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Is Guided Exercise Effective in Reducing the Cancer-Related Fatigue Syndrome of Cancer Survivors at Working-Age? – A Meta-Analysis

Mindert körperliche Aktivität bei Krebsüberlebenden im erwerbstätigen Alter das krebsinduzierte Fatigue Syndrom? Eine Meta-Analyse

REVIEW

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Summary

› **Background and Objectives:** Due to innovative treatment methods and promising therapies in oncology, the number of cancer survivors has increased during recent years. The productivity and the ability to return to normal everyday life after recovery depend on the extent of the cancer-related chronic fatigue syndrome (CRF). The more severe the syndrome, the lower the physical and psychological performance of the patients. The purpose of this meta-analysis was to explore the effectiveness of guided physical activity to reduce CRF among adult, employed cancer survivors.

› **Methods:** Based on a systematic literature search, the statistical data from randomized-controlled trials published between 2007 and 2016 were integrated into a meta-analysis. The methodological quality of the selected trials was evaluated using the PEDro scale. The data were summarized by a meta-analytic statistic in the randomized effects model. Cohen's d was calculated and the homogeneity and sensitivity were verified. The influences of moderating conditions were examined by regression analysis.

› **Results:** The eleven integrated studies revealed a significant – however, heterogeneous – global effect d =0.46 (95% CI: 0.16 – 0.77). The intervention length could explain the variance between the studies: The shorter the intervention, the stronger the effect. A publication bias could not be detected.

› **Conclusion:** The meta-analysis confirms the results from previously-published meta-analyses. Physical activity performed by cancer survivors can reduce CRF. The effectiveness ranges from low to moderate. However, the original studies are lacking methodological quality. The preferred outcome measures are self-report instruments prone to biases.

Zusammenfassung

› **Problemstellung:** Aufgrund neuer Behandlungsmethoden und erfolgsversprechender Therapieansätze in der Onkologie ist die Anzahl der Krebsüberlebenden in den vergangenen Jahren gestiegen. Die Leistungsfähigkeit der Erkrankten und die Rückkehr in ihren normalen Alltag hängen maßgeblich mit dem Ausmaß des tumorbedingten Chronischen Fatigue-Syndroms (CRF) zusammen. Je ausgeprägter das Syndrom, desto geringer das physische und psychische Leistungsvermögen. Das systematische Review untersucht, ob körperliche Aktivität bei Krebsüberlebenden, die im erwerbsfähigen Alter sind, zur Reduktion des CRF beiträgt und wie groß der Effekt ist.

› **Methoden:** Nach einer systematischen Literaturrecherche wurden die Daten von elf randomisiert-kontrollierten Primärstudien (2007-2016), die Krebsüberlebende im erwerbsfähigen Alter unabhängig von ihrer Krebsentität untersuchten, im Modell zufälliger Effekte zu einer Meta-Analyse integriert. Die Qualität der ausgewählten Primärstudien wurde mithilfe der PEDro-Skala beurteilt. Cohen's d wurde auf Homogenität und Sensitivität geprüft. Moderator-Einflüsse wurden über eine Regressionsanalyse aufgedeckt.

› **Ergebnisse:** Die meta-analytische Integration der Primärstudieneffekte lieferte einen signifikanten, jedoch heterogenen globalen Effekt von d =0.46 (95% Cl, 0.16; 0.77). Die Interventionslänge erklärte die Varianz zwischen den Studien: Je kürzer die Interventionsdauer, desto stärker der Effekt. Ein Publikationsbias wurde nicht aufgedeckt.

› **Diskussion:** In echten experimentellen Settings scheint körperliche Aktivität die mit dem CRF assoziierten Gefühle der Müdigkeit und der Leistungsschwäche zu reduzieren. Der Effekt ist gering bis moderat. Er ist unabhängig von der Art der körperlichen Aktivität. In den Studien wurden Selbstreportmessungen als Outcomes bevorzugt, die für Verzerrungen anfällig sind.

