Psychological effect of exercise in women with breast cancer receiving adjuvant therapy: what is the optimal dose needed?

M. Carayol¹,²*, P. Bernard¹, J. Boiché¹, F. Riou¹, B. Mercier¹, F. Cousson-Gélie¹, A. J. Romain¹, C. Delpierre² & G. Ninot¹

¹Laboratory Epsilon EA 4556 Dynamics of Human Abilities and Health Behaviors, University of Montpellier, Montpellier; ²INSERM UMR 1027, Paul Sabatier University, Toulouse, France

Received 3 February 2012; revised 13 July 2012; accepted 16 July 2012

Background: Several meta-analyses have examined the role of exercise interventions in improving psychological outcomes in cancer survivors but most did not focus on adjuvant therapy period and did not investigate the optimal dose of exercise needed. The present meta-analysis examines the impact of exercise interventions delivered at this particular period on fatigue, anxiety, depression, and quality of life (QoL) as well as dose–response relationships between volume of prescribed exercise and these psychological outcomes.

Materials and methods: Randomized, controlled trials that proposed an exercise intervention to patients with breast cancer undergoing chemotherapy and/or radiotherapy were systematically identified and coded. Psychological outcomes effect sizes were calculated and analyzed for trends using linear and quadratic regressions.

Results: Pooled effects of the 17 included studies revealed improvement for all outcomes, significant for fatigue, depression, and QoL with pooled estimates ranging from 0.2 to 0.5 favoring intervention. Significant inverse associations of the volume of prescribed exercise with fatigue and QoL were observed.

Conclusions: Exercise intervention improved fatigue, depression, and QoL in patients with breast cancer receiving adjuvant therapy. Prescription of relatively low doses of exercise (<12 MET h/week) consisting in ~90–120 min of weekly moderate physical exercise seems more efficacious in improving fatigue and QoL than higher doses.

Key words: anxiety, breast cancer, depression, exercise, fatigue, quality of life

Introduction

With over 1 million cases per year worldwide, breast cancer is the most common cancer affecting women [1]. In France, it is responsible for 36.7% of all women cancer cases. While mortality decreases, the French incidence rate (world age-standardized) has almost doubled, from 56.8 in 1980 to 101.5 in 2005 [2] which increases the number of women receiving adjuvant cancer therapy and then living with its side-effects. Indeed, current cancer treatments produce deleterious physiological and psychological effects including pain, decreased cardiac function, muscle wasting, weight gain, cancer-related fatigue, and psychological distress, resulting in impaired quality of life (QoL) and affecting cancer prognosis for some of them [3, 4].

Prevalence of mood disorders in cancer patients has been recently summarized [5]. Prevalence of depression including minor and major depressive episodes as well as dysthymia and...
its associated 95% confidence interval (95% CI) reached 20.7% (95% CI 12.9–29.8), and prevalence of anxiety disorders has been estimated to 10.3% (95% CI 5.1–17.0) in nonpalliative care settings. Compared with general population, cancer patients scored significantly higher on anxiety and depression subscales of the Hospital Anxiety and Depression Scale [6], showing scores twice as high as those observed in the general population [7]. In another study, fatigue and QoL measured in patients with breast cancer shortly after adjuvant therapy appeared also as significantly deteriorated compared with general population, and QoL impairment was strongly associated with fatigue and depression scores [8].

Even though the relationship of psychological distress with cancer survival remain inconclusive because of inconsistent findings and measures of psychosocial variables across studies, a systematic review of available evidence in patients with breast cancer reported that most of the studies showed a significant relationship between psychosocial factors and survival [9]. Additionally, the association of mental health, particularly depression in women, and QoL with obesity has been well documented [10, 11], and obesity has been identified to affect breast cancer prognosis [12]. This evidence emphasize the role of psychological factors in disease survival and justifies the need to find adequate supporting care which could have beneficial effects on these prognosis factors for cancer patients.

