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EFFECTS OF EXERCISE INTERVENTION ON SLEEP AND SURVIVAL IN ADVANCED CANCER SURVIVORS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT – *Objective:* The effectiveness of exercise in addressing sleep disturbance and improving survival outcomes among advanced cancer survivors remains inconsistent. To evaluate and synthesize the effectiveness of exercise on sleep disturbance and survival in advanced cancer survivors.

Materials and Methods: Databases of the Cochrane Library, PubMed, PsycINFO, CINAHL, EMBASE, and China National Knowledge Infrastructure (CNKI) were searched. A total of 12 randomized controlled trials (RCTs) were included. A total of 12 RCTs with 1313 participants of advanced cancer survivors were included. Outcomes were assessed using the revised Cochrane risk-of-bias tool in RevMan. A random-effects model was used, and the results are presented as summary standardized mean differences (SMDs) with their 95% confidence intervals (CIs). To explore sources of heterogeneity, a meta-regression was conducted using Stata 15.0.

Results: Meta-analysis revealed a significant inverse association between exercise levels and subjective sleep quality (SMD = -0.42, 95% CI: -0.70 to -0.13). Meta-regression identified a significant moderating effect of gender proportion on exercise's impact on sleep disturbance (95% CI: 0.36 to 1.32, p = 0.002). Subgroup analysis indicated that exercise significantly reduced sleep disturbance, specifically in cohorts with ≤50% female participation (SMD = -0.63, 95% CI: -0.92 to -0.34). Conversely, pooled data showed no significant effect of exercise interventions on overall survival in advanced cancer survivors.

Conclusions: Long-term exercise should help improve sleep, especially for male patients with advanced cancer. The impact of exercise intervention on survival should be assessed not only at advanced stages of cancer, but also from early exercise habits. More evidence is needed from randomized trials of exercise interventions on survival in advanced cancer survivors.

KEYWORDS: Exercise, Advanced cancer, Sleep disturbance, Survival, Meta-analysis.

INTRODUCTION

Sleep problems can occur at any stage of cancer, but they are particularly prevalent among those who have survived advanced cancer[1]. Sleep disturbances may be caused by the cancer itself, stress related to the cancer, symptoms of the cancer, and/or symptoms of the cancer treatment. These disturbances may become chronic or worsen as the symptoms become more complex towards the end of life[2]. Sleep disruption can include difficulty falling asleep, difficulty staying asleep, awakening up early, and frequent complaints of non-restorative sleep and poor sleep efficiency[3]. A multicenter, prospective observational study reported that 70.5% of the 174 participants with locally advanced or metastatic cancer experienced poor sleep quality, predominantly women at 57.5%[4]. Another prospective study found that 58% of 292 patients with advanced cancer complained of deteriorating sleep quality, primarily manifested as sleep duration of less than 6 hours and sleep latency of at least 30 minutes or more[5]. By contrast, the average sleep duration in the general population is 6.5-7.5 hours per night, with an average sleep latency of 15-20 minutes[5,6].

Sleep disturbances may significantly worsen the physical and psychological distress of advanced cancer patients, directly undermining their quality of life and compromising survival outcomes[5,7,8]. Unsurprisingly, emerging evidence suggests that disturbed sleep is a predictor of mortality in advanced cancer. Specifically, a non-linear association exists, with both extremes of sleep duration correlating with increased mortality risk after adjustment for contributing factors[6]. Instead, better sleep efficiency, less sleep disturbance, and shorter wakefulness were significantly associated with reduced overall mortality in women with advanced breast cancer[9].

Previous research has explored various non-pharmacological interventions to alleviate sleep disturbances in patients with advanced cancer. Among these, exercise has emerged as a particularly promising strategy due to its safety, cost-effectiveness, and multifaceted benefits for physical and psychological well-being[8]. Additionally, greater physical activity was a significant predictor of increased survival time in advanced breast cancer[10]. Although the benefit of exercise for sleep problems in cancer patients has been established, existing meta-analyses on exercise and sleep in cancer have focused exclusively on early-stage disease[11], creating a significant evidence gap for advanced cancer patients who endure a greater symptom burden. Consequently, there is a critical need to synthesize evidence specific to this population. This meta-analysis of randomized controlled trials (RCTs) therefore seeks to evaluate the effectiveness of exercise in improving sleep disruption and survival rates among advanced cancer survivors.

MATERIALS AND METHODS

The meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered at Prospero with the ID number CRD42024576080.

Literature Search

Searched databases included the Cochrane Library, PubMed, PsycINFO, CINAHL, EMBASE, and China National Knowledge Infrastructure (CNKI) up to August 2024. Search terms were as follows: (a) aerobic exercise (AE), or resistance training (RT), or strength training (ST), or mixed AE/RT/ST, or Yoga, or Tai chi; (b) sleep quality, or sleep disturbance, or poor sleep, or sleep; (c) advanced cancer survivors. The reference lists of related reviews were manually searched. There were no search limitations in publication date or language.

Criteria for Study Inclusion/Exclusion

The inclusion criteria: 1) participants were adult aged over than 18 years and diagnosed with advanced cancer (stage IIIb/IV of lung cancer; stage IV of colorectal cancer; or metastatic breast cancer; or locally advanced/metastatic mixed cancer) with a score of the Eastern Cooperative Oncology Group (ECOG) performance status, or Zubrod performance status, or WHO performance status less than 2, or Karnofsky Performance Scale (KPS) scores ≥ 80 (P); 2) exercises intervention was aerobic exercise (AE), resistance training (RT), strength training (ST), mixed AE/RT/ST, Tai chi, and/or Yoga (I); 3) outcome variables were sleep quality, sleep disturbance, sleep efficiency and/or survival rate (O); 4) the study design was a RCT.

The exclusion criteria were: 1) the protocol of an interventional program without results section; 2) the intervention contains comprehensive multidisciplinary healthy support; 3) the physical exercises intervention combined with nutritional counselling sessions.

Risk of Bias and Quality of Evidence

The quality of RCTs was judged by the Cochrane Collaboration's tool in the light of the random sequence generation, allocation concealment, completeness of outcome data, blinding of evaluators and participants, and other sources of bias and attrition bias. Each study was categorized as unclear, high, or low risk of bias for each domain[12]. Disagreements were evaluated and resolved by the third reviewer. Publication bias was examined using trim and fill analysis in Stata version 15 (Stata Corp LP, College Station, TX, USA).