KEY WORDS:
Cancer Related Fatigue, Cancer Survivor, Physical Activity, Meta-Analysis

SCHLÜSSELWÖRTER:
Cancer Related Fatigue, Krebsüberlebende, körperliche Aktivität, Meta-Analyse

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Introduction

After intensive mental or physical work, people often experience a state of exhaustion, which can be considered a normal physiological reaction. Sometimes feeling exhausted after a workout is even pleasant. Quite different from this state is the chronic fatigue or fatigue syndrome (CRF). It appears independent of previous strain. Affected people feel a prolonged state of physical, mental, cognitive and emotional fatigue. The CRF is common amongst cancer survivors. It does not correlate with age-related functional capacity of those affected and is not a state which ends with cancer treatment (e.g. chemotherapy). CRF persists even after cancer therapy ends (6).

CRF is the most common complication that occurs during cancer and cancer treatment. It severely restricts the quality of life of patients years after completing therapy (40) and it influences the daily lives of cancer survivors (7). The syndrome makes it difficult to return to "normality" even years after acute treatment (6).

Table 2

Qualitative assessment using the PEDro scale.Y=Yes, N=No, -=no details, 1=eligibility criteria were specified, 2=subjects were randomly allocated to groups, 3=allocation was concealed, 4=the groups were similar at baseline regarding the most important prognostic indicators, 5=there was blinding of all subjects, 6=there was blinding of all therapists who administered the therapy, 7=there was blinding of all assessors who measured at least one key outcome, 8=measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups, 9=all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analysed by "intention to treat", 10=the results of between-group statistical comparisons are reported for at least one key outcome, 11=the study provides both point measures and measures of variability for at least one key outcome. In total 10 points can be achieved, criterion 1 does not count towards the total score.

	1	2	3	4	5	6	7	8	9	10	11	TOTAL
Milne et al., 2007 (29)	Y	Y	-	Y	N	N	N	N	Y	Y	Y	5
De Backer et al., 2008 (2)	Y	Y	-	Y	-	N	N	-	-	Y	Y	4
Van Weert et al., 2010 (43)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Donnelly et al.,2011 (12)	Y	Y	Y	Y	-	-	-	Y	Y	Y	Y	7
Cantarero-Villanueva et al., 2011 (9)	Y	Y	Y	Y	-	-	-	Y	-	Y	Y	6
Littman et al., 2012 (25)	Y	Y	-	Y	-	-	-	Y	Y	Y	Y	6
Saarto et al., 2012 (36)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Cantarero-Villanueva et al., 2013 (10)	Y	Y	Y	Y	-	-	Y	Y	N	Y	Y	7
Kampshoff et al., 2015 (20)	Y	Y	Y	Y	-	-	Y	Y	Y	Y	Y	8
Schmitt et al., 2016 (37)	Y	Y	Y	Y	N	N	N	Y	-	Y	Y	6

Depending on the sample and the method of collection, different prevalences of CRF can be found in the literature. According to Wagner and Cella (44), an estimated 60% to 96% of patients suffer from CRF, according to Meneses-Echávez, González-Jiménez and Ramirez-Vélez (28) it affects up to 100% of cancer patients. Lawrence et al. (23) reported a similarly high prevalence rate with up to 91%. By contrast, the rates given by Piper and Cella (33) are much lower, ranging from 17% to 30%. According to Singer et al. (41) 34% of surveyed patients complained of symptoms of fatigue and exhaustion six months after discharge from hospital.

The symptomatics of CRF are complex. The complaints vary inter-individually (40). They entail feelings of exhaustion, lack of energy, lack of interest and memory disorders. Patients also complain of loss of motivation. They report depressive moods, loss of concentration, attention deficits, decreased physical performance, all coupled with an unusually strong feeling of fatigue and the increased need for rest and sleep (17).