In this line, some evidence is already accumulated from intervention studies, showing that exercise interventions are likely to improve fatigue, anxiety, depression, and QoL in the population of cancer survivors [13–19]. However, in most systematic reviews, the authors pooled data from studies that investigated the effect of exercise on psychological factors during different periods of cancer therapy [13–16]. One meta-analysis specifically focused on adjuvant therapy period but included few studies as literature search was closed in 2006 [18]. Two others were interested in adjuvant therapy period but both did not investigate dose–response relationship, one mixed cancer sites [19] and the other one focused only on fatigue [20]. Based on these reviews, recommendations regarding exercise prescription have been formulated with regard to the management of fatigue [21–23]. However, these conclusions and guidelines cannot be inferred to cancer adjuvant therapy period, taking into account the particular pattern of experienced side-effects during this period. Based on the reviewing of 22 high internal validity randomized, controlled trial (RCTs), the American College of Sports Medicine concluded that exercise is safe for cancer patients undergoing chemotherapy and radiotherapy [23]. Therefore, we carried out a meta-analysis of RCTs to investigate the effects of an exercise prescription on fatigue, anxiety, depression, and QoL in patients with breast cancer receiving adjuvant therapy and to explore the relationships between the volume of targeted exercise and the effects observed on these psychological outcomes. We hypothesized (i) that exercise groups would show greater reductions in fatigue, anxiety, depression, and larger increases in QoL than control groups, as indicated by summary effect sizes significantly different from zero and (ii) that prescribed dose of exercise would explain a significant amount of effect sizes.

**methods**

**literature search**

MEDLINE, PsycINFO, Pascal, PSYArticles, and Cochrane electronic databases were searched until July 2011 with no language restriction (for search algorithms, see supplementary Figure S1, available at *Annals of Oncology* online). In addition, references of included studies and relevant reviews and meta-analyses [13–16, 18–20, 23] were manually searched.

**selection of studies**

Studies were included in our meta-analysis if they met the following criteria: (i) participants were adult women diagnosed with breast cancer, (ii) presented a randomized, controlled experimental design, (iii) included an intervention program involving physical activity (yoga-based interventions were included whereas relaxation-based were not), (iv) intervention program was scheduled during adjuvant cancer therapy (chemotherapy and/or radiotherapy), (v) assessed at least one psychological outcome among fatigue, anxiety, depression, and QoL, (vi) provided pre- and postintervention data to calculate standardized mean differences (SMDs).

**data extraction**

Descriptive data regarding participants, study methodology and intervention characteristics were recorded by two independent coders and any discrepancies were resolved by discussion. Postintervention assessment data were favored as it best reflects the intervention effect, and this assessment time was predominantly reported. When outcomes were assessed with several tools, validated and specific cancer tools were favored. Regarding QoL, evaluation, in order of preference, total Functional Assessment Cancer Therapy (FACT)-B, total FACT-G, total FACT-An, and General Health SF-36 subscale scores were extracted. Vitality SF-36 subscale was considered as a measure of fatigue (reversed score). When the State Trait Anxiety Inventory was used, the state scale score was recorded.

**methodological standards**

A quality score based on 10 methodological criteria specifically chosen for the evaluation of exercise intervention RCTs and mostly derived from PEDro Scale [24] was calculated for each included study. Two investigators independently scored the studies and any disagreements were resolved by discussion.

**exercise dose calculation**

Targeted exercise volume was estimated using metabolic equivalent for task (MET), where 1 MET accounts for 3.5 ml O2/kg/min. Corresponding MET values for a given exercise intervention were coded from the Compendium of Physical Activity [25]: 5 and 3.8 METs were, respectively, assigned to moderate- and low-intensity aerobic physical activity; strength-training physical activity was coded 3.5 METs; warm-up and cool-down were estimated 2.5 METs if no more detail related to their content was provided; yoga and stretching activities were coded 2.5 METs. Exercise sessions were frequently composed of several types of exercise with different intensity levels, e.g. exercise intervention of Battaglini et al. [26]: initial cardiovascular activity (6–12 min), followed by a stretching session (5–10 min), resistance training (15–30 min), and cool-down (8 min). Incrementation in the duration of sessions was taken into account in the estimation of exercise volume by computing the average duration. Two different estimations of targeted volume of exercise were calculated: (i) Weekly exercise dose = \( \sum_{i=1}^{n} \) (METs) \( \times (\text{bout duration}) \times (\text{frequency}) \), in
MET h/week, where one exercise session is composed of $i$ physical activities, the intensity of physical activity $i$ is in METs, the average duration of physical activity $i$ is in hours, and frequency is the number of sessions per week; (ii) total exercise dose = weekly exercise dose $\times$ intervention length in MET h, where intervention length is in weeks. After calculation, the data were examined for outliers. Any weekly exercise dose greater than three standard deviations away from the mean would be considered outlier and removed from the analysis.