Study Selection and Data Extraction

Two independent reviewers (Y.L., and Z.Z.) screened titles and abstracts. Full texts were then imported into EndNote (Version X9, Clarivate Analytics) when studies were highly relevant to the inclusion criteria. Afterwards, three additional independent researchers (S.L., W.T., and M.H.) carefully reviewed the full texts using the self-developed Checklist for verifying eligibility (Figure 1).

The primary outcome of the included trials was the efficacy of exercise interventions on sleep and survival for advanced cancer survivors, compared with the control group. Included studies used different outcome measures to evaluate the sleep quality, and most studies employed the Pittsburgh Sleep Quality Index (PSQI) and the insomnia item of the EORTC QLQ-C30 for subjective measures.

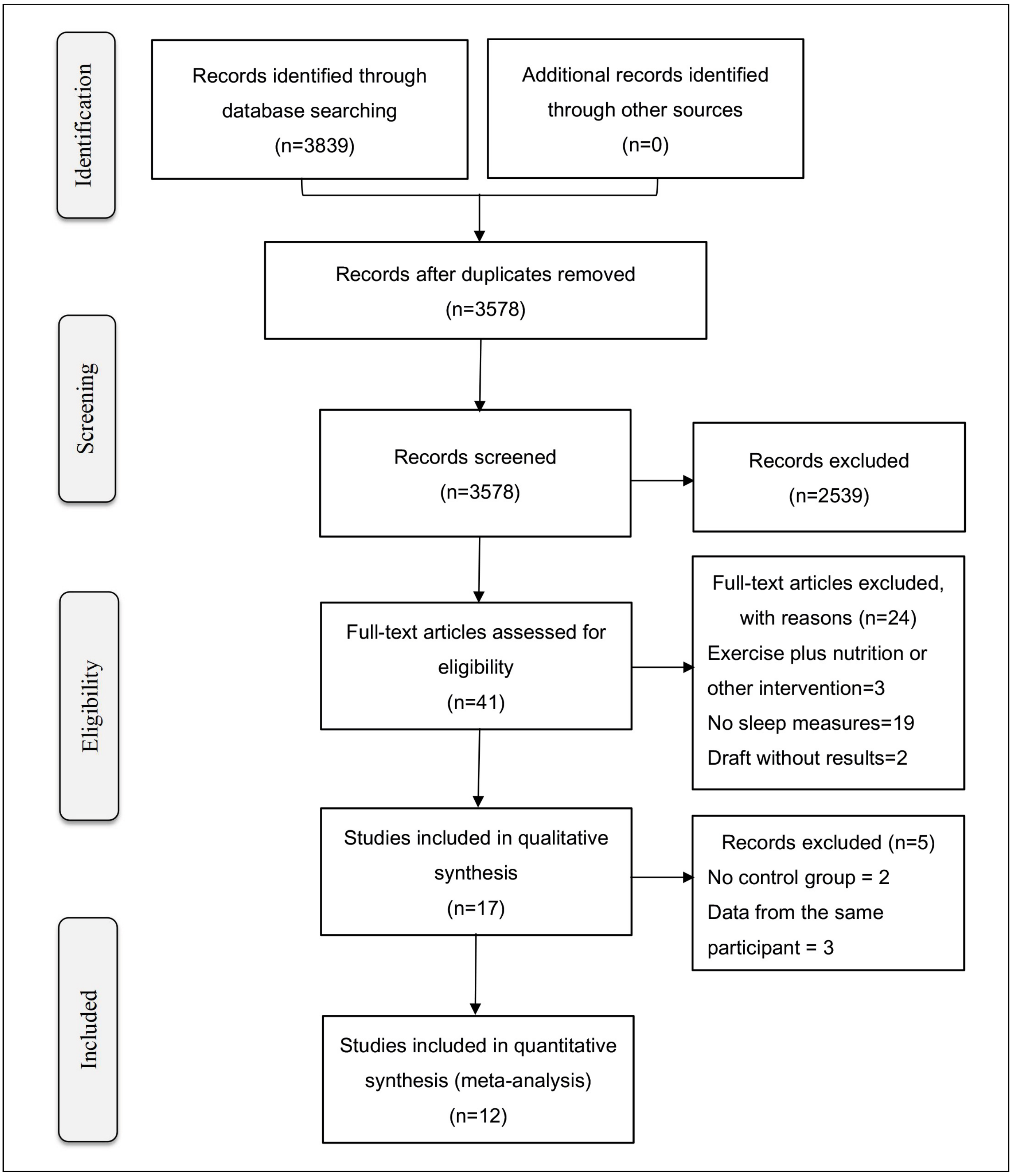


Figure 1. Flow chart of study selection process.

PSQI is a 24-item scale that measures sleep disturbance during the past month along seven dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The scores on these seven dimensions are summed to yield a global score. An individual's average score that exceeded the cut-off score of 5 was considered to be a poor sleeper[13]. The EORTC QLQ-C30 assesses general aspects of health-related quality of life (QoL) of patients with cancer, including five functional scales (i.e., physical, role, cognitive, emotional, social), three symptom scales (i.e., fatigue, pain, nausea and vomiting), a Global Health Status/QoL scale, a number of single items assessing additional common symptoms of cancer (i.e., dyspnea, loss of appetite, insomnia, constipation, diarrhea), and a single item measuring the financial impact of disease. Among these, the insomnia item is reported on a 1 to 4 verbal response scale with response options of 'not at all', 'a little', 'quite a bit', and 'very much'. The score ranges from 0 to 100, with a high score representing a high level of sleep problems[14]. One study used the Pittsburgh Insomnia Rating Scale with 65 items, which was designed to assess the severity of insomnia in clinical settings. The higher scores represent worse sleep quality[15]. Another study utilized the Sleep Quality Numeric Rating Scale (Sleep Quality NRS), which is an eleven-point numeric rating scale to assess pain and sleep quality, with higher scores indicating greater pain intensity and better sleep quality[16]. In this analysis, the Sleep Quality NRS scores were reverse-coded for directional consistency with the PSQI, in which higher values indicate worse sleep quality.

