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The effects of physical activity, fast-mimicking diet and psychological interventions on cancer survival: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Health professionals are often asked if non-pharmacological interventions prolong life. This review aims to evaluate the effects of physical activity, fast-mimicking diet (FMD) and psychological interventions on survival in all cancers.

Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs). Only RCTs of physical activity, FMD and psychological interventions (including counselling, cognitive and other psychotherapies) in cancer patients that reported survival outcomes were included.

Data sources: CENTRAL, MEDLINE, Embase, CINAHL, APA PsycINFO, Web of Science, ICTRP and ClinicalTrials.gov from inception to January 2020 were searched without language restrictions. The protocol was prospectively registered at PROSPERO (CRD42019160944).

Results: Thirty-one RCTs (9 on physical activity and 22 on psychological interventions) were included in the final analysis after evaluation of 60,207 records from our initial search. No eligible RCT on FMD was reported. RCTs on group psychological interventions (41.9 %) and in patients with breast cancer (38.7 %) were the most common. Most evaluated short-term interventions and in primary or adjuvant settings. Only one of 9 (11 %) RCTs on physical activity and 8 of 22 (36 %) RCTs on psychological interventions were associated with improved overall survival. Only group psychological interventions in breast cancer had adequate number of RCTs to allow a meta-analysis to be performed. It demonstrated a trend towards improved overall survival (HR -0.20, 95 %CI -0.49 to 0.10), particularly in RCTs that evaluated long-term (>6 months) therapies (HR -0.29, 95 %CI -0.59 to 0.01).

Conclusion: Longer term interventions starting early in the patients' care journey in primary and adjuvant settings have shown the most promise for improving survival. Better designed RCTs including survival outcomes are particularly needed in non-breast cancers.

Abbreviations: DFS, disease-free survival; RCT, randomized controlled trial; FMD, fasting-mimicking diet; QoL, quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, Prospective Register of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, the Cumulative Index to Nursing and Allied Health Literature the WHO ICTRP:International Clinical Trials Registry Platform Portal; SIGN, The Scottish Intercollegiate Guidelines Network; OS, overall survival; PFS, progression-free survival; RoB 2, Cochrane risk-of-bias tool for randomized trials; REML, random-effects restricted maximum likelihood.

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1. Background

Earlier diagnosis and improved treatments have significantly prolonged cancer survival rates in most cancers.[1–3] Research on survivorship recognizes patients with cancers require multidisciplinary support to rehabilitate and return to normal life.[2,4] Interventions to support cancer survivorship do not only improve quality of life (QoL),[2,4–8] but also have the potential to improve survival (e.g. through secondary prevention of disease recurrence or separate primary cancers).[8–11]

Non-pharmacological and non-invasive interventions play key roles in supporting patients with cancers, and patients are often keen to know if these interventions prolong life.[1,2,12] However, few RCTs have focused on evaluating survival outcomes, which are sometimes assessed as a secondary outcome without sufficient power in individual studies to detect potentially significant differences.[2,4] Attempts have been made to review high-quality evidence of selected dietary interventions for cancer survivors,[5,6] but few reviews have focused on their impact on survival outcomes.[1,5,6,8,12,13] A recent Cochrane review by Burden and co-workers[8] concluded that dietary interventions had no significant benefit on survival in adult cancer survivors. However, despite recent evidence suggesting the benefits of fasting-mimicking diets (FMDs) on modifying metabolic health and risks of cancers,[14] this Cochrane review[8] did not include the potential use of FMDs as a dietary intervention to improve outcomes.

The levels of physical activity have been associated with better cancer prognosis in multiple tumour types in observational studies.[10,11] However, specific interventions to increase physical activity have not consistently demonstrated survival benefits in patients with cancer, especially in RCTs.[15] Moreover, promoting long-term adoption of any behavioural and psychological intervention is challenging.[13] Similarly, psychological interventions have been shown to improve fatigue[16] and QoL[5,6,12,17] in patients with cancers, but their influence on survival outcomes have not been thoroughly investigated in different cancer types.[5,6,12,17]

In this systematic review and meta-analysis, we aimed to assess all reported RCTs that had evaluated the effectiveness of physical activity, FMD and psychological interventions on improving survival in patients with cancers.

2. Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[18] The protocol was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO) registry (CRD42019160944).

2.1. Inclusion and exclusion criteria- patients

Only RCTs that had aimed to evaluate the effects of physical activity, FMD and psychological interventions in adults with confirmed diagnoses of cancers were included.

In addition, only RCTs that evaluated overall survival (OS) and/or disease-free survival (DFS), defined as the interval between successful treatment and the time to progression of the cancer treated (for RCTs in primary/adjuvant settings), and/or progression-free survival, defined as the interval from diagnosis to the date of progression of their cancers (i.e., time to progression; for RCTs in metastatic setting). When possible, hazard ratio of death was used as the summary measure for comparison.