Although nearly 31% of patients surveyed in post-cancer care report reduced levels of physical activity, over the past few years, physical activity has become an important module of oncological follow-up in addition to psycho-oncological rehabilitation (4). The size of the positive effect of physical activity varies. In a recent publication on the PACES-Study (Adaptive Pacing, Graded Activity and Cognitive Behavior Therapy, a Randomized Evaluation) written by White et al. (45) the effect sizes vary from zero effect to moderate effect sizes. A controversy about the effectiveness of physical activity aiming at reducing CRF started in the Journal of Health Psychology with an editorial by Geraghty (13). This controversy is – among other critique – fueled by the fact that self reports are often used to operationalize the CRF outcome variables. Self reports are susceptible to bias in treatment studies.

However, looking beyond the controversy surrounding PACES – without ignoring it – primary studies, meta-analyses and narrative reviews all suggest positive benefits of regular physical activity for long-term cancer survivors. Physical activity had a positive effect on physical and mental functions (6) and reduced CRF (22). Schmitz et al. (38) found that CRF levels were already decreasing immediately after ending a single session of physical activity and that higher fatigue levels were noted on non-exercise days than on active days. In addition, the authors found a link between duration of exercise and CRF reduction: the longer the exercise on a given day, the greater the reduction in CRF on the same day. Excessive intensities and/or duration of physical activity could, however, also increase CRF (38). Kindlon (21) discussed those negative effects of a workout. The effect of physical activity on the CRF thus appears dose-dependent (5).

We believe that a comprehensive analysis of the influence of physical activity on CRF would provide future researchers with a foundation for guiding subsequent interventions. Herein, we present a meta-analysis of interventions that have utilized guided physical activity to reduce CRF symptoms. Unlike previous analysis, we restrict the sample to working people and integrate only results of randomized controlled trials (RCT). We expect a reduction of CRF and examine possible conditions that moderate the effect size.

Method

The meta-analysis follows the recommendations of the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) checklist (30).

Search Strategy and Inclusion Criteria

An intensive search of electronic databases (Cochrane Library", "Psyindex", "Psycline", PubMed, "MEDLINE") was conducted in December 2016. We sought RCTs (English language), published between 2007 and 2016. The search string used across all data-bases was: "cancer survivor AND physical activity AND cancer-related fatigue", individually and combined.

Only RCTs intervening in order to increase the activity volume of the members of the experimental group were included. The control group subjects either received no intervention to promote physical activity or they were guided in therapeutic exercise or physiotherapy based on the recommendations given to treat CRF (7). Control groups could also be set up as a waiting control group. RCTs that grouped their subjects into clusters (e.g., different hospitals) and studies using crossover designs were also included in our meta-analysis.

Both sexes, different forms of cancer treatment and cancer entities have been included. Study participants had to be of working age (18 to 65 years old) and able to follow a guided exercise program. Studies are included if they used questionnaires or other self-report instruments and reported an overall fatigue value as an outcome variable.