Data Synthesis

The RCTs were grouped according to the outcome variables of sleep quality and survival rate. The sleep quality from the included trials was combined into two subgroups of subjective and objective scores in the analysis: sleep disturbance (subjective) and sleep efficiency (objective). If an identified study represented multiple comparisons (intervention arms) such as aerobic exercises and Tai chi, or outcomes at different time points of the post-intervention and the end point of the follow-up, each comparison between the intervention group and the control group was identified as a separate trial. The sample size in the control group was divided evenly among the comparisons to avoid double-counting the subjects and consequent unit-of-analysis error[17].

Statistical Analysis

The mean difference in sleep disturbance and sleep efficiency at the post-intervention and the last observation of the follow-up were extracted to conduct the comparison. The mean difference was achieved by the value at the endpoint subtracted from the value at baseline. If the standard deviations (SDs) were reported only for the baseline and the end time point in both the intervention and control groups, then SDs for various time changes from baseline were calculated by the following formula, assuming a correlation coefficient (Corr) = 0.8[18].

$$SD_{\text{change}} = \sqrt{(SD_{pre-intervention})^2 + (SD_{post-intervention})^2 - (2 \times Corr \times SD_{pre-intervention} \times SD_{post-intervention})}$$

Review Manager 5.4 (RevMan 5.4) was utilized to perform the meta-analysis for each group[19]. Higgins' I^2 statistic, ranging from 0% to 100%, indicated the degree of heterogeneity among the included studies, and scaled the proportion of inconsistency[20]. Standardized mean differences (SMDs) and their corresponding 95% confidence interval (95% CI) were utilized to estimate the pooled effects of the included trials on sleep disturbance and sleep efficiency. The random effects model was used to calculate effect sizes to provide more balance in the weight of individual studies, and the summary effect was more conservative[21,22]. Meta-regressions were performed using Stata version 15 for sensitivity analysis to evaluate heterogeneity with respect to the study characteristics. We performed individual regression models for exercise duration and gender differences. A trim and-fill approach and Begg's and Egger's tests were performed to investigate possible publication bias.

The efficacy of exercise intervention on survival was evaluated by combining study-specific Hazard ratios (HRs) and 95% CIs with random-effects meta-analysis models using log-transformed HR (log HR). Following the approach proposed by Parmar et al (1998)[23], if HR and its variance were not presented, the log HR was estimated from the published survival curves of the included studies, with survival results for both groups at time points along the survival curves to estimate the HR and 95% confidence intervals between the intervention and the control groups. The probability (*p*) value of ≤ 0.05 was considered statistically significant.

RESULTS

Quality Assessment and Publication Bias Analysis

The rating for each record according to the seven domains was defined by the Cochrane Collaboration tool and is shown in Figure 2. The assessment of each risk of bias, expressed as a percentage of all included studies according to the authors' judgment, is shown in Supplementary Figure 1. Publication bias was initially confirmed using funnel plot analysis to verify the validity of the study results, followed by correction using Duval and Tweedie's trim-and-fill method[24]. The corrected effect size of sleep disturbance obtained using the latter method was 0.29 (95% CI: 0.47 to 0.83), which represented a subtle upregulation from the original effect size of 0.23. Therefore, the results of this study were considered to be acceptable. Additionally, Begg's and Egger's test values of sleep disturbance were 0.36 and 0.63, respectively, indicating no significant public bias in the identified studies.

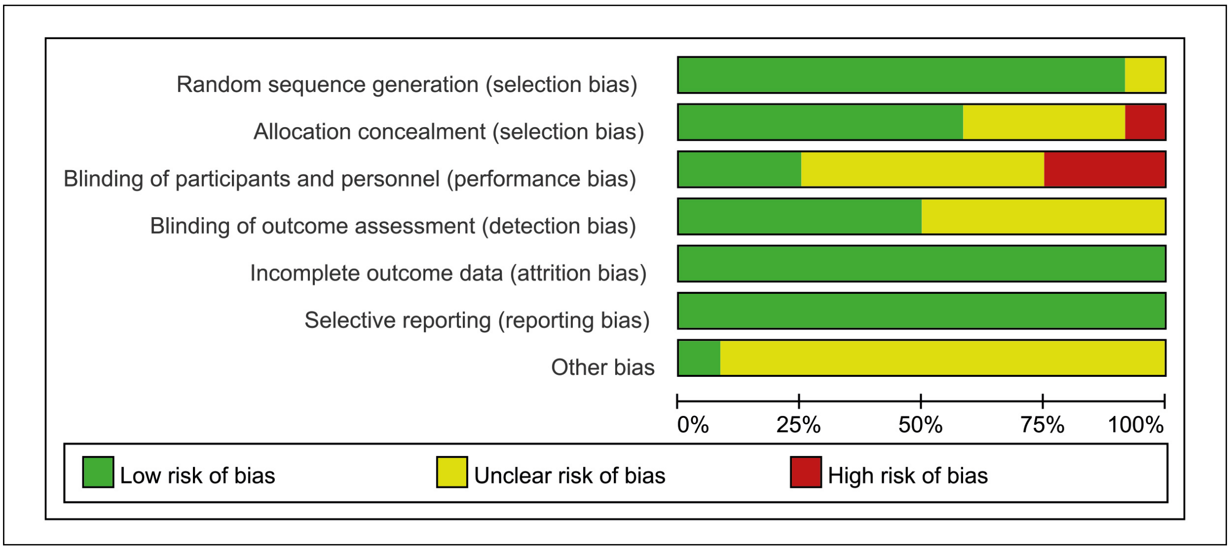


Figure 2. Graph of Risk of Bias (RoB) for each study according to the seven domains defined by Cochrane Collation's tool.

Overview of the Included Studies

A total of 1,313 participants from 12 studies were included in the present study. The basic characteristics and significant measures of the studies are summarized in Table 1. Overall, all the included studies were RCTs. The majority of participants were female adults living with metastatic breast cancer or advanced lung cancer. The average age was around or above 50 years old. At baseline, the participants could have poor sleep, as the mean values of PSQI were all above 5[8, 25-27]. The insomnia scores of the EORTC QLQ-C30 ranged from 18.33 to 40.30[28-31], and the Insomnia Rating Scale scores were 43.03 or higher in the included studies, suggesting the mild or moderate insomnia distress experienced by patients[32].