**effect sizes and dose–response analyses**

Because all included studies reported continuous measures, pre- and postintervention mean scores and standard deviations (SDs) as well as number of subjects in experimental and control groups were extracted for all outcomes of interest to calculate Hedges’ $g$ [27] as the measure of SMD, difference between the outcome mean values of the intervention and control groups divided by the pooled standard deviation [27, 28]. Five authors were contacted regarding missing information and three provided it [26, 29, 30]. Signs of effect sizes were set so that negative effect sizes for fatigue, anxiety, and depression and positive effect sizes for QoL indicated improvements in favor of intervention participants. To assess the effect of intervention on outcomes of interest, summary effect sizes were estimated by weighting SMDs by the inverse of their variance based on random effects models [31]. Heterogeneity was tested with Cochran’s chi-square test (Q) to assess the consistency of associations. To quantify the extent of heterogeneity, we estimated the between-study variance ($I^2$). $I^2$ statistic describes the proportion of variability in SMDs due to the heterogeneity between studies; homogeneous studies should have an $I^2$ value of 0. Publication bias was searched by using Egger’s [32] and Begg’s [33] tests.

Regression analysis was used to explore the relationship of targeted weekly and total exercise dose with fatigue, anxiety, depression, and QoL effect sizes. Weights estimated from intervention effect analyses were applied to studies in regression models. First, linear models were used; if not statistically significant ($F$-statistic), quadratic models were processed. When neither linear nor quadratic models reached significance, the most significant was presented in the result section. $R^2$ indicates the proportion of variance explained by statistical models. Sensitivity analyses were carried out according to potential confounders, previously identified in meta-analyses [13, 16], which could confound dose–response relationships: intervention length, poor quality studies, and exercise intervention combined with nutrition. All statistical analyses were carried out by using Stata software version 11 [34].

**results**

**studies characteristics**

The literature search initially identified 1011 articles. 879 articles were excluded due to (i) inappropriate population (mixed cancer sites or no patients with breast cancer), (ii) no exercise intervention, (iii) no RCT design, (iv) no outcome of interest among fatigue, anxiety, depression, and QoL, (v) intervention period scheduled after adjuvant cancer therapy, (vi) lack of statistical information and inability to obtain it from authors [35, 36], or (vii) provided follow-up results only [37]. Seventeen studies met all inclusion criteria and were thus included in this meta-analysis (see supplementary Figure S1, available at *Annals of Oncology* online). While 14 studies involved one intervention group, three studies provided two different intervention arms [30, 38, 39] leading to the inclusion of 20 intervention groups (748 subjects), each one compared with one control condition (632 controls). Studies characteristics are summarized in Table 1. The median age of included patients was 50.5 years old. All patients with breast cancer have been diagnosed with nonmetastatic cancer and were undergoing adjuvant therapy, i.e. chemotherapy and/or radiotherapy during exercise intervention. Regarding methodological quality, median score was 7, ranging from 2 to 9 (see supplementary Table S1, available at *Annals of Oncology* online). Of the 17 studies, 15 provided at least five quality criteria but no study met all of them. Most of the studies specified inclusion criteria and provided measures and comparisons of outcomes. More than half of the studies reported exercise session adherence >60% and drop-out <15% with associated reasons of drop-out, but <8 studies used intent-to-treat analysis and reported concealed allocation of subjects. Researchers were blinded to patients’ allocation group in only three studies.

