

## 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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**Running head:** Meta-analyses on moderators of psychosocial intervention effects on cancer-related fatigue

**Keywords:** psychosocial interventions; fatigue; breast cancer; prostate cancer; moderators; individual patient data meta-analysis

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## ABSTRACT

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**Introduction:** Fatigue is a common adverse effect of cancer and cancer treatment. Psychosocial interventions can reduce cancer-related fatigue effectively. However, it is still unclear if intervention effects differ across subgroups of patients. This meta-analysis 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, using likelihood ratio 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:  $\beta=-0.19$  [95% confidence interval (95%CI)=-0.30;-0.08]; prostate cancer:  $\beta=-0.11$  [95%CI=-0.21;-0.00]). In both patient groups, intervention effects did not differ by sociodemographic characteristics, clinical characteristics, baseline levels of fatigue or other symptoms. In patients with breast cancer, statistically significant larger effects were found for cognitive behavioral therapy as intervention strategy ( $\beta=-0.27$  [95%CI=-0.40;-0.15]), fatigue-specific interventions ( $\beta=-0.48$  [95%CI=-0.79;-0.18]), and interventions that only targeted patients with clinically relevant levels of fatigue ( $\beta=-0.85$  [95%CI=-1.40;-0.30]).

**Conclusions:** Our findings support the use of psychosocial interventions for fatigue across subgroups of patients with non-metastatic breast and prostate cancer. A specific focus on decreasing fatigue in subgroups with high levels of fatigue seems beneficial.

## KEY POINTS

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**Question:** What are relevant moderators of the effect of psychosocial interventions on cancer-related fatigue in patients with non-metastatic breast and prostate cancer?

**Findings:** In both patient groups, the effect of psychosocial interventions on fatigue did not differ by sociodemographic characteristics, clinical characteristics, baseline levels of fatigue or other symptoms. In patients with breast cancer, larger effects were found for cognitive behavioral therapy as intervention strategy, fatigue-specific interventions, and interventions that only targeted patients with clinically relevant levels of fatigue.

**Meaning:** Our findings support the use of psychosocial interventions for fatigue across subgroups of patients with non-metastatic breast and prostate cancer.

## ABSTRACT

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**Importance:** Fatigue is a common adverse effect of cancer and cancer treatment. Psychosocial interventions can reduce cancer-related fatigue effectively, but it is unclear if intervention effects differ across subgroups of patients.

**Objective:** This meta-analysis aimed at evaluating moderator effects of (1) sociodemographic and (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.

**Data sources:** Data were retrieved from the Predicting Optimal Cancer Rehabilitation and Supportive care (POLARIS) database. Studies in this database were identified through PubMed, EMBASE, PsycINFO, and CINAHL.

**Study Selection:** We included randomized controlled trials (RCTs) from the POLARIS database that had examined the effect of (a) psychosocial interventions on (b) fatigue in (c) women with breast cancer or men with prostate cancer (d) with non-metastatic disease.

**Data extraction and Synthesis:** The Preferred Reporting Items for Systematic review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) guidelines were followed. Potential moderators were studied with meta-analyses of pooled IPD from 14 RCTs through linear mixed-effects models with interaction tests, using likelihood ratio tests to determine the significance of moderators.

**Main Outcomes and Measures:** Fatigue was the primary outcome. 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:  $\beta=-0.19$  [95% confidence interval (95%CI)=-0.30;-0.08]; prostate cancer:  $\beta=-0.11$  [95%CI=-0.21;-0.00]). In both patient groups, the intervention effects did not differ by sociodemographic characteristics, clinical characteristics, baseline levels of fatigue or other symptoms. In patients with breast cancer, statistically significant larger effects were found for cognitive behavioral therapy as intervention strategy ( $\beta=-0.27$  [95%CI=-0.40;-0.15]), for interventions that only targeted patients with clinically relevant levels of fatigue ( $\beta=-0.85$  [95%CI=-1.40;-0.30]), and for fatigue-specific interventions ( $\beta=-0.48$  [95%CI=-0.79;-0.18]).

**Conclusion and Relevance:** Our findings support the use of psychosocial interventions for fatigue across subgroups of patients with non-metastatic breast and prostate cancer, and particularly cognitive behavioral therapy for patients with breast cancer. A specific focus on decreasing fatigue in subgroups with high levels of fatigue seems beneficial.