Exercise interventions encompass various modalities, including aerobic exercises[8,25,26,29,30], strength training[33], mixed aerobic/resistance/strength training[28,31], Tai Chi[8,25], and Yoga[27,32]. The duration of the exercise intervention ranged from 2 to 16 weeks. Five studies carried out exercise for a maximum of 8 weeks[26-28,33,34], while the others lasted at least 12 weeks or more[8,25,29,30-32,35].

Effects of Exercise on Sleep in Advanced Cancer Survivors

The subjective sleep disturbance or insomnia was measured by the PSQI[8,25,26], Pittsburgh Insomnia Rating Scale (IRS)[32], Insomnia Symptom Numeric Rating Scales[33], and the insomnia subscale of EORTC-QLQ-C30[27-31].

Table 1. The basic characteristics and major measures of the included studies.

Author	Country	Participants	Cancer type & stage	Motor Function	Intervention	Comparison	Measurements
Cheung et al[25], 2021	Hong Kong, China	Female: 46.7% n=30 $PSQI_{baseline}$:	Lung cancer (stage IIIb /IV)	KPS scores ≥80	1) A 12-week Tai chi exercise (30 minutes at least 3 times per week). n=9 Age: 61.11±7.01 years $PSQI_{baseline}$: 8.44 2) A 12-week Aerobic exercise (30 minutes twice per week). n=10 Age: 61.00±12.12 years $PSQI_{baseline}$: 5.30 Follow-up: 6-month/1-year	Self-management [physical activity by the World Health Organization (WHO)] Age: 58.36±9.32years n=11 $PSQI_{baseline}$: 8.18	PSQI; Wrist-worn accelerometers (Actigraph)
Porter et al[27], 2019	USA	Female: 100% n=63	Metastatic Breast cancer	Excluded if ECOG Performance Status rating ≥ 3 or KPS scores < 60	An 8-week yoga intervention (eight 120-minute weekly). n=43 Age: 56.3±11.6 years $PSQI_{baseline}$:8.00 Follow-up: 3-/6-month	A supportive care Age: 59.4±11.3 years n=20 $PSQI_{baseline}$: 5.50	PSQI
Rao et al[32], 2017	India	Female: 100% n=91	Metastatic Breast cancer	Zubrod's performance status 0–2 (ambulatory >50% of time)	A 12-week yoga session (60 minutes two times per week). n=45 Age: 48.9±9.1 years $IRS_{baseline}$: 43.03 Follow-up: none.	Standard care Age: 50.2±9.2 years n=46 $IRS_{baseline}$: 55.77	IRS
Cheville et al[33], 2013	USA	Female: 47% n=66	Mix cancer (stage IV)	Ambulatory Post Acute Care (AM-PAC) Computer Adaptive Test (CAT) scores between 50 and 75	An 8-week Rapid, Easy, Strength Training (REST) (at least twice a week for a total of four sessions). n=33 Age:63.8± 12.5 years Sleep $NRS_{baseline}$: 58.57 Follow-up: 1-year.	Usual care Age: 65.5 ± 8.9 years n=33 Sleep $NRS_{baseline}$: 68.92	Sleep Quality NRS; Overall Survival

Continued

Table 1 *(Continued)*. The basic characteristics and major measures of the included studies.

Author	Country	Participants	Cancer type & stage	Motor Function	Intervention	Comparison	Measurements
Takemura et al[8], 2024	Hong Kong, China	Female: 54% n=226	Lung cancer (stage IIIb/IV)	ECOG Performance Status of 0 to 2	1) Aerobic exercise (AE) for 16 weeks (8 supervised group exercise sessions, 2 sessions per month). n=75 Age: 61.43± 8.29 years $PSQI_{baseline}$: 5.01 2) Tai chi (twice weekly for 16 weeks). n=76 Age:61.67± 7.39 years $PSQI_{baseline}$: 5.92 Follow-up: 1-year	Control received written information on the World Health Organization's recommended level of physical activity Age: 61.12± 10.38 years n=75 $PSQI_{baseline}$: 5.75	PSQI; Overall survival
Ligibel et al[30], 2016	USA	Female: 100% n=101	Metastatic Breast cancer	ECOG Performance Status of 0 to 1	AE: a 16-week, moderate-intensity aerobic exercise program (150 minutes of moderate intensity exercise per week). n=48 Age:49.3± 9.6 years $Insomnia_{baseline}$: 33.3 Follow-up: none.	wait-list control group Age: 50.7± 9.4 years n=53 $Insomnia_{baseline}$: 40.3	Insomnia item of EORTC-QLQ-C30
Dhillon et al[26], 2017	Australia	Female: 45% n=112 Age range: 34- 80 years	Lung cancer (stage IIIb/IV)	ECOG performance status (PS)≤2	AE: an 8-week aerobic exercise (eight weekly sessions). n=56 $PSQI_{baseline}$: 9.59 Follow-up: 6-month.	Usual care n=56 $PSQI_{baseline}$: 10.06	PSQI Overall survival
Bade et al[29], 2021	USA	Female: 75% n=40	Lung cancer (stage IIIb/IV)	Excluded if enable to walk safely	A 12-week "normal" activity level through establishing a step count recommended by an accelerometer. n=20 Age: 66.55± 7.28 years $Insomnia_{baseline}$: 18.33 Follow-up: uncertain.	Usual care Age: 63.20±9.80 years n=20 $Insomnia_{baseline}$: 25.00	Insomnia item of EORTC-QLQ-C30

Table 1 *(Continued)*. The basic characteristics and major measures of the included studies.