2.2. Inclusion and exclusion criteria- interventions

Physical activity was not limited to exercise, and include other activities involving body movements that are done as part of playing, working, active transportation, household chores and recreational activities. All psychological interventions, such as mindfulness, counselling, cognitive behavioural therapy and psychoeducation, were included. There are no limitations on the setting, duration and delivery of these interventions.

RCTs included patients who were receiving additional experimental pharmacological and/or invasive adjuvant treatments, which were not the standards of care for their malignancies, were excluded.

2.3. Comparators

Comparators are the control groups in the included trial. Types of controls were divided into “usual care” and “alternative care” groups in the quantitative analysis, representing studies comparing an intervention to usual care and alternative interventions, respectively.

2.4. Outcomes

The primary outcomes are OS, PFS and DFS.

2.5. Information sources and search

The literature search was conducted in January 2020 and updated in March 2020. The search was carried out on the following databases from inception to present: Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library; MEDLINE(R) and Embase via Ovid; the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and APA PsycINFO using EBSCOhost; Web of Science Core Collection; the WHO International Clinical Trials Registry Platform Portal (ICTRP); and ClinicalTrials.gov. Both text words and indexing related to cancer, survival, physical activity, FMD and psychological interventions were used. The Scottish Intercollegiate Guidelines Network (SIGN) randomized controlled trials search filter was adjusted for each database. One reviewer (PC) developed the search strategies, which were reviewed by EYLL, and conducted the search. The full search strategies are available as a supplementary document (Supplementary document 1).

We also performed further searches to ensure all relevant material were found, including hand-searches of the reference lists of the selected papers and searches of the grey literature (via OpenGrey and WorldCat). No language restrictions were imposed.

2.6. Study selection

Two researchers (EC and HM) screened the titles retrieved from the literature search to determine studies which appeared relevant to the study. Two researchers (EC and HM) then assessed abstracts against the inclusion criteria to determine that they were eligible for full text analysis. Eligible trials were read in full, and any uncertainties with regards to eligibility were resolved by involvement of a third researcher (EYLL). Where studies had multiple publications, the trial reports with the most comprehensive follow-up data were included as the primary reference and additional information was supplemented from the other publications.

2.7. Data extraction and management

EYLL pre-designed the data extraction form. It was piloted by two independent reviewers (EC and HM) and amendments were made after discussions with EYLL. EC and HM then used this form to extract data for analysis. Variables included the location of the research team, publication date, patient demographics (including age, gender, smoking status, performance status, body mass index, ethnicity), survival data (both overall survival and disease-free survival) and a summary of other reported outcomes. Data were summarized by all reviewers, a graphical summary was generated using Prism (v8.0, GraphPad, La Jolla, CA). Meta-analysis, assessments of heterogeneity and risks of biases were performed using STATA® Version 16 (StataCorp, USA).

2.8. Assessment of risk of bias in included studies

The risks of bias of each study for measuring survival outcomes were assessed by the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) and presented in Supplementary Fig. 1.[19] Sensitivity analysis was performed to evaluate the influence of studies at high risks of bias on the results of the meta-analysis.

2.9. Measures of treatment effects

The timing of interventions was prospectively divided into three treatment groups, 1) primary treatments - interventions started before and during patients' primary curative treatments for their cancers; 2) adjuvant treatments- interventions for patients who were in remission (i.e. disease-free) following their primary cancer treatments; 3) palliative treatment- interventions for patients with advanced and/or metastatic diseases. In addition, studies were evaluated by the type of interventions and by cancer type. Short-term interventions were defined as interventions that were less than or equal to 6 months.

Meta-analysis and relevant sensitivity analyses were performed by the type of interventions and cancer type when there were sufficient RCTs. To account for statistical heterogeneity, the random-effects restricted maximum likelihood (REML) model was used.

When hazard ratios were not reported, reported time-to-event data were used to estimate hazard ratios, using established methods described by Tierney and co-workers.[20] Forrest plots of hazard ratios were generated using STATA® Version 16 (StataCorp, USA). Funnel plot was used to assess publication bias, and tested by using the Egger's test. Sensitivity analyses were performed to evaluate the influence of studies with high risks of bias and the different types of controls used in the included studies.