# **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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## **INTRODUCTION**

Fatigue is one of the most commonly reported adverse effects of cancer and cancer treatment.<sup>1-4</sup> Cancer-related fatigue is associated with a compromised quality of life and can persist for many years after treatment completion.<sup>5,6</sup> Several interventions have been developed to manage cancer-related fatigue. Results of a recent, large meta-analysis indicated that non-pharmacological interventions (exercise and psychosocial interventions like cognitive behavioral therapy and stress management) had statistically significant, moderate effects on cancer-related fatigue, in contrast to pharmaceutical interventions that showed statistically significant but very small effects.<sup>7</sup>

It is still unclear what types of evidence-based interventions work best for which subgroups of patients.<sup>8,9</sup> 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.<sup>10</sup> 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).<sup>7,11-13</sup> 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.<sup>14,15</sup>

The use of individual patient data instead of aggregate data in a meta-analysis allows for a more reliable and detailed examination of moderators of intervention effects.<sup>14,15</sup> 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.<sup>16</sup> This collaborative group has been established to share data of RCTs that evaluated the effects and moderators of non-pharmacological interventions for patients with cancer.<sup>16</sup> Previous individual patient data meta-analyses from the POLARIS study examined the effects and moderators of exercise interventions on various outcomes including fatigue and health-related quality of life,<sup>17-22</sup> and moderators of the effect of psychosocial interventions on health-related quality of life.<sup>18</sup>

This will be the first individual patient data meta-analysis 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.<sup>23,24</sup> 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.<sup>23-30</sup>

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.<sup>7</sup> In this way, we studied moderator effects in two relatively homogeneous groups of patients with cancer.

The aims of the current individual patient data meta-analysis 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 cancer-related fatigue in patients with non-metastatic breast and prostate cancer.

## **METHODS**

### *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).<sup>31</sup> 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.<sup>16</sup>

### *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. 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%). 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.<sup>18</sup> The search strategy and data extraction have been described<sup>18</sup>. 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. The Cunningham criteria were used to classify all psychosocial interventions in five categories in hierarchical order, from little to more active patient participation.<sup>32</sup> 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.<sup>32</sup> An overview from a review on psychosocial interventions in patients with cancer was used to specify the intervention strategies that were applied.<sup>33</sup> The quality of the included studies was rated with the 'risk-of-bias' tool of the Cochrane Collaboration by two authors independently<sup>34</sup> and has been reported previously.<sup>18</sup> This quality rating was based on the aspects random sequence generation, allocation concealment, incomplete outcome, and incomplete



reporting.

### *Potential moderators*

Potential moderators that were tested were based on previous, original RCTs or meta-analyses in patients with cancer.<sup>23,25-30,35</sup> 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 validated cut-off score was available (score ≤50 on Short Form-36 Item Health Survey vitality subscale (SF-36),<sup>36</sup> score ≥40 on European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 fatigue subscale (EORTC-QLQ),<sup>37</sup> and score ≥35 on Checklist Individual Strength, subscale Fatigue Severity (CIS-fatigue)<sup>38</sup>).

Intervention characteristics did not vary within studies. This means that analyses of intervention characteristics could only be based on aggregate data. The following intervention-specific characteristics were included:

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

### *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. 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 included a random intercept on study level to control for clustering of patients within studies. This resulted in a between-group difference in z-scores, corresponding to a Cohen's d effect size (0.2 to 0.5 was considered as small, 0.5 to 0.8 as moderate,  $\geq 0.8$  as large).<sup>39</sup>

Sociodemographic, treatment characteristics and pooled z-scores for 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.

## RESULTS

### *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),<sup>40-43</sup> no patients with non-metastatic disease were included or status of metastases was unknown (k=2),<sup>44,45</sup> no patients with breast or prostate cancer were included (k=1),<sup>46</sup> or the tested intervention was not at least a coping skills training intervention (k=1).<sup>47</sup> 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 (Figure 1).<sup>48-61</sup>

### *Study characteristics*

Ten of the 14 studies included patients with breast cancer,<sup>48-57</sup> two studies only included patients with prostate cancer,<sup>58,59</sup> and the other two studies included patients with both tumor types.<sup>60,61</sup> Most studies were conducted in the United States (k=4)<sup>52,53,55,59</sup> and the Netherlands (k=4).<sup>49,51,57,60</sup> Sample sizes ranged from 30<sup>51,55</sup> to 734.<sup>58</sup> Patients with clinically relevant levels of fatigue were only selected in one of the 14 studies.<sup>51</sup> Five different self-report questionnaires were used to measure fatigue, with the Short Form-36 Item Health Survey vitality subscale (SF-36) vitality subscale as most frequently used questionnaires in five studies.<sup>49,54,55,58,59</sup> A usual care condition<sup>48,50,53-55,57-61</sup> or waiting list control condition was used as control group<sup>49,51,52,56</sup> (Appendix, Table A1).

### *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 1).

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 1).

Mean levels of fatigue and other symptoms are shown for each different questionnaire in Table A2 and A3 (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.

