β=-0.27 [95%CI=-0.40;-0.15] versus β=0.03 [95%CI=-0.20;0.25]). The one study that only included patients with clinically relevant levels of fatigue (27) showed a clearly larger intervention effect on fatigue (p=0.02) compared to studies that included all patients irrespective of their fatigue level (β=-0.85 [95%CI=-1.40;-0.30] versus β=-0.17 [95%CI=-0.28;-0.05]). Additionally, the two interventions that were specifically aimed at reducing fatigue (27, 36) had significantly larger effects on fatigue (p=0.03) than generic interventions or interventions that were aimed at other symptoms like menopausal symptoms or psychological distress (respectively β=-0.48 [95%CI=-0.79;-0.18] versus β=-0.15 [95% CI=-0.27;-0.03]). The variables related to timing of delivery of the intervention,

intervention duration, number of sessions, professional guidance, leading profession, delivery mode, and type of delivery did not significantly moderate the intervention effect (Table 4).

4. DISCUSSION

These individual patient data meta-analyses showed statistically significant, small overall effects of psychosocial interventions on fatigue in patients with breast and prostate cancer. Intervention effects did not differ significantly between patients with different sociodemographic characteristics, clinical characteristics, baseline levels of fatigue and pain. In patients with breast cancer, we observed strongest effects of CBT, fatigue-specific interventions and interventions that only targeted patients with clinically relevant levels of fatigue.

Potential moderators of psychosocial interventions for cancer-related fatigue have been studied in only a few previous meta-analyses based on aggregate data that included patients with various cancer types (2, 4-6). With regard to our sociodemographic characteristics, only age has previously been explored as a potential moderator. In line with our results, age did not significantly moderate intervention effects (2). Based on our data, there is no evidence that specific demographic or clinical characteristics are of importance for the effect of interventions on cancer-related fatigue.

Our finding that CBT was more effective than other psychosocial intervention strategies in patients with breast cancer corresponds with a previous meta-analysis (2). It should be noted that subcategories of other interventions have encompassed a variety of different intervention strategies. However, according to our eligibility criteria, all intervention strategies were focused on the acquisition of skills aimed at cognitive or behavioral change (16). In this sense, the interventions in the other category were comparable. Our sample size was too small to explore specific components or ingredients within intervention strategies. This is important for a further improvement of interventions for cancer-related fatigue. Head-to-head comparisons could also provide more insight into the effectiveness of different intervention strategies.

Other significant moderators of the intervention effect in patients with breast cancer were the delivery of a fatigue-specific intervention and the selection of patients with clinically relevant levels of fatigue at baseline. A higher effectiveness of fatigue-specific interventions was also reported in a previous meta-analysis of Kangas et al. (4), showing a larger effect size for psychosocial interventions that included cancer-related fatigue as a specific aim. A similar conclusion was drawn in a Cochrane systematic review that showed a higher effectiveness for fatigue-specific interventions compared to non-specific interventions (47). Results of other meta-analyses have also suggested that patients with higher fatigue levels benefit more from interventions for fatigue than patients without significant fatigue levels (48,49). In the present meta-analyses, less than half the patients reported clinically relevant levels of fatigue at baseline (27% of patients with breast cancer and 41% of patients with prostate cancer). This probably is an important reason for the relatively small overall effect size observed compared to previous meta-analyses (2,5). It might also explain why mean baseline levels of fatigue and other symptoms were not significant moderators of the intervention effect (against expectations). As severe fatigue is more often reported by patients treated with

chemotherapy (1), we could have expected that interventions for fatigue were more effective in these patients. This was not the case, which may have to do with the relatively low number of patients with clinically relevant baseline levels of fatigue as well.

The present study focused on patients with breast cancer or prostate cancer, which reflects the vast majority of studies that have been conducted so far. There was a lack of eligible studies in the POLARIS database to enable analyses in patients with other types of cancer. Future research will be needed to examine if our findings can be generalized to patients with other types of cancer. Further, we only tested single interactions; however, these interactions are probably part of a more complex network of interactions related to fatigue and other symptoms that still need to be unraveled. Further exploration of relevant interactions is important to better understand what types of interventions are most effective for patients with cancer-related fatigue. Intervention-specific variables could only be tested in patients with breast cancer, but not in patients with prostate cancer due to the limited number of studies in the latter group.