3. Results

3.1. Study selection

Fig. 1 represents the PRISMA flow diagram. In total, 60,207 references were retrieved and full text of 67 studies were further assessed for eligibility; 36 were excluded as they did not satisfy one or more of the inclusion criteria. Thirty-one studies (9 on physical activity and 22 on psychological interventions) met the inclusion criteria. No eligible RCT on fast-mimicking diet in cancer was identified. Nine studies were included in the meta-analyses from 10 suitable RCTs (one did not provide sufficient time-to-event data to estimate hazard ratios[21]). Studies

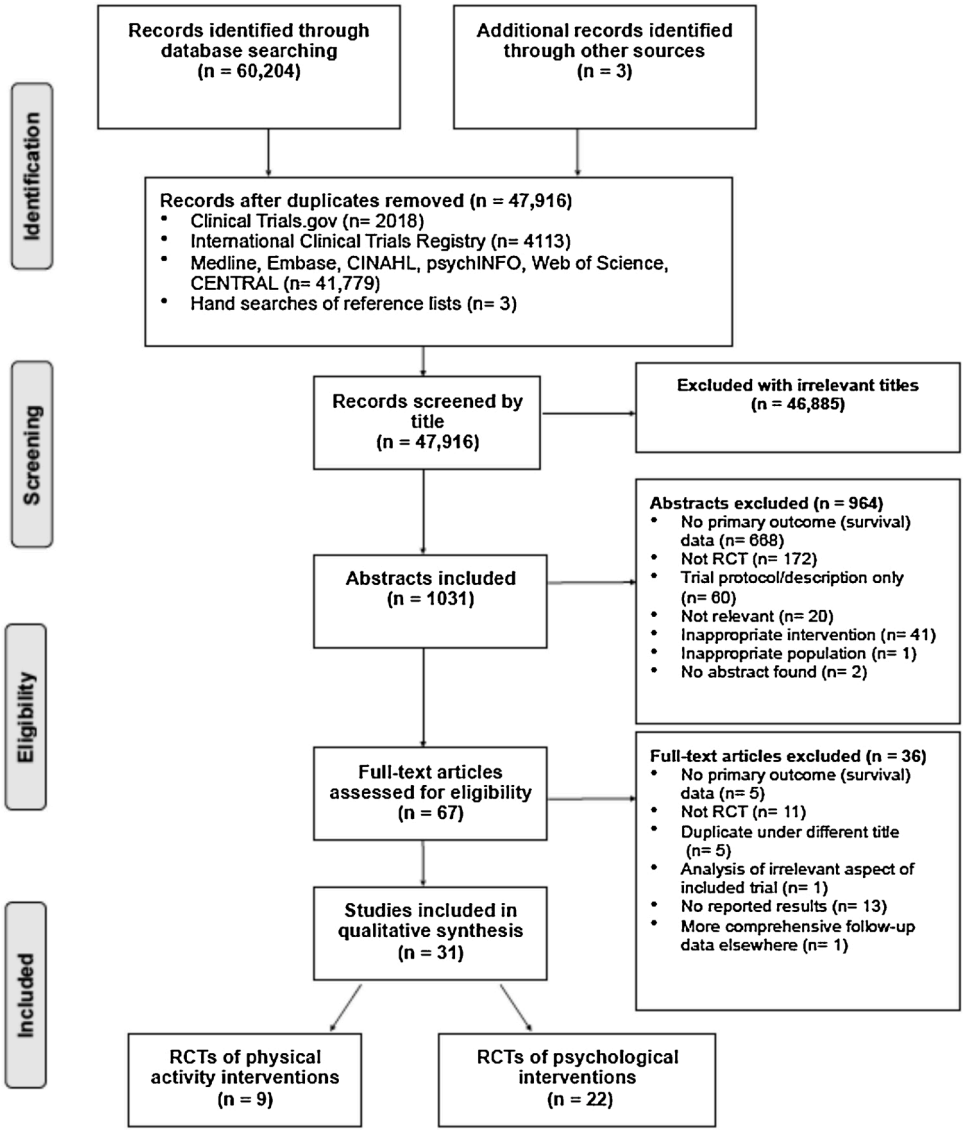

Fig. 1. PRISMA flow diagram of this systematic review.

excluded after full-text assessments are summarized in Supplementary Table 1.

3.2. Study characteristics

Key features of the included studies (n = 31) are summarized in Fig. 2. RCTs in patients with breast cancer (38.7 %) and on group psychological interventions (41.9 %) were the most common (Fig. 2a-b). In addition, psychological interventions were more likely to be tested in palliative care settings than physical activity (Fig. 2c). The majority evaluated short-term interventions (Fig. 2d).

3.3. Survival and other outcomes

Survival outcomes are summarized in Tables 1 and 2. All interventions compared to usual care unless otherwise stated in the tables. No PFS was reported in the identified RCTs in metastatic setting, hence only DFS rates were summarised. Additional outcomes of the reported studies are summarized in Supplementary Table 2. Only one of 9 (11 %) included RCTs on physical activity,[22] which investigated a 32-week individualized aerobic and resistance exercise programme in patients with breast cancer, was associated with improved overall survival. In contrast, 8 of 22 (36 %) RCTs on psychological interventions reported improved survival outcomes; 7 of 13 (54 %) and 1 of 9 (11 %) in the primary/adjuvant and palliative settings, respectively. Two of 7 (28.6 %) individual psychological intervention studies, versus 5 of 15 (33.3 %) group psychological intervention studies, were associated with improved survival. All three studies on counselling did not demonstrate improved overall survival. One of 6 (16.7 %) studies on cognitive therapies, versus 6 of 13 (46.2 %) studies on other psychological interventions, were associated with improved survival.