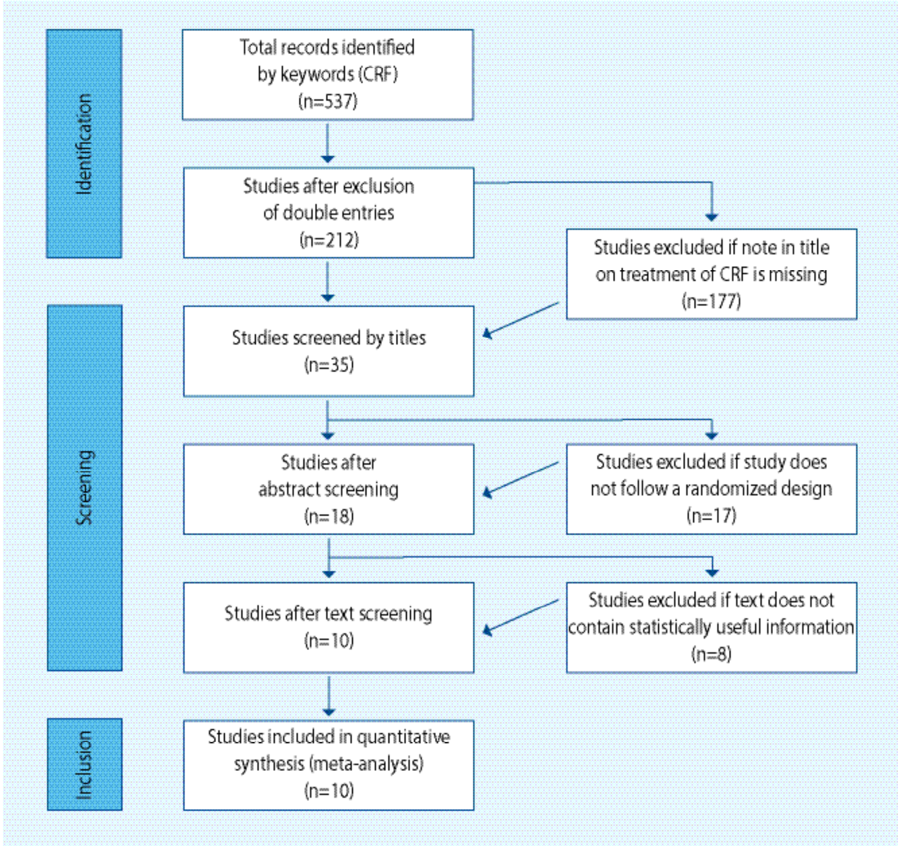

Figure 1

Flow diagram of study selection.

Coding and Evaluation of the Studies

All studies that met the inclusion criteria were coded and included with information on their main characteristics: general information on the study (author, year of publication, country in which the study was conducted and source of publication), information on study participants (sex, mean age, cancer entity, treatment method), information on the study design (data acquisition, cluster or crossover design), information on the type and/or treatment of the control group (without intervention, with an alternative intervention or a waiting control group) and additional information (intervention implementation, location, length, focus of training, training implementation, questionnaire for recording the CRF). Quantitative statistical data were used to record the sample size, the mean value of outcome variables and the standard deviation of both groups. If primary studies failed to report descriptive statistical indices like the mean and/or the standard deviation, the p-value was registered. Only some of the primary studies showed the standardized mean difference (Cohen's "d") and thus an effect size.

The methodological quality of the primary studies was assessed using the German-language version of the PEDro scale of the 'Physiotherapy Evidence Database', where a higher cumulative score indicates a higher methodological quality and points less to the risk of bias (15).

Meta-Analytic Procedures

The software program "R Version 3.3.3" with the packages comput.es and metafor was used for the meta-analytical calculations (34).

Insofar as Cohen's "d" could not be obtained directly from the studies, the effect size was calculated indirectly from the other statistical parameters. In order to increase the impact of studies in which a larger number of subjects participated, all studies were weighted by their inverse outcome variance.

In the meta-analytical model, heterogeneity of the primary studies was assumed. The individual effects were therefore integrated into the random effects model. The global effect was tested for homogeneity. As one parameter, the χ^2-test Cochrane's Q was calculated as a reliable indicator of heterogeneity and, as a second parameter, the I^2 according to Higgins and Thompson (16) was estimated from Cochrane's Q, which provides information about the proportion of the total variation in the study estimates due to heterogeneity.

In the case of proven heterogeneity, a moderator analysis was carried out using the mixed-effects model with the a priori assumed moderator variables: duration of the intervention period (shorter than 12 weeks, 12 weeks, longer than 12 weeks), type of intervention (guided versus mixed; i.e. autonomous and guided training), focus of the intervention (muscle power versus stamina) and intervention method (mixed or pure form to increase physical activity), mixed form consists of interventions to increase muscle power and stamina, whereas the pure form represents a training of muscle power or stamina or yoga).