Author	Country	Participants	Cancer type & stage	Motor Function	Intervention	Comparison	Measurements
Adamsen et al[28], 2009	Denmark	Female: 72.9% n=269	Mixed advanced cancer	WHO performance status of 0 or 1	A 6-week mixed aerobic/ resistance (nine hours per week). n=135 Age: 47.2±10.7 years $Insomnia_{baseline}$: 22.7 Follow-up: none.	Usual care Age: 47.2±10.6 years n=134 $Insomnia_{baseline}$: 32.7	Insomnia item of EORTC-QLQ-C30
Mikkelsen et al[31], 2022	Denmark	Female: 57.1% n=84	Mixed cancer (locally advanced or metastasis)	ECOG performance status score ≤2	A 12-week mixed aerobic/ resistance (twice weekly in sessions of 60 minutes). n=41 Age, median (IQR): 72.1 (67.3-74.5) years $Insomnia_{baseline}$: 26.00 Follow-up: none.	Usual care Age, median (IQR): 71.5 (68.5-75.3) years n=43 $Insomnia_{baseline}$: 18.60	Insomnia item of EORTC-QLQ-C30
Oldervoll et al[35], 2011	Norway	Female: 62.1% n=231	Mixed cancer (locally advanced or metastasis)	KPS score≥60	An 8-week mixed aerobic/ resistance (twice weekly in sessions of 50-60 minutes). n=121 Age: 62.6±11.3 years Follow-up: 1-year.	Usual care Age: 62.2±10.7 years n=110	Overall survival
Rief et al[34], 2016	Germany	Female: 45% n=60	Mixed cancer (locally advanced or metastasis)	KPS score≥70	A 2-week resistance training (30 mins from Monday to Friday) + home practice (3 times a week till 6 months). n=30 Age: 61.3±10.1 years Follow-up: 1-year.	Passive physical therapy Age: 64.1±10.9 years n=30	Overall survival

Abbreviations: PSQI, the Pittsburgh Sleep Quality Index; IRS, Pittsburgh Insomnia Rating Scale; Sleep Quality NRS, A Sleep Quality Numeric Rating Scale; KPS, Karnofsky Performance Scale; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; WTO, World Health Organization.

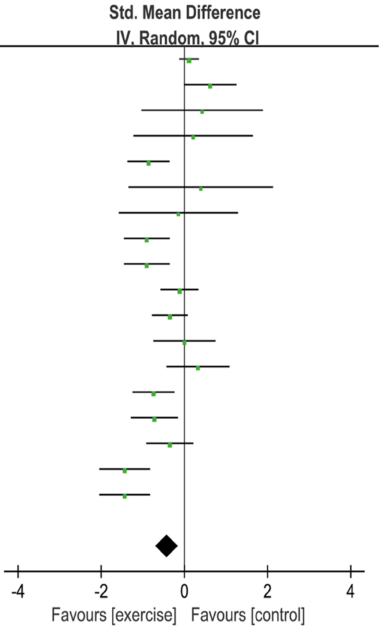
Ten of the included studies were pooled into the forest plot for assessing subjective sleep quality (Figure 3a). Exercise intervention exerted a statistically significant effect on sleep disturbance (SMD: -0.42, 95% CI: -0.70 to -0.13, p = 0.005), with a moderate to high heterogeneity (I^2 = 76%). Furthermore, meta-regression analysis indicated that the gender difference significantly influenced the effect of exercise on relieving sleep disturbance (95% CI: 0.36 to 1.32, p = 0.002), rather than the duration of the exercise intervention (95% CI: -0.50 to 0.41, p = 0.84). The exercise intervention was effective in improving subjective sleep quality for participants who were 50% or less female (SMD: -0.63, 95 %CI: -0.92 to -0.34, p <0.001), but not when most participants were female (SMD: 0.01, 95% CI: -0.34 to 0.35, p = 0.98). Interestingly, when the duration of the exercise was at least 12 weeks or longer, the exercise intervention could reduce sleep disturbance in advanced cancer survivors (SMD: -0.04, 95% CI: -0.77 to -0.04, p = 0.03), as shown in Table 2.

The sleep efficiency was recorded as an objective indicator using an actigraph. Two of the included studies reported the sleep efficiency status after 12- or 14-week exercise intervention (Figure 3b). There was a trend toward improvement in sleep efficiency of the advanced lung cancer patients after exercise interventions of aerobic exercise or Tai Chi (SMD: 0.25, 95% CI: -0.01 to 0.51, p = 0.06).

A Subjective sleep quality

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Adamsen 2009, Mixed AE/RT	-4.3	16.31	135	-6.3	19.04	134	8.0%	0.11 [-0.13, 0.35]
Bade 2021, AE	0.58	6.37	20	-3.49	6.52	20	6.0%	0.62 [-0.02, 1.25]
Cheung 2021, AE	0.44	5.44	5	-2.27	5.7	3	2.7%	0.43 [-1.03, 1.89]
Cheung 2021, TC	-0.93	5.51	5	-2.27	5.7	3	2.7%	0.21 [-1.23, 1.65]
Cheville 2013,ST	-1.46	1.88	33	0.11	1.71	33	6.7%	-0.86 [-1.37, -0.36]
Chueng 2021, AE,1-y follow-up	0.44	5.44	4	-2.27	5.7	2	2.1%	0.39 [-1.35, 2.13]
Chueng 2021, TC,1-y follow-up	-2.5	3.79	5	-1.84	4.23	3	2.7%	-0.15 [-1.58, 1.29]
Dhillon 2017, AE	-0.26	0.54	28	0.26	0.59	28	6.4%	-0.91 [-1.46, -0.35]
Dhillon 2017, AE, 1-y follow-up	-0.26	0.54	28	0.26	0.59	28	6.4%	-0.91 [-1.46, -0.35]
Ligibel 2016, AE	-11.5	34.5	32	-7.8	28.9	43	6.9%	-0.12 [-0.57, 0.34]
Mikkelsen 2022, Mixed AE/RT	-4.6	29.2	41	3.9	17.9	43	7.1%	-0.35 [-0.78, 0.08]
Porter 2019, YG	-1	2.03	22	-1	2.52	10	5.4%	0.00 [-0.75, 0.75]
Porter 2019, YG, 6-m follow-up	-1.4	2.18	21	-2.1	1.89	10	5.3%	0.33 [-0.43, 1.08]
Rao 2017, YG	-3.73	4.09	33	4.32	14.79	31	6.7%	-0.74 [-1.25, -0.24]
Takeruma 2024, AE	-4.85	2.94	38	-2.68	3	19	6.4%	-0.72 [-1.29, -0.16]
Takeruma 2024, AE, 1-y follow-up	-4.21	3.24	37	-3.02	3.49	18	6.4%	-0.35 [-0.92, 0.21]
Takeruma 2024, TC	-7.06	3.01	38	-2.68	3	19	6.1%	-1.44 [-2.05, -0.82]
Takeruma 2024, TC, 1-y follow-up	-7.06	3.01	38	-2.68	3	19	6.1%	-1.44 [-2.05, -0.82]
Total (95% CI)			**563**			**466**	**100.0%**	**-0.42 [-0.70, -0.13]**