Other reported outcomes of the included studies are summarized in Supplementary Table 2. When reported, the majority of studies reported improvements of anxiety, depression and QoL-related outcomes. One study also reported shortened length of hospital stay and related costs post-operatively.[23]

The identified RCTs were highly heterogenous, and therefore we restricted our meta-analysis to only interventions that had previously been evaluated in high number of RCTs. Only RCTs investigating psychological interventions in breast cancer (n = 9) were further evaluated by a meta-analysis because of the limited numbers of eligible RCTs in other groups (Fig. 3). In total, 1687 participants were included in this analysis (667 in studies of short-term interventions and 1018 in studies of long-term interventions). Although there was no overall statistical difference in hazard ratios in patients who received these interventions (-0.20; 95 % CI -0.49 to 0.10), a trend towards improved survival was observed particularly in RCTs that evaluated long-term (>6 months) interventions (-0.29; 95 % CI -0.59 to 0.01). Further sensitivity analyses suggested that neither studies at high risks of bias nor different types of controls influenced the results of the meta-analysis (Supplementary Fig. 2).

3.4. Assessment of the risks of bias

The risk of bias assessment of the included studies is summarized in Fig. 4 (assessments of individual studies are summarized in Supplementary Fig. 1). While all studies had no significant missing data and survival outcome measurements, most did not report deviations from intended interventions. Nine of the 31 (29 %) included studies were deemed to be at high-risk of bias. Blinding was not possible in all the RCTs reported. Funnel plot of the studies included in the meta-analysis and the Egger's test did not detect significant publication bias (Supplementary Fig. 2; p = 0.086).

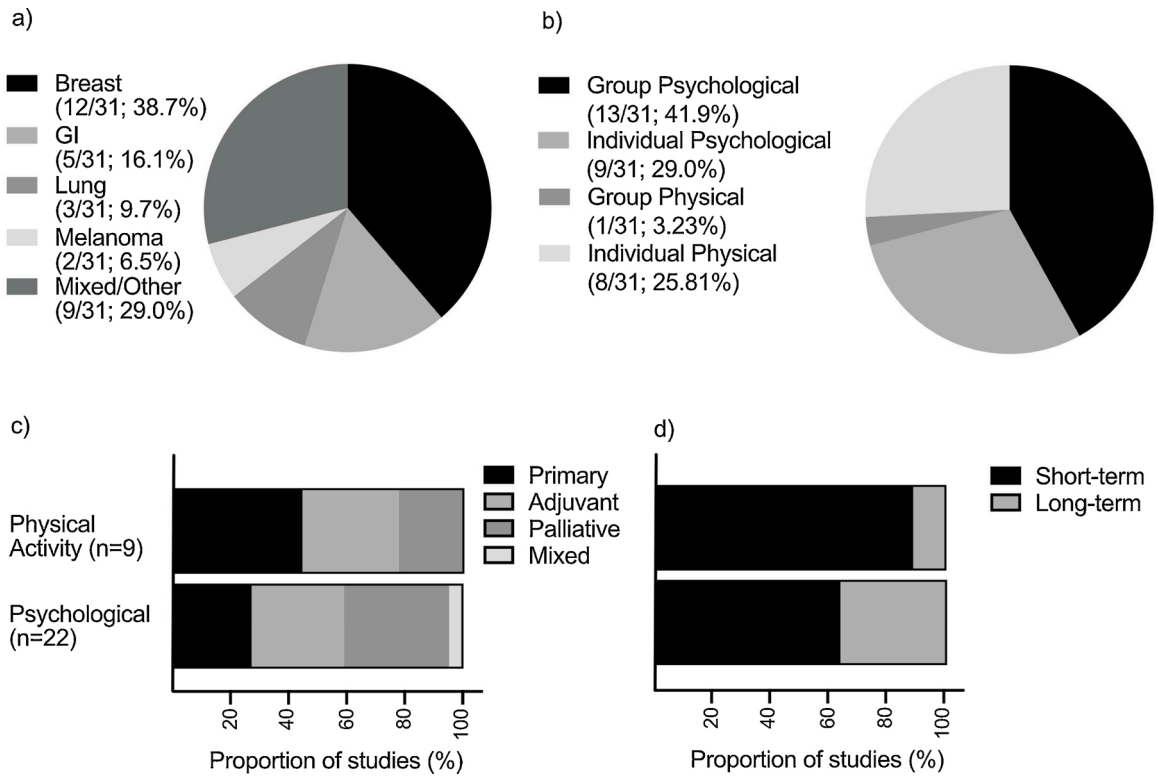

Fig. 2. Key features of the included studies (n = 31). a) Number of studies by cancer type; b) number of studies by the type of interventions evaluated; c) number of studies by the timing of the interventions; d) number of studies by the duration of the interventions. Short-term interventions were defined as those that were less than or equal to 6 months.