4.1 Study limitations

The findings among patients with breast cancer of significant moderator effects of the delivery of a fatigue-specific intervention and selection of patients with clinically relevant fatigue must be interpreted with caution, because these factors were assessed in only a few RCTs that tested the same intervention protocol (36,45). This means that these findings may be confounded by other intervention characteristics, such as the content of the intervention or the expertise of the trained therapists who provided the intervention at a specialized treatment center for fatigue (36,45). The significance of both moderators needs to be replicated in further studies to obtain a stronger level of evidence.

Moreover, our literature search was not specifically focused on cancer-related fatigue but on quality of life, and not all authors of eligible studies were able or willing to share their data. Additionally, we used data that were available in the POLARIS database. Consequently, this could have introduced data availability bias (50), as the studies may not fully reflect the entire evidence base of studies on the efficacy of psychosocial interventions on fatigue. In particular, our results on moderators with small subsets of studies might have been different (and more certain) if more recent studies had been included. More studies would also facilitate forming more specific subgroups, for instance by specifying data on specific types of surgery, radio-, chemo- and/or hormone therapy. The effect sizes of the psychosocial interventions in this study on fatigue in patients with breast and prostate cancer were smaller compared to the moderate effect size reported in a meta-analysis with more up-to-date studies (2). However, even if a data availability bias would have resulted in an over- or underestimation of the overall intervention effect, our results on moderator effects could still be valid.

4.2 Clinical implications

Findings of this paper indicate that psychological interventions for fatigue can be used across

subgroups of patients with non-metastatic breast or prostate cancer, with CBT being particularly effective for patients with breast cancer. Previous studies have already shown that more broadly focused psychosocial interventions can result in improvement across a range of outcomes like distress (33,34), subjective well-being (42,43), and quality of life (33,38,43,46). If fatigue is a main symptom, a specific focus of interventions on decreasing fatigue seems beneficial for breast cancer patients with clinically relevant levels of fatigue.

5. Conclusions

Our results showed that the effect of psychosocial interventions on fatigue in patients with breast and prostate cancer was not significantly moderated by any sociodemographic characteristics, clinical characteristic, or baseline levels of fatigue or pain. In patients with breast cancer, larger effects were found for CBT as intervention strategy, fatigue-specific interventions, and interventions that only targeted patients with clinically relevant levels of fatigue.

CONFLICT OF INTERESTS

The authors declare no potential conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Studies evaluating the effects of psychosocial interventions on fatigue (N=14)

Study	Country	Eligible patients[1]	Baseline fatigue screening[2]	Fatigue instrument	Type control group	INTERVENTION CHARACTERISTICS							
						Fatigue-specific	Timing	Strategy	Duration, mean (SD)	Sessions, mean	Professional guidance	Delivery mode	Type of delivery
Patients with breast cancer													
Arving, 2007	SWE	143	No	QLQ-C30 fatigue	UC	No	During treatment	PST[a]	17 weeks	4	Nurse or psychologist	Individual	Face-to-face
Duijts, 2012	NL	212	No	SF-36 vitality	WL	No	Post treatment	CBT[b]	6 weeks	6	Psychologist and social workers	Group	Face-to-face
Gellaitry, 2010	UK	93	No	POMS fatigue	UC	No	Post treatment	EW[c]	<1 week	-	-	-	Self-guided
Gielissen, 2006	NL	30	Yes	CIS fatigue	WL	Yes	Post treatment	CBT[b]	26 weeks	13	Psychologist	Individual	Face-to-face
Graves, 2003	USA	32	No	POMS fatigue	WL	No	During + post treatment	SCT[d]	8 weeks	8	PhD candidate/ trained intern	Group	Face-to-face
Heiney, 2003	USA	66	No	POMS fatigue	UC	No	Post treatment	CSI[e]	6 weeks	6	Group therapist	Group	Telephone
Mann, 2012	UK	96	No	SF-36 vitality	UC	No	Post treatment	CBT[b]	6 weeks	6	Psychologist	Group	Face-to-face
Northouse, 2005	USA	30	No	SF-36 vitality	UC	No	During + post treatment	DT[f]	12 weeks	5	Nurse	Couple	Face-to-face + telephone
Savard, 2005	CAN	57	No	MFI global fatigue	WL	No	Post treatment	CBT[b]	8 weeks	8	Psychologist	Group	Face-to-face

Table 1. Studies evaluating the effects of psychosocial interventions on fatigue (N=14)