**interventions characteristics**

Intervention characteristics are listed in Table 2. Most of interventions exclusively involved physical exercise followed by flexibility exercises and/or relaxation in four of them [26, 40–42], except one intervention group that was prescribed a low-fat and high-vegetable diet in addition [30] and one study that involved partners of women with breast cancer to encourage them to practice [43]. Mean (±SD) length of interventions was 17 (±8) weeks with 4 (±1) exercise sessions per week lasting 39 (±10) min on average. The mean (±SD) targeted volume of exercise was 10.6 (±5.4) MET h/week and 197 (±176) MET h, taking into account intervention length. No outliers were identified. Of the 20 interventions, six involved only supervised exercise sessions whereas 10 included only home-based sessions. Seven studies reported the use of motivation theory in intervention development. When reported, the adherence rates varied from 26% [30] to 93.8% [44] (see Table 2).

**overall intervention effects**

Table 3 presents summary effect sizes for all outcomes. Controlled comparisons of pre- and postintervention indicated that exercise intervention significantly reduced fatigue, anxiety, and depression but only borderline significance was reached for anxiety ($P = 0.06$). Moreover, exercise intervention significantly improved QoL. Forest plots are presented in supplementary Figure S2, available at *Annals of Oncology* online. Cochran’s $Q$ test revealed heterogeneity among studies that investigated fatigue, QoL, and anxiety. No evidence of publication bias was identified by Begg’s and Egger’s tests ($P > 0.10$ for all outcomes).

**dose–response effects**

**weekly exercise dose**

Regression analyses exploring the relationships between weekly prescribed dose of exercise and SMDs revealed significant linear model for QoL and significant quadratic models for fatigue and anxiety (Table 4), explaining 14%, 19%, and 21% of variance, respectively. Inverse dose–response relationships were observed for fatigue and QoL, implying that SMDs magnitude decreased as exercise dose increased (Figure 1). According to
these trends, effect on fatigue would be observed below a targeted exercise dose of 12 MET h/week, while the cutoff value for QoL would be closer to 20 MET h/week. The trend in the anxiety data showed a U-shaped relationship, suggesting that SMDs magnitude increased as exercise dose approached 400 MET h and increased for extreme doses of exercise. Regarding depression, although neither the linear nor quadratic models were significant, a trend in linear regression (P = 0.10) suggested an inverse dose–response relationship.

sensitivity analyses
Linear dose–response relationships were identified among (i) fair methodological quality studies (score ≥ 5) in fatigue but not in anxiety, (ii) longer duration intervention studies (≥ 18 weeks) in QoL and anxiety but significance was not reached in fatigue and depression, (iii) exercise focused interventions in depression, borderline significance was reached in QoL (P = 0.06) but not in anxiety (see Table 5). All identified linear relationships revealed reversed associations of outcomes with exercise dose.

discussion
This meta-analysis showed that exercise leads to significant decreases of fatigue and depression as well as significant increase of QoL in patients with breast cancer receiving...
A decrease was also observed in anxiety but only reached borderline significance ($P = 0.06$). To our knowledge, our study is the first meta-analysis exploring dose–effect relationship of exercise with fatigue, anxiety, and depression in patients with breast cancer. Our results revealed that greater decrease in fatigue and increase in QoL were observed with weak weekly targeted exercise doses, <12 MET h/week, as well as long duration interventions (≥18 weeks) for QoL. These findings generate the hypothesis that the prescription of a 20-week exercise program targeting 8–10 MET h/week could be well adapted for patients with breast cancer receiving adjuvant therapy.

As recommended, this program would combine both aerobic and resistance exercises [45] and then could consist in one resistance session for principal muscular groups and two moderate intensity aerobic sessions per week, each session lasting ~30–45 min. Regarding intervention effects, modest to medium improvements were observed in psychological variables of interest and are consistent with findings of a recent meta-analysis that investigated effects of exercise on fatigue during adjuvant therapy [20]. Another review from 2005 that selected high-quality studies and included no more than four publications reported nonsignificant improvements of anxiety.
depression, and QoL within