Results

Review Procedure

Study selection was conducted following six phases (see Figure 1). During the initial stage, all citations from each database query were imported into a central citation manager (Citavi-5). During the second step, all double entries were excluded. In the next phase, the titles for publications that referenced physical activity and CRF were screened, removing those that definitively did not match inclusion criteria. In the following phase, the abstracts of the remaining articles were examined and those articles that did not meet criteria were excluded. During the final phase, full-text citations were reviewed to make sure that all criteria were met. From those eligible, all study descriptives were extracted and tabulated.

In total, ten primary studies (see Table 1) with a total of 1,497 subjects were included in the analysis. A study by Kampshoff et al. (20) reported two interventions to increase physical activity. The effects of the two study arms were included separately in the meta-analysis.

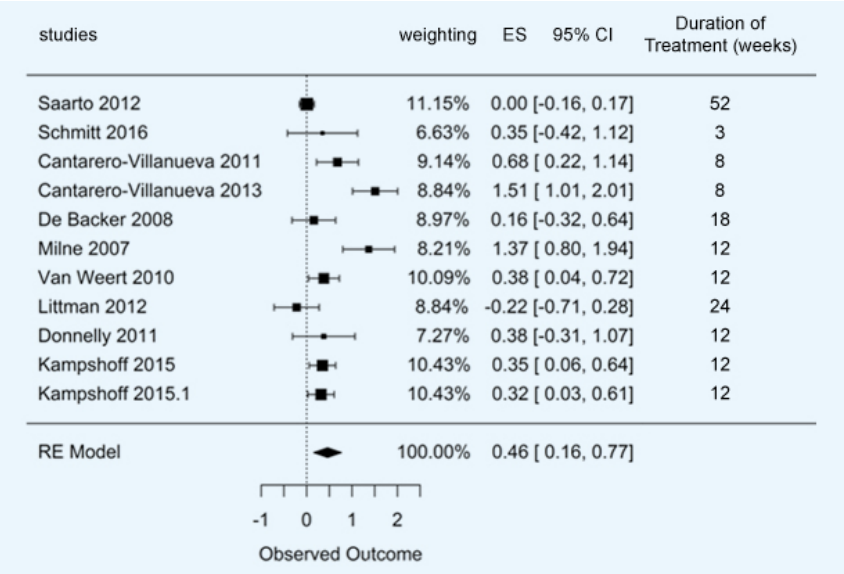

Figure 2

Forest Plot of effect sizes (Cohen's d) per study.

Quality Assessment

In order to assess quality at the study level, the PEDro Scale was used (15). Table 2 provides information about the quality of the primary studies. The PEDro scale addresses ten categories of threats to study validity. Each category has to be answered with "yes" (criterion fulfilled) or "no" (criterion not fulfilled). Table 2 shows that none of the integrated primary studies achieved the full score (i.e. 10 points)

Data Synthesis

The meta-analysis of the 10 studies included indicates that physical activity reduces CRF. As can be seen in the Forrest plot (see Figure 2), the analysis yielded a statistically significant overall effect-size of d=0.46 (95% CI: 0.16-0.77; z=2.9; p<.0001).

The homogeneity test yielded a value of 56.14 according Cochrane's Q with an associated p-value of p <.0001. Also, the calculated I^2 with 85.68% shows a statistically significant heterogeneity of the primary study effects, supporting the use of the random effects meta-analysis.

However, neither the funnel plot (Figure 3) nor the calculation of the "fail-safe N" identifies any significant bias from study selection. After calculating the "fail-safe N" according to Rosenthal, 169 primary studies would be necessary to push the determined overall effect below the level of significance. As a guideline for a tolerance level, Rosenthal suggests a value of 5*k+10≤X, where k is the number of integrated primary study effects (35).