Table 1
Summary of survival outcomes of all studies in primary/adjuvant settings (n = 20).

First author, year	Cancer type; stage	Settings	Sample size N (I vs C)	Interventions; duration (frequency)	Survival outcomes
Physical activity (n = 7)					
LaStayo 2011[24]	Mixed; mixed	Adjuvant	40 (20 vs 20)	Individual resistance exercise; 14 weeks (3 times per week)	OS: statistical test of difference not reported. I = 8.5 years vs C = 8.3 years. DFS: not reported.
Yeo 2012[25]	GI; localized	Primary	102 (54 vs 48)	Individual walking exercise; 12 weeks (weekly)	OS: no difference. HR = 1.3 (95 % CI 0.7−2.5; p = 0.560). DFS: not reported.
Courneya 2014[26]	Breast; localized	Adjuvant	242 (160 vs 82)	Individual resistance exercise and aerobic exercise; 12 weeks (3 times per week)	OS: no difference. HR = 0.60 (95 %CI 0.27−1.33). DFS: no difference. HR = 0.68 (95 % CI 0.37−1.24).
Courneya 2014[27]	Lymphoma; mixed	Primary	122 (60 vs 62)	Group aerobic exercise; 12 weeks (3 times per week)	OS: not reported. DFS: no difference. HR = 1.06 (95 % CI 0.56–2.00; p = 0.860).
Karenovics 2017[28]	Lung; localized	Primary	151 (74 vs 77)	Individual high-intensity interval training; 3 weeks (3 times per week)	OS: no difference. I = 93.2 % vs 90.9 % at 1 year; p = 0.506. DFS: not reported.
Dhillon 2017[29]	Lung; mixed	Primary	111 (56 vs 55)	Individual tailored exercise; 8 weeks (weekly)	OS: no difference. Log rank p = 0.75. DFS: not reported.
Hayes 2017[22]	Breast; localized	Adjuvant	337 (207 vs 130)	Individual aerobic and resistance exercises; 32 weeks (weekly)	OS: **improved**. HR = 0.45 (95%CI 0.20−0.97; p = 0.040). DFS: HR = 0.66 (95 % CI 0.38−1.17; p = 0.160).
Psychological interventions (n = 13)					
Fawzy 1993[30]	Melanoma; localized	Primary	68 (34 vs 34)	Group psychoeducation; 6 weeks (weekly)	OS: **improved**. I = 31/34 (91%) vs C: 24/34 (71%) survived at 6 years. Log rank p = 0.030. DFS: I = 30/34 vs C: 31/34 at 6 years.
Kissane 2004[31]	Breast; localized	Adjuvant	303 (154 vs 149)	Group cognitive existential therapy*; 20 weeks (weekly)	OS: no difference. HR 1.35 (95 %CI 0.76−2.39; p = 0.370). DFS: not reported.
Boesen 2007[32]	Melanoma; localized	Primary	262 (131 vs 131)	Group psychoeducation; 6 weeks (weekly)	OS: no difference. HR 1.3 (95 %CI 0.5−3.5). DFS: no difference. HR 0.73(95 %CI 0.3−1.9).
Küchler 2007[33]	GI; localized	Primary	271 (136 vs 125)	Individual psychotherapy; 1 week (not reported)	OS: **improved**. HR 0.69 (95%CI 0.52−0.92; p = 0.013) DFS: not reported
Andersen 2008[34]	Breast; localized	Adjuvant	227 (114 vs 113)	Group psychoeducation; 52 weeks (weekly for 4 month and monthly for 8 months)	OS: **improved**. HR 0.51 (95%CI 0.28−0.93; p = 0.028). DFS: **improved**. HR 0.553 (95%CI 0.32−0.96; p = 0.034).
Ross 2009[35]	GI; localized	Adjuvant	249 (125 vs 124)	Individual psychosocial intervention; 24 months (10 visits with telephone calls)	OS: no difference. I: 50/125 (40 %) vs C: 52/124 (41 %). Log-rank p = 0.69. DFS: not reported.
Boesen 2011[21]	Breast; localized	Adjuvant	186 (89 vs 97)	Group cognitive existential therapy; 8 weeks (weekly)	OS: statistical test of difference not reported. I = 83/89 (93 %) vs C = 94/97 (97 %). DFS: not reported.
Choi 2011[9]	Mixed; mixed	Adjuvant	237 (118−119)	Individual cognitive behavioural therapy; 20 weeks (every 2 weeks)	OS: no difference. HR: 1.07 (95 %CI 0.75−1.53; p = 0.710). DFS: not reported.
Guo 2013[36]	Mixed; localized	Adjuvant	178 (89 vs 89)	Group psychosocial intervention; 9 weeks (2 times per week)	OS: no difference. I = 83.1 % vs C = 84.3 %. Log rank p = 0.925. DFS: no difference. I = 79.8 % vs C = 76.4 %. Log rank p = 0.527.
Zhang 2013[23]	GI; localized	Primary	60 (31 vs 29)	Individual psychoeducation intervention; 3 weeks (3 times per week)	OS: no difference. I = 64.3 % v C = 55.6 % at 4 years. Log rank p = 0.446. DFS: not reported.
Stagl 2015[37]	Breast; localized	Primary	240 (120 vs 120)	Group cognitive behaviour therapy**; 10 weeks (weekly)	OS: **improved**. HR 0.21 (95%CI 0.05−0.93; p = 0.040). DFS: no difference. HR 0.45 (95 %CI 0.17−1.18; p = 0.083).
Bao 2019[38]	AML; mixed	Adjuvant	220 (110 vs 110)	Individual psychoeducation intervention; 12 weeks (weekly)	OS: **improved**. HR 0.653 (95%CI 0.43−1.00; p = 0.045). DFS: no difference. HR 0.747 (95 %CI 0.54−1.04; p = 0.071).
Wang 2019[39]	GI; localized	Adjuvant	136 (68 vs 68)	Individual psychoeducation intervention; 12 weeks (monthly)	OS: **improved**. Median survival- I = 37 (IQR 28−46) months vs C = 32 (IQR 27−37) months. Log rank p = 0.026. DFS: not reported