Study	Coun-try	Eligible patients[1]	Baseline fatigue screening[2]	Fatigue instru-ment	Type control group	INTERVENTION CHARACTERISTICS							
						Fatigue-specific	Timing	Stra-tegy	Duration, mean (SD)	Sessions, mean	Professional guidance	Delivery mode	Type of delivery
Vd Berg, 2015	NL	150	No	QLQ-C30 fatigue	UC	No	Post treatment	CBT[b]	16 weeks	-	-	-	Self-guided
Patients with prostate cancer													
Chambers, 2013	AUS	734	No	SF-36 vitality	UC	No	Pre + post treatment	CBT[b]	7 weeks	5	Nurse	Indivi-dual	Telephone
Northouse, 2007	USA	195	No	SF-36 vitality	UC	No	During + post treatment	DT[f]	17 weeks	5	Nurse	Couple	Face-to-face
Patients with breast (B) and prostate (P) cancer													
Goeden-dorp, 2010	NL	B: 70 P: 34	No	CIS fatigue	UC	Yes	During treatment	CBT[b]	30 (11.3) weeks	6	Psychologist	Indivi-dual	Face-to-face
Johansson, 2008	SWE	B: 112 P: 45	No	QLQ-C30 fatigue	UC	No	During treatment	CBT[b]	12 weeks	Median 3	Psychologist	Indivi-dual	Face-to-face

Notes. [1]Number of patients from each study that were eligible and included in the meta-analyses. [2]Screening at baseline to select patients with fatigue.
Abbreviations: CIS fatigue=Checklist Individual Strength, subscale Fatigue Severity; Ftf=face-to-face therapy; MFI global fatigue=Multidimensional fatigue inventory, global fatigue score; POMS fatigue =Profile of Mood State fatigue subscale; QLQ-C30 fatigue=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 fatigue subscale; SF-36 vitality= Short Form-36 Item Health Survey vitality subscale; Tel=telephone; UC=usual care; WL=waiting list.
Intervention strategies: [a]Problem Solving Therapy: focuses on generating, applying, and evaluating solutions to identified problems. [b]Cognitive Behavioral Therapy: focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment. [c] Expressive Writing: individuals write about their thoughts and feelings related to a personally stressful or traumatic life experience. [d]Social Cognitive Theory: experimental skill-building intervention based on the view that people learn by watching others. [e]Coping Skills Intervention: focuses on the acquisition of new cognitive skills aimed at cognitive or behavioral change. [f] Dyadic Therapy: focuses on modifying problematic interactions within a relationship through conjoint sessions with partners.

Table 2. Patient characteristics at baseline

	Patients with breast cancer		Patients with prostate cancer	
	Intervention (*n*=565)	**Control (*n*=526)**	**Intervention (*n*=500)**	**Control (*n*=508)**
Sociodemographic characteristics				
Age, mean (SD) years	52.7 (9.7)	53.3 (9.7)	62.2 (8.1)	61.9 (8.0)
Age in categories, *n* (%)				
<50 years	204 (36)	208 (40)	29 (6)	24 (5)
50-70 years	322 (57)	284 (54)	373 (75)	395 (78)
≥70 years	38 (7)	32 (6)	98 (20)	89 (18)
Unknown	1 (<1)	2 (<1)	-	-
Married/living with a partner, *n* (%)				
Yes	381 (67)	333 (63)	414 (83)	422 (83)
No	112 (20)	119 (23)	63 (13)	64 (13)
Unknown	72 (13)	74 (14)	23 (5)	22 (4)
Education level, *n* (%)				
Low/middle	210 (37)	227 (43)	229 (46)	227 (45)
High	138 (24)	135 (26)	247 (49)	259 (51)
Unknown	217 (38)	164 (31)	24 (5)	22 (4)
Cancer treatment type				
Surgery, *n* (%)				
Yes	561 (99)	526 (100)	229 (46)	266 (52)
No	4 (1)	-	259 (52)	237 (47)
Unknown	-	-	12 (2)	5 (1)
Radiotherapy, *n* (%)				
Yes	462 (82)	432 (82)	211 (42)	220 (43)
No	100 (18)	94 (18)	272 (54)	280 (55)
Unknown	3 (<1)	-	17 (3)	8 (2)
Chemotherapy, *n* (%)				
Yes	360 (64)	355 (68)	-	-
No	204 (36)	171 (33)	500 (100)	508 (100)
Unknown	1 (<1)	-	-	-
Hormone therapy, *n* (%)				
Yes	296 (52)	299 (57)	146 (29)	155 (31)
No	219 (40)	177 (34)	339 (68)	345 (68)
Unknown	50 (9)	50 (10)	15 (3)	8 (2)

Notes. Baseline characteristics did not differ significantly between the intervention and control group in (i) patients with breast and (ii) prostate cancer. Abbreviation: SD=Standard deviation.