The moderator analysis, which was conducted on the basis of the heterogeneity of the primary studies, identifies the duration of the intervention period as a significant moderator influencing the effect size (b=-0.4695; z=-3.27; p<.001): the shorter the period of the intervention, the greater the reduction of CRF.

The study by Canterero-Villanueva et al. (9) is an example of the approach of a study with a short duration of intervention and a strong effect size (Cohen's d=0.68; p<.001 in favor of the intervention group). These authors examined 78 breast cancer survivors (averaging 49 years of age) who underwent various cancer treatment modalities. The impact of an eight-week treatment program on the CRF was investigated. The randomized controlled intervention included a multi-modal training program consisting of a 90-minute workout (low-intensity strength training, endurance and relaxation) that took place three times a week.

Discussion

According to Cohen, the result of the overall effect size of d=0.46 is defined as "small". It misses the threshold of a medium effect size, which is set by convention at d=0.50, but only just. Lipsey and colleagues (24) believe that many studies underestimate the true effect size by using small samples, sample-based significance tests and survey instruments that are not completely reliable. All this concerns the present selection of primary studies, too.

The result of the meta-analysis confirms the previous evidence: physical activity contributes to a moderate reduction of CRF. Previous studies report that physical activity has a positive effect on cancer-related fatigue both during and after cancer treatment (4, 5, 8, 28, 31, 42).

A recent meta-analysis reports a decrease in CRF due to physical activity, which manifests itself in an effect size of d=0.32 (95% CI: 0.13-0.52) (11). Other meta-analyses as well as narrative reviews reporting similar effect sizes include patients regardless of their treatment status. The studies have in common their statement that physical activity can contribute to the reduction of CRF, and the effect is also usually low to moderate (11, 18). However, because these studies have included patients regardless of their treatment status, their informative value is reduced. Most meta-analyses also include cancer survivors of all ages, with most of the study participants at retirement age. Juvet et al. (19) reported analyses in which only cancer survivors of selected cancer entities (mostly breast cancer) were treated. A d=0.32 (95% CI: 0.14-0.49) also points to a small effect size.

The distinction of the analysis reported here in relation to similar meta-analyses is the exclusive integration of experimentally-determined primary study effects, which were carried out after the end of a recent cancer therapy. Other differences to other analyses are the exclusive integration of working-age cancer survivors and the inclusion of various cancer entities.

However, several factors in the present meta-analysis also limit its informative value. Thus, despite predefined criteria, only limited uniformity could be established between the primary studies, as the variables and constructs differed in the samples and in the operationalization of the CRF due to the characteristics of the subjects. However, the moderator analysis shows no influence of the survey methods and the thus operationalized constructs

Although we solely included randomized-controlled primary studies in the meta-analysis, the quality of the integrated primary studies differed. So the meta-analytical outcome may also suffer from the integration of low-quality primary studies. For meta-analyses, this is a frequently lamented fact that will only change if treatment studies are based on the specifications of CONSORT (39) (see also http://www.consort-statement.org/, [24th October 2017]) and consistently control possible distortions. Despite the experimental design, the research area suffers from lack of consistent implementation of methodological quality criteria, which should be based on the specifications of CONSORT, for example, in order to reduce the risk of distortions. On the basis of the meta-analytic data obtained here, an experimental design would be desirable that contrasts on the one hand different treatment durations and on the other hand uses more reliable outcome variables and not only self-reported data. For the latter, it would also be necessary to conduct research in advance on the validity of bio-psychological data that reliably informs about the subjective and functional health of those affected by CRF.