All interventions compared to usual care unless otherwise stated. Compared to *3 relaxation classes alone; **Compared to a 1-day psychoeducational self-help classroom seminar. I = intervention group; C = control group; GI = gastrointestinal; OS = overall survival; DFS = disease-free survival.

4. Discussion

4.1. Main findings

Patients who have survived cancer often seek advice from health professionals for additional interventions that could prolong life. This is a comprehensive review of all RCTs on physical activity and psychological interventions in cancer to evaluate their impact on survival.

The majority of included RCTs evaluated psychological interventions (22 of 31, 69 %; Fig. 2). Physical activity and group psychological interventions had previously been recommended in palliative care settings to improve QoL.[6,12,15,51] All 3 included RCTs on counselling (a type of individual psychological intervention) did not demonstrate survival benefit. There was no apparent difference between the benefits of individual versus group psychological interventions on survival (28.6 % versus 33.3 %; Section 3.3). In this study, improved survival outcomes were identified in patients who received early interventions in primary or adjuvant treatment settings. Our results suggest that these interventions should be introduced early in a patient's recovery journey (Tables 1–2).

Our meta-analysis also suggested that longer term psychological interventions (>6 months) have the potential to improve survival (Fig. 3). Further evaluations are warranted to evaluate the positive trends observed and clarify the settings in which such interventions could be beneficial. Moreover, there is limited evidence from RCTs on the benefits of the evaluated interventions for patients with non-breast

Table 2
Summary of survival outcomes of all studies in palliative settings (n = 11).

First author, year	Cancer type; stage	Sample size N (I vs C)	Interventions; duration (frequency)	Survival outcomes
Physical activity (n = 2)				
Oldervoll 2011[40]	Mixed; metastatic	231 (121 vs 110)	Individual tailored exercise; 8 weeks	OS: no difference. HR = 1.24 (95 % CI 0.90–1.70; p = 0.180).
Rief 2016[41]	Mixed; metastatic	60 (30 vs 30)	Individual resistance exercise*; 2 weeks	OS: no difference. HR = 0.68, p = 0.303.
Psychological interventions (n = 9)				
Linn 1982[42]	Mixed; metastatic	120 (62 vs 58)	Individual counselling; 52 weeks (>1 per week)	OS: statistical test of difference not reported. Mean survival: I = 3.7 months vs C = 4.4 months.
Spiegel 1989[43]	Breast; metastatic	86 (50 vs 36)	Group psychosocial therapy; 52 weeks (weekly)	OS: **improved**. Mean survival I = 36.6 months vs C = 18.9 months. Log rank p < 0.01.
Cunningham 1998[44]	Breast; mixed	66 (30 vs 36)	Group cognitive behavioural therapy**; 35 weeks (weekly)	OS: no difference. Median survival I = 28.2 (95 %CI 25.8–51.7) months vs C = 23.6 (95%CI 18.9–34.9) months. Log rank p = 0.35.
Edelman 1999[45]	Breast; metastatic	121 (60 vs 61)	Group cognitive behavioural therapy; 8 weeks (weekly)	OS: statistical test of difference not reported. Median survival I = 11.6 (IQR 7.1–17.5) months vs C = 12.8 (IQR 7.56–17.8) months.
Goodwin 2001[46]	Breast; metastatic	235 (158 vs 77)	Group psychotherapy; 52 weeks (weekly)	OS: no difference. HR 1.06 (95 %CI 0.78–1.45; p = 0.72).
Kissane 2007[47]	Breast; metastatic	227 (147 vs 80)	Group psychotherapy***; 52 weeks (weekly)	OS: no difference. HR 0.92 (95 %CI 0.69–1.24; p = 0.6).
Spiegel 2007[48]	Breast; metastatic	125 (64 vs 61)	Group psychotherapy****; 52 weeks (weekly)	OS: no difference. HR 0.93 (95 %CI 0.62–1.40; p = 0.73)
Geerse 2016[49]	Lung; mixed	223 (110 vs 113)	Individual counselling; 25 weeks (not stated)	OS: no difference. Median survival I = 10.3 (95 %CI 6.5–14.1) months vs C = 10.1 (95%CI 7.6–12.6)
Lloyd Williams 2018[50]	Mixed; metastatic	57 (33 vs 24)	Individual counselling; 2 weeks (not stated)	OS: no difference. Median survival I = 5.2 months vs C = 3.4 months. Mann Whitney U test p = 0.07.