Table 3. Potential moderators of the effect of psychosocial interventions on cancer-related fatigue on patient-level

	χ2 [df], *p*-value
Patients with breast cancer	
Socio-demographic characteristics	
Age (continuous)	3.23 [1], 0.07
Age (<50 versus 50-70 versus ≥70 years)	4.42 [2], 0.11
Having a partner (yes versus no)	0.35 [1], 0.55
Education level (low versus middle or high)	0.40 [1], 0.53
Cancer treatment type	
Surgery (yes versus no)	2.61 [1], 0.11
Radiotherapy (yes versus no)	0.64 [1], 0.42
Chemotherapy (yes versus no)	0.04 [1], 0.84
Hormone therapy (yes versus no)	0.02 [1], 0.89
Baseline level of fatigue and other symptoms	
Fatigue (continuous)	1.53 [1], 0.22
Clinically relevant fatigue (yes/no)	1.10 [1], 0.29
Depression (continuous)	0.01 [1], 0.94
Anxiety (continuous)	0.02 [1], 0.89
Pain (continuous)	2.48 [1], 0.12
Insomnia (continuous)	1.31 [1], 0.25
Patients with prostate cancer	
Socio-demographic characteristics	
Age (continuous)	0.01 [1], 0.91
Age (<50 versus 50-70 versus ≥70 years)	0.78 [2], 0.68
Partner status (yes versus no)	3.44 [1], 0.06
Education level (low versus middle/high)	0.26 [1], 0.61
Type of cancer treatment	
Surgery (yes versus no)	0.21 [1], 0.65
Radiotherapy (yes versus no)	0.14 [1], 0.71
Hormone therapy (yes versus no)	0.19 [1], 0.66
Baseline level of fatigue and other symptoms[1]	
Fatigue (continuous)	0.19 [1], 0.66
Clinically relevant fatigue (yes/no)	0.04 [1], 0.84
Pain (continuous)	0.19 [1], 0.66

Notes. Chi-square test with corresponding degrees of freedom (df) and *p*-values of the likelihood ratio test of the difference between models with and without interactions (χ2) are presented. All analyses are controlled for the level of fatigue at baseline.

[1]As data on the symptoms depression, anxiety, and insomnia were administered in only 7% of patients with prostate cancer, these variables were not tested as moderators in this patient sample. *p<0.05.

Table 4. Intervention-related moderators of psychosocial interventions on fatigue in patients with breast cancer

	β (95% CI)	χ2 [df], *p*-value
Type of intervention strategy		5.67 [1], 0.02*
Cognitive behavioral therapy (k=7)	-0.27 (-0.40; -0.15)*	
Other (k=5)	0.03 (-0.20; 0.25)	
Selection of patients with clinically relevant levels of fatigue		5.23 [1], 0.02*
Yes (k=2)	-0.85 (-1.40; -0.30)*	
No (k=10)	-0.17 (-0.28; -0.05)*	
Fatigue-specific intervention		4.62 [1], 0.03*
Yes (k=1)	-0.48 (-0.79; -0.18)*	
No (k=11)	-0.15 (-0.27; -0.03)*	
Timing (during (n=387) versus post cancer treatment (n=704)[1]		0.04 [1], 0.84
Intervention duration (<12 (k=6) versus ≥12 weeks (k=6)))		1.32 [1], 0.25
Number of sessions (<6 (k=5) versus ≥6 (k=7))		0.41 [1], 0.52
Professional guidance (yes (k=10) versus no (k=2))		2.91 [1], 0.09
Leading profession (psychologist (k=5) versus other (k=5))[2]		2.45 [1], 0.12
Delivery mode (individual (k=4) versus couple or group (k=6))[2]		3.34 [1], 0.07
Type of delivery (face-to-face (k=9) versus telephone (k=1))[2]		0.76 [1], 0.38

Notes. The table presents regression coefficients (β) with 95% confidence intervals (CI) of the effect of psychosocial interventions stratified per intervention-related moderator subgroup, and chi-square tests (χ2) with corresponding degrees of freedom (df) and *p*-values of the likelihood ratio test of the difference between models with and without interaction term. All analyses are based on study-level data and controlled for the level of fatigue at baseline. Abbreviations: k=number of studies, n=number of participants. *p<0.05.
[1]As data on this variable varied within studies, its analysis was based on individual patient data.
[2]Data of studies testing self-guided interventions were excluded.