To determine a treatment effect does not mean to explain the effect. Various hypotheses are currently being discussed for the positive effect of guided physical training on CRF, which we will only mention here for completeness, but not comment on (a description of the exact processes can be found, for instance, in the work of Al-Majid and colleagues, 2009 (1), or in the work of LaVoy and colleagues, 2016 (22)). The mechanisms hypothezised include: improvements of cardiovascular fitness and an increase in muscle mass (1), the release of anti-inflammatory cytokines (46), which leads to endocrine and metabolic changes (14), which in turn lead to changes in processes of the central nervous system, the neuromuscular metabolism (32) and influences the circadian rhythm (14). It is stated that those biological and physiological changes trigger further reactions and adaptations in the body, that manifest themselves in mental, behavioural and social mechanisms and are predominantly hormonally rooted. Especially those hormones that are secreted due to physical activity lead to changes which are reflected in an improved quality and quantity of sleep and which counteract loss of appetite (14). On the mental level, altered hormone levels could lead to a reduction of worry and stress as well as to a reduction of depressive moods (26). Furthermore, physical activity could strengthen self-esteem and self-efficacy, thereby restoring confidence in patients' own performance (3).

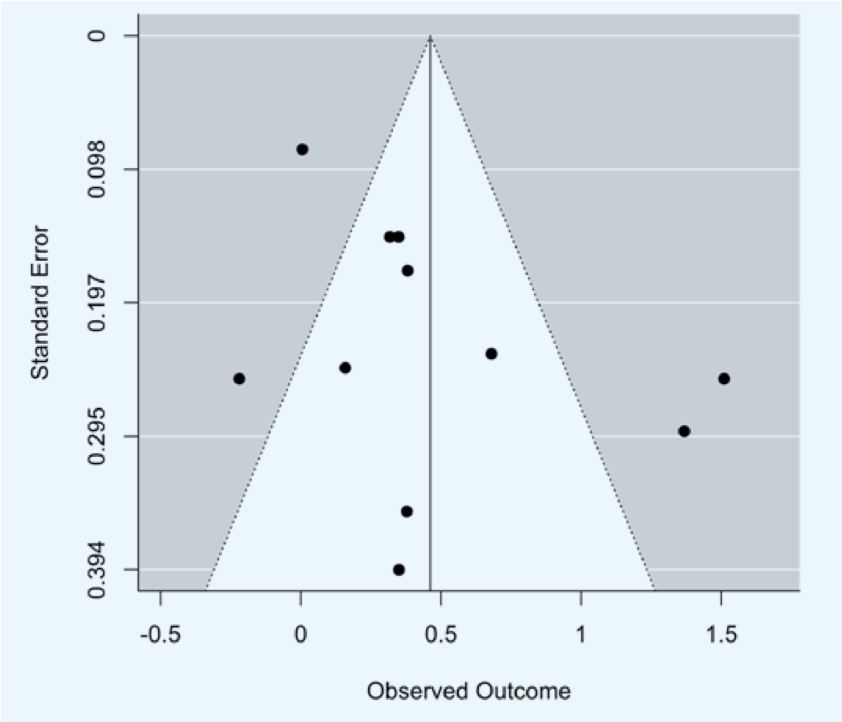

Figure 3

Funnel plot.

Conclusion for Pracitical Use

The results of the present analysis, in line with previously-published studies, indicate that supplementing conventional care-based cancer follow-up, regardless of cancer entity or treatment status, may help reduce CRF. The moderator analysis indicates the length of intervention as significant for effectiveness. Shorter interventions even lead to a greater reduction of CRF than longer-lasting interventions.

Aerobic endurance training combined with strength training seems to be the most effective strategy when aiming at reducing CRF. Previous publications have refrained from prescribing a certain volume (defined as duration x intensity) of the physical activity on a flat-rate basis. The reason given is that the feasibility of training depends on numerous factors (tumor entity, therapeutic procedure, previous sport experience, physical conditions and fatigue state) (3). A research group around McNeely et al. (27) refers above all to the dependence of stress intensity on the fatigue level. The present meta-analysis should also direct the focus to the length of an intervention period. To register changes in the health condition of those affected by CRF, outcome variables should be measured repeatedly, not just at the beginning and the end of treatment.