All interventions compared to usual care unless otherwise stated. Compared to *passive physical therapy; **home study cognitive behavioural package; ***3 relaxation classes each lasting 1 h over 3 weeks; ****self-directed education. I = intervention group; C = control group; OS = overall survival.

cancers.

Despite the increasing popularity of FMDs amongst cancer survivors, no RCT on FMDs has reported improved cancer survival outcome.[52,53] A randomized cross-over trial of patients with breast and ovarian cancers evaluated QoL and tolerance to chemotherapy after short-term FMD during chemotherapy.[52] Another more recent multi-center Phase 2 RCT on short-term FMD in patients with localized breast cancer during neoadjuvant chemotherapy demonstrated safety and potential improvements of radiological responses.[53] Larger and sufficiently powered RCTs are required to evaluate the benefits of fasting in cancers.

4.2. Strengths and limitations

In contrast to previous reports, we focused on survival outcomes, which has not been comprehensively evaluated in previous systematic reviews, and did not restrict to RCTs on specific cancer type to allow a broad overview on the effects of these interventions on cancer survival.[1,5,6,12,13,16,17] In contrast to two recent systematic reviews on physical activity,[10,11] our protocol was prospectively registered and no date or language restrictions were used. Despite the renewed interests on physical activity and psychological therapy for cancer survivors, we only identified 31 RCTs that have evaluated these interventions. Due to their heterogeneity, we were not able to include most RCTs for meta-analysis.

4.3. Recommendations for future studies

Survival outcomes are not commonly reported in RCTs on physical activity and psychological therapies. This review challenges this omission. Ideally, large RCTs on these non-pharmacological interventions should be conducted, but the large sample size required is likely to limit the focus on survival outcomes. Core outcome sets ensure researchers measure and report those outcomes that are most likely to be relevant to users of their research.[54] By including survival outcomes being part of the core outcome set for RCTs on non-pharmacological interventions in cancers, it will ensure their reporting and allow meta-analyses of survival outcomes.[55–57]

Numerous observational studies and clinical trials on physical activity and psychological interventions have been reported. Psychological interventions have been demonstrated to significantly reduce fear of cancer recurrence,[58] fatigue[16] and other patient-reported psychological outcomes.[59] These studies also suggested larger beneficial effects were associated with shorter follow-up periods, complementing our results suggesting longer-term interventions demonstrated a trend towards larger survival benefits. Consistent with this study, interventions around the time of primary treatment of cancer has previously been shown to reduce distress and anxiety, as well as systemic inflammatory response.[60] Other factors, including age[59] and type[58] of psychological interventions, are likely to contribute to the potential benefits of these