Heterogeneity: Tau² = 0.26; Chi² = 70.35, df = 17 (P < 0.00001); I² = 76%
Test for overall effect: Z = 2.82 (P = 0.005)



B Objective sleep efficiency

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cheung 2021, AE	-2.84	9.33	5	-0.41	9.94	3	3.3%	-0.22 [-1.66, 1.22]
Cheung 2021, TC	-0.36	9.7	5	-0.41	9.94	3	3.3%	0.00 [-1.43, 1.44]
Chueng 2021, AE,1-y follow-up	-0.87	11.71	4	1.52	11.66	2	2.3%	-0.16 [-1.87, 1.54]
Chueng 2021, TC,1-y follow-up	0.97	11.19	5	1.52	11.66	3	3.3%	-0.04 [-1.47, 1.39]
Takeruma 2024, AE	1.88	10.21	38	-0.7	7.89	19	22.2%	0.27 [-0.29, 0.82]
Takeruma 2024, AE, 1-y follow-up	3.71	9.21	37	0.03	6.53	18	21.0%	0.43 [-0.14, 1.00]
Takeruma 2024, TC	1.7	10.09	38	-0.7	7.89	19	22.3%	0.25 [-0.30, 0.80]
Takeruma 2024, TC, 1-y follow-up	2.37	9.85	38	0.03	6.53	19	22.3%	0.26 [-0.29, 0.81]
Total (95% CI)			**170**			**86**	**100.0%**	**0.25 [-0.01, 0.51]**

Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 7 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)

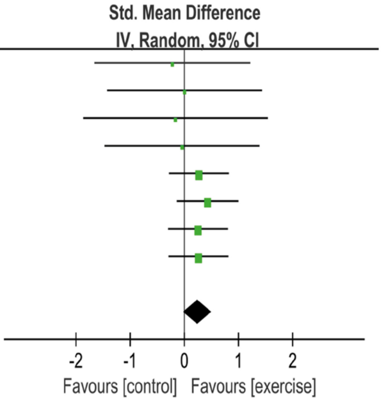


Figure 3. Forest plot summarizing the effects of exercise intervention on: (A) sleep disturbance; (B) sleep efficiency.

Table 2. Differences in duration and gender of exercise intervention for sleep disturbance.

Groups	SMD	95%CI		*p*-value	I^2 (%)
Gender difference					
Half the women	-.63	-.92	-.34	<.001[a]	53.2
Female majority	.01	-.34	.35	.98	64.4
Exercise Duration					
≥12w	-.40	-.77	-.04	.03[b]	70.5
≤8w	-.29	-.72	.15	.19	77.2

Note, [a] represents $p < .05$; [b] represents $p < .01$.

Effects of Exercise on Survival in Advanced Cancer Survivors

Five studies of RCTs were included in the meta-analysis[8,26,33-35]. The exercise modality contains resistance training[35], aerobic exercise[8,26,33,34], and mind-body exercise of Tai chi[8], with the exercise intervention duration ranging from 2 weeks to 16 weeks (Figure 4). Current evidence suggests that exercise intervention at an advanced stage of cancer did not have a significant impact on overall survival (HR: 0.83, 95 % CI: 0.60 to 1.15, $p = 0.25$).

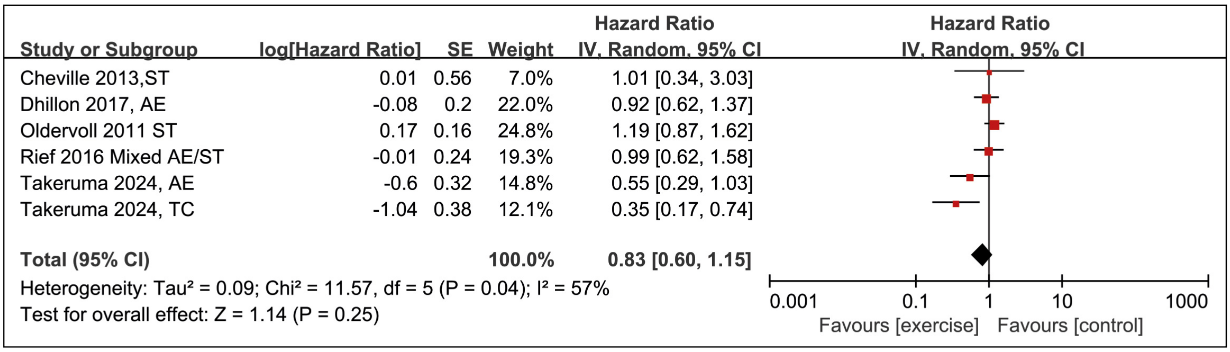


Figure 4. Forest plot summarizing the effects of exercise intervention on survival.

DISCUSSION

The present meta-analysis showed that there could be a positive association between longer duration of exercise intervention and less sleep disturbance. However, it appeared that the effect of exercise on sleep disturbance was feeble in women with advanced cancer. Both aerobic exercise and Tai Chi could slightly enhance sleep efficiency in advanced lung cancer. Current evidence did not support the effectiveness of exercise on survival in advanced cancer when the results of the five included trials were combined, and further studies are needed.

Exercise intervention was recommended as an adjunctive therapy to facilitate the comprehensive care for patients with advanced cancer, due to its physical and psychological benefits[36]. Sleep problems were consistently associated with higher cancer-related fatigue[37]; therefore, Rodríguez-Cañamero et al (2020)[36] summarized data from 15 studies that primarily synthesized the effects of exercise interventions on alleviating cancer-related fatigue, while also postulating improvements in independence, quality of life, and sleep in patients with advanced cancer. Takemura et al (2020)[11] pooled the effect sizes of aerobic exercise and mind-body exercise and suggested that aerobic exercise for more than 3 months was more effective than mind-body exercise in improving poor sleep quality in patients with early-stage cancer. Consistent with previous studies, the present study supported that exercise interventions could significantly mitigate sleep disturbance and marginally increase sleep efficiency in patients with advanced-stage cancer. Only 2 of the 12 included RCTs reported the efficacy of aerobic exercise and Tai

Chi on sleep efficiency in advanced lung cancer survivors[8,25]. Thus, more large-scale studies are needed to test the aerobic exercise and Tai Chi interventions on sleep efficiency in advanced cancer survivors with various types of cancer.