However, despite all the positive effects that have been reported to date, it should not be forgotten that physical activity can also lead to negative effects. This fact should prevent one from using physical activity indiscriminately. Physical activity is not risk-free, especially for patients suffering of CRF.

Conflict of Interest

The first author declares that she was financially supported by the department „Kultur, Sport, Freizeit" of the Robert Bosch GmbH, Stuttgart, Germany.

Table 1

Main aspects of the meta-analytic integrated RCTs.

AUTHORS	YEAR	CHARACTERISTICS	N	CONTROL GROUP	TYPE AND DURATION OF THE TREATMENT	RELEVANT OUTCOMES FOR THE META-ANALYSIS	RESULTS
Milne et al.	2007	RCT with crossover design Patients with breast cancer after mixed treatment Average age 55 years	58	untreated, waiting control group	12-week exercise program (endurance and strength training)	Schwartz Cancer Fatigue Scale (SCFS)	After the 12-week intervention, IG decreased from 15.7 (4.1) to 11.9 (3.2). For the CG, the value increased from 16.5 (4.0) to 17.7 (4.7).
De Backer et al.	2008	Cluster randomized (by location of treatment) Mixed cancer entities; chemotherapy Average age 48 years	90	untreated	18-week strength training (high-intensity training and interval training)	Multidimensional Fatigue Inventory (MFI)	The 18-week strength training significantly contributed to the reduction of CRF with a difference of 4 units on the questionnaire.
Van Weert et al.	2010	RCT Mixed cancer entities; mixed treatments Average age 49 years	209	untreated, waiting control group	12-week exercise program (endurance and strength training)	Multidimensional Fatigue Inventory (MFI)	After the 12-week intervention, IG CRF levels had dropped from 15.6 (3.3) to 11.6 (3.8) and CG's values dropped from 15.1 (3.3) to 13.1. (4.1).
Donnelly et al.	2011	RCT	33	untreated	12-week exercise program (endurance and strength training)	Multidimensionale Fatigue Symptom Inventory; Functional Assessment in Chronic Illness Therapy-Fatigue Subskala	Significant reduction in CRF values from pre- to posttreatment
Canterero-Villanueva	2011	RCT breast cancer; mixed treatments Average age 49 years	78	untreated	8-week exercise program (endurance and strength training)	Piper Fatigue Skala (PFS)	Cohens d = 0.68; p < .001 in favor of the IG
Littman et al.	2012	Block randomized (by age, BMI and cancer stage) breast cancer; mixed treatment; Overweight patients Average age 60 years	63	untreated, waiting control group	6-month yoga program	Fatigue-Skala (FACIT-F)	Significant reduction of the CRF. The more frequently the subjects trained under guidance, the greater the reduction of the CRF
Saarto et al.	2012	RCT Breast cancer; mixed treatment Average age 52 years	573	untreated	12 month exercise program (endurance and strength training, focus on endurance)	Fatigue-Skala (FACIT-F)	no significant differences between the two groups
Cantarero-Villanueva et al.	2013	RCT Breast cancer; mixed treatment Average age 48 years	68	untreated	8-week aquagym program	Piper Fatigue Skala (PFS)	Cohen's d = 1.51; p< .001 in favor of the IG
Kampshoff et al.	2015	RCT Mixed cancer entity; chemotherapy Average age 54 years	277	2 treatment groups: Untreated control group, waiting control group	12-week exercise program (endurance and strength training) Intervention Group1: High Intensity Training Intervention Group 2: Low-to-moderate-intensity training	Multidimensional Fatigue Inventory (MFI)	Significant reduction of CRF in both groups from pre- to posttreatment. No significant differences between the two treatment groups.
Schmitt et al.	2016	RCT breast cancer Mixed type of treatment Average age 53 years	28	Control group received a low-to-moderate intensity training	3-week endurance training (high-intensity interval training)	Multidimensional Fatigue Inventory (MFI)	Cohen's d = 0.35; p <0.05 in favor of the IG

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