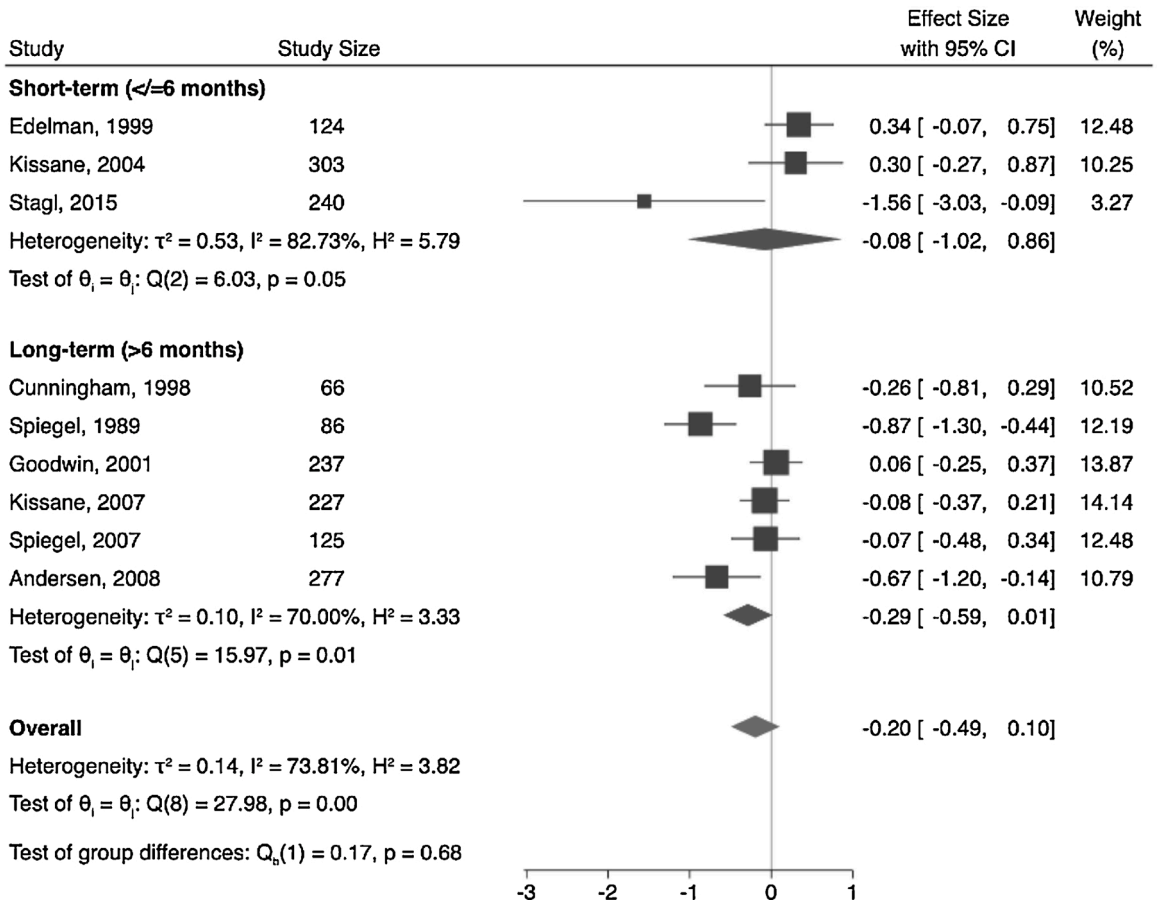

Fig. 3. Forest plot of hazard ratios and 95 % confidence intervals of all RCTs on psychological interventions in breast cancer by duration of treatment (n = 9).

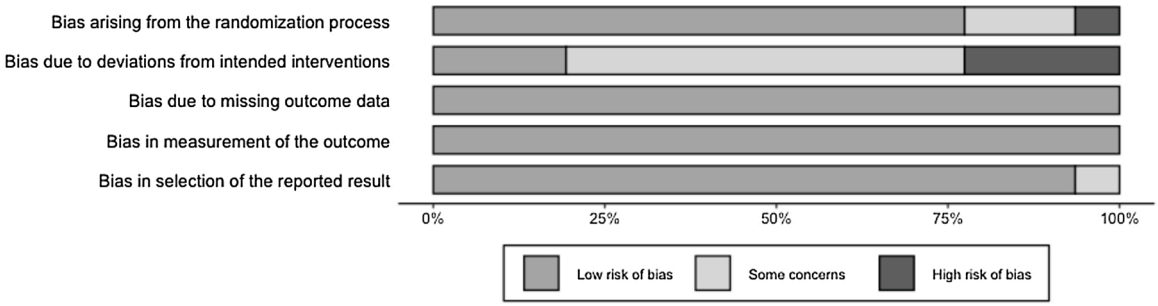

Fig. 4. Summary of the risks of bias assessment of all included studies (n = 31).

interventions. Moreover, the majority of studies evaluated face-to-face interventions- other methods of delivery remain under-explored.[58,59] To comprehensively evaluate the effectiveness of these therapies, concerted efforts to perform well-designed and sufficiently powered RCTs are crucial, especially in non-breast cancers. Future studies should consider the timing of interventions and characteristics related to patients and interventions when designing their protocols.

4.4. Conclusions

In summary, this systematic review evaluated all RCTs on physical activity and psychological interventions in cancers that had reported survival outcomes. Longer term interventions starting early in the patients' care journey in primary and adjuvant settings have shown the most promise for improving survival. FMDs require further evaluation in RCTs to assess their benefits in improving oncological outcomes. Well-designed and sufficiently powered RCTs are needed to evaluate the benefits of physical activity and psychological interventions, particularly in non-breast cancers.

Author statement

EYLL contributed to the conception of the research question and drafted this manuscript. EC and HM contributed to the conception of the research questions and acted as reviewers. PC developed and conducted the searches. All authors have contributed to this manuscript.

Ethics approval and consent to participate

This is a systematic review of primary studies. Further ethical approval is not required.

Consent for publication

All authors have given their consent to publish. No patient identifying details are included.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional files.

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Declaration of Competing Interest

No financial and non-financial competing interests to declare.

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None.

Appendix A. Supplementary data

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