The study found that greater exercise over a longer period of time could predict better sleep quality. It is worth noting that the current evidence on exercise interventions shows gender differences in improving participants' sleep quality, with males experiencing more significant improvements than females. On the one hand, the average age of the participants was almost 50 years old; when menopause occurs, women are at increased risk for sleep disturbances during periods of hormonal change[38]. On the other hand, about circadian rhythms, women exhibit earlier circadian timing and shorter circadian period lengths[39]. These physiological differences may influence the effectiveness of exercise interventions in improving sleep quality in women with advanced cancer. Given the marked gender disparities in exercise response observed among advanced cancer survivors, it is critically imperative to advance research on tailored exercise regimens. Future investigations should place particular emphasis on comparative analyses of exercise intervention efficacy in alleviating sleep disturbances between male and female patients with advanced cancer.

Unfortunately, pooled analyses of existing RCTs indicated that exercise training did not significantly improve the overall survival rate of patients with advanced cancer. This finding is consistent with previous meta-analyses of RCTs, which have shown no significant difference between exercise training and usual care in reducing the mortality risk of advanced cancer patients[40]. However, cohort study results supported the positive effect of long-term physical activity in lowering mortality rates[10,40]. Due to the widespread benefits and various modalities of physical activity, it has attracted more and more people involved in daily physical exercise. Before patients were diagnosed with advanced cancer, they might have been engaging in physical activities. Therefore, future RCTs should not only record the total amount of exercise in the groups during the intervention period, but also assess the exercise habits and physical activity levels at baseline, which may more accurately reflect the efficacy of exercise on overall survival. Additionally, the log HRs of the three included trials were estimated from the published survival curves; thus, the results of the estimated log HRs might be subject to underestimation of the true influence of exercise intervention on survival[23].

Limitations

There are several limitations that merit further consideration. First, four of the 12 included studies were feasibility or pilot studies with small sample sizes, which could lead to publication bias in the results. Secondly, only two studies assessed the objective sleep efficiency, with scores over 85% at baseline. Although the mean baseline sleep scores of the sample were within the cut-off values, some of the participants in the included studies may not have had sleep problems. Thirdly, there were inconsistencies in the duration and modality of exercise intervention in the included studies, so the advantages of aerobic exercise, including mind-body exercises, compared with anaerobic exercise are still under investigation. Last but not least, it is possible that the log HRs, approximated from published survival curves, underestimated the true treatment effect of exercise. Accordingly, the observed benefit was underestimated due to the inherent limitations of this estimation method.

CONCLUSIONS

This meta-analysis of available RCTs demonstrated that both aerobic exercise and Tai Chi mind-body exercise could modestly improve sleep efficiency in patients with advanced lung cancer. Additionally, potential gender differences were observed in the impact of exercise interventions on sleep quality among advanced cancer survivors. Specifically, greater physical activity appeared to be associated with improved sleep quality in male patients; however, there is currently insufficient evidence to confirm a similar effect in female patients. Therefore, further rigorously designed RCTs are required, with a particular focus on comparative analyses of the impact of exercise interventions on alleviating sleep disorders in male and female patients with advanced cancer. Notwithstanding these findings on sleep outcomes, no significant association was observed between higher levels of exercise intervention at advanced cancer stages and reduced mortality risk. Given the widespread adoption of physical activity, future studies are recommended to systematically record physical activity levels from baseline throughout the intervention period to elucidate its impact on overall survival better.

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The authors declare no conflict of interest.

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REFERENCES

1. Mystakidou K, Parpa E, Tsilika E, Pathiaki M, Patiraki E, Galanos A, et al. Sleep quality in advanced cancer patients. J Psychosom Res 2006; 62: 527-533.
2. Hearson B, McClement S. Sleep disturbance in patients with advanced cancer. Int J Palliat Nurs 2008; 14: 30-37.
3. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol 2001; 19: 895e908.
4. Davies AN, Patel SD, Gregory A, Lee B. Observational study of sleep disturbances in advanced cancer. BMJ Support Palliat Care 2017; 7: 435-440.
5. Collins KP, Geller DA, Antoni M, Donnell DM, Tsung A, Marsh JW, et al. Sleep duration is associated with survival in advanced cancer patients. Sleep Med 2017; 32: 208-212.
6. Dean GE, Redeker NS, Wang YJ, Rogers AE, Dickerson SS, Steinbrenner LM, Gooneratne NS. Sleep, mood, and quality of life in patients receiving treatment for lung cancer. Oncol Nurs Forum 2013; 40: 441-451.
7. Lin PH, Liu JM, Hsu RJ, Chuang HC, Chang SW, Pang ST, Chang YH, Chuang CK, Lin SK. Depression Negatively Impacts Survival of Patients with Metastatic Prostate Cancer. Int J Environ Res Public Health 2018; 15: 2148.
8. Takemura N, Cheung DST, Fong DYT, Lee AWM, Lam TC, Ho JC, Kam TY, Chik JYK, Lin CC. Effectiveness of Aerobic Exercise and Tai Chi Interventions on Sleep Quality in Patients with Advanced Lung Cancer: A Randomized Clinical Trial. JAMA Oncol 2024; 10: 176-184.
9. Palesh O, Aldridge-Gerry A, Zeitzer JM, Koopman C, Neri E, Giese-Davis J, Jo B, Kraemer H, Nouriani B, Spiegel D. Actigraphy-measured sleep disruption as a predictor of survival among women with advanced breast cancer. Sleep 2014; 37: 837-842.
10. Palesh O, Kamen C, Sharp S, Golden A, Neri E, Spiegel D, Koopman C. Physical Activity and Survival in Women With Advanced Breast Cancer. Cancer Nurs 2018; 41: E31-E38.
11. Takemura N, Cheung DST, Smith R, Deng W, Ho KY, Lin J, Kwok JYY, Lam TC, Lin CC. Effectiveness of aerobic exercise and mind-body exercise in cancer patients with poor sleep quality: a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2020; 53: 101334.
12. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ 2011; 343: d5928.
13. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiar Res 1989; 28: 193e213.
14. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85: 365-376.
15. Veqar Z, Moiz JA, Hussain ME. Psychometric Analysis of the Pittsburgh Insomnia Rating Scale among University Population of Poor Sleepers in India. N Am J Med Sci 2014; 6: 161-167.