#### *Intervention characteristics*

Two of the 14 studies tested an intervention that was specifically aimed at treating cancer-related fatigue<sup>51,60</sup>. The intervention was provided post cancer treatment in 7 of 14 studies.<sup>49-51,53,54,56,57</sup> The duration of the interventions ranged from four days<sup>50</sup> to 30 weeks,<sup>60</sup> with a mean duration of 12 weeks. The most commonly applied intervention strategy (7 of 14 studies) was cognitive behavioral therapy.<sup>49,51,54,56-58,60,61</sup> Other intervention strategies were dyadic therapy,<sup>55,59</sup> problem solving therapy,<sup>48</sup> expressive writing,<sup>50</sup> social cognitive therapy,<sup>52</sup> and coping skills intervention.<sup>53</sup> Two interventions were self-guided.<sup>50,57</sup> The other interventions had a mean of seven sessions (range 3<sup>61</sup> to 13<sup>51</sup>) and were mostly guided by a psychologist (k=5),<sup>51,54,56,60,61</sup> delivered individually (k=5)<sup>48,51,58,60,61</sup> and face-to-face (k=10)<sup>48,49,51,52,54-56,59-61</sup> (Appendix, Table A1).

#### *Overall intervention effect*

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

#### *Potential moderators based on individual patient data*

Age (continuous and categories <50/50-70/ $\geq 70$  years), being married and/or living with a partner, education level, type of cancer treatment, and baseline levels of fatigue (continuous and dichotomous), depression, anxiety, pain, and insomnia did not significantly moderate the intervention effect on fatigue, neither in women with breast cancer nor in men with prostate cancer (Table 2).

#### *Potential intervention-related moderators in patients with breast cancer*

Given the small number of studies among patients with prostate cancer (k=4), 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 cognitive behavioral therapy was used as a intervention strategy compared with other intervention strategies like expressive writing and social cognitive therapy (respectively  $\beta=-0.27$  [95%CI=-0.40;-0.15] versus  $\beta=0.03$  [95%CI=-0.20;0.25]). The one study that only included patients with clinically relevant levels of fatigue<sup>51</sup> showed a clearly larger intervention effect on fatigue ( $p=0.02$ ) compared to studies that included all patients irrespective of their fatigue level ( $\beta=-0.85$  [95%CI=-1.40;-0.30] versus  $\beta=-0.17$  [95%CI=-0.28;-0.05]). Additionally, the two interventions that were specifically aimed at reducing fatigue<sup>51,60</sup> 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  $\beta=-0.48$

[95%CI=-0.79;-0.18] versus  $\beta$ =-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 3).

## DISCUSSION

This individual patient data meta-analysis 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, or other symptoms. Our findings support the use of psychosocial interventions for fatigue across subgroups of patients with non-metastatic breast and prostate cancer. This is particularly the case for cognitive behavioral therapy, because we observed stronger effects for this intervention strategy in patients with breast cancer compared to other intervention strategies. We also found larger effects for fatigue-specific interventions and for 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.<sup>7,11-13</sup> 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.<sup>7</sup> 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 cognitive behavioral therapy was more effective than other psychosocial intervention strategies corresponds with a previous meta-analysis.<sup>7</sup> 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.<sup>32</sup> 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.<sup>8,10</sup>

Other significant moderators of the intervention effect were the delivery of a fatigue-specific intervention and selection of patients with clinically relevant levels of fatigue at baseline. These findings must be interpreted with caution since these factors were assessed in only a few RCTs that tested the same intervention protocol.<sup>51,60</sup> This means that other factors may also be responsible for the higher intervention effect, like the content of the intervention or the expertise of the trained therapists who provided the intervention at a specialized treatment center for fatigue.<sup>51,60</sup>

A higher effectiveness of fatigue-specific interventions was also reported in a previous meta-analysis of Kangas et al.,<sup>11</sup> 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.<sup>62</sup> 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.<sup>21,63</sup> In the present meta-analysis, 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.<sup>7,12</sup> 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,<sup>1</sup> 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.

Main strengths of our study include the well-defined samples of patients with non-metastatic breast and prostate cancer, and the availability of a large amount of individual patient data that enabled us to test multiple moderators of the effect of interventions for cancer-related fatigue. However, this study also has limitations. The 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. 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. Moreover, 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.<sup>7</sup> However, even if a retrieval bias would have resulted in an underestimation of the overall intervention effect, our results on moderator effects could still be valid.

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.<sup>64</sup> Further exploration of relevant interactions is important to better understand what types of interventions are most suitable for patients with cancer-related fatigue.

In conclusion, 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 other symptoms. Our findings indicate that psychological interventions for fatigue can be used across subgroups of patients with non-metastatic breast or prostate cancer, with cognitive behavioral therapy being particularly effective for patients with breast cancer. A specific focus of interventions on decreasing fatigue in subgroups with clinically relevant levels of fatigue seems beneficial.

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