16. Buchanan DR, O'Mara AM, Kelaghan JW, Minasian LM. Quality-of-life assessment in the symptom management trials of the National Cancer Institute-supported Community Clinical Oncology Program. J Clin Oncol 2005; 23: 591-598.
17. Musa-Veloso K, Venditti C, Lee HY, Darch M, Floyd S, West S, Simon R. Systematic review and meta-analysis of controlled intervention studies on the effectiveness of long-chain omega-3 fatty acids in patients with nonalcoholic fatty liver disease. Nutr Rev 2018; 76: 581-602.
18. Borenstein M, Hedges LV, Higgins JP. Introduction to meta-analysis. John Wiley & Sons, USA; 2011.
19. The Nordic Cochrane Centre (TCC). Review Manager (RevMan). Cochrane Training. Available at: https://Training.Cochrane.Org/Onlinelearning/CoreSoftware-Cochrane-Reviews/Revman (accessed December 7, 2024).
20. Sandercock P. The authors say: 'The data are not so robust because of heterogeneity'—so, how should I deal with this systematic review? Cerebrovasc Dis 2011; 31: 615-620.
21. Chen H, Manning AK, Dupuis J. A method of moments estimator for random effect multivariate meta-analysis. Biometrics 2012; 68: 1278-1284.
22. Higgins JPT, Thomas J, Chandler J et al. Cochrane handbook for systematic reviews of interventions (2nd ed.). The Cochrane Collaboration and John Wiley & Sons, USA; 2019.
23. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815-2834.
24. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. J Am Stat Assoc 2002; 95: 89-98.
25. Cheung DST, Takemura N, Lam TC, Ho JCM, Deng W, Smith R, Yan Y, Lee AWM, Lin CC. Feasibility of Aerobic Exercise and Tai-Chi Interventions in Advanced Lung Cancer Patients: A Randomized Controlled Trial. Integr Cancer Ther 2021; 20: 15347354211033352.
26. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, Lewis C, Hui R, Blinman P, Clarke SJ, Boyer MJ, Vardy JL. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. Ann Oncol 2017; 28: 1889-1897.
27. Porter LS, Carson JW, Olsen M, Carson KM, Sanders L, Jones L, Westbrook K, Keefe FJ. Feasibility of a mindful yoga program for women with metastatic breast cancer: results of a randomized pilot study. Support Care Cancer 2019; 27: 4307-4316.
28. Adamsen L, Quist M, Andersen C, Møller T, Herrstedt J, Kronborg D, Baadsgaard MT, Vistisen K, Midtgaard J, Christiansen B, Stage M, Kronborg MT, Rørth M. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ 2009; 339: b3410.
29. Bade BC, Gan G, Li F, Lu L, Tanoue L, Silvestri GA, Irwin ML. "Randomized trial of physical activity on quality of life and lung cancer biomarkers in patients with advanced stage lung cancer: a pilot study". BMC Cancer 2021; 21: 352. doi: 10.1186/s12885-021-08084-0. Erratum in: BMC Cancer 2024; 24: 1409.
30. Ligibel JA, Giobbie-Hurder A, Shockro L, Campbell N, Partridge AH, Tolaney SM, Lin NU, Winer EP. Randomized trial of a physical activity intervention in women with metastatic breast cancer. Cancer 2016; 122: 1169-1177.
31. Mikkelsen MK, Lund CM, Vinther A, Tolver A, Johansen JS, Chen I, Ragle AM, Zerahn B, Engell-Noerregaard L, Larsen FO, Theile S, Nielsen DL, Jarden M. Effects of a 12-Week Multimodal Exercise Intervention Among Older Patients with Advanced Cancer: Results from a Randomized Controlled Trial. Oncologist 2022; 27: 67-78.
32. Rao RM, Vadiraja HS, Nagaratna R, Gopinath KS, Patil S, Diwakar RB, Shahsidhara HP, Ajaikumar BS, Nagendra HR. Effect of Yoga on Sleep Quality and Neuroendocrine Immune Response in Metastatic Breast Cancer Patients. Indian J Palliat Care 2017; 23: 253-260.
33. Cheville AL, Kollasch J, Vandenberg J, Shen T, Grothey A, Gamble G, Basford JR. A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. J Pain Symptom Manage 2013; 45: 811-821.
34. Rief H, Bruckner T, Schlampp I, Bostel T, Welzel T, Debus J, Förster R. Resistance training concomitant to radiotherapy of spinal bone metastases - survival and prognostic factors of a randomized trial. Radiat Oncol 2016; 11: 97.
35. Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, Oredalen E, Frantzen TL, Lesteberg I, Amundsen L, Hjermstad MJ, Haugen DF, Paulsen Ø, Kaasa S. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. Oncologist 2011; 16: 1649-1657.
36. Rodríguez-Cañamero S, Cobo-Cuenca AI, Carmona-Torres JM, Pozuelo-Carrascosa DP, Santacruz-Salas E, Rabanales-Sotos JA, Cuesta-Mateos T, Laredo-Aguilera JA. Impact of physical exercise in advanced-stage cancer patients: Systematic review and meta-analysis. Cancer Med 2022; 11: 3714-3727.
37. Crowder SL, Li X, Himbert C, Viskochil R, Hoogland AI, Gudenkauf LM, Oswald LB, Gonzalez BD, Small BJ, Ulrich CM, Ose J, Peoples AR, Li CI, Shibata D, Toriola AT, Gigic B, Playdon MC, Hardikar S, Bower J, Siegel EM, Figueiredo JC, Jim HSL. Relationships Among Physical Activity, Sleep, and Cancer-related Fatigue: Results From the International ColoCare Study. Ann Behav Med 2024; 58: 156-166.
38. Pengo MF, Won CH, Bourjeily G. Sleep in Women Across the Life Span. Chest 2018; 154: 196-206.
39. Lok R, Qian J, Chellappa SL. Sex differences in sleep, circadian rhythms, and metabolism: Implications for precision medicine. Sleep Med Rev 2024; 75: 101926.
40. Takemura N, Chan SL, Smith R, Cheung DST, Lin CC. The effects of physical activity on overall survival among advanced cancer patients: a systematic review and meta-analysis. BMC Cancer 2021; 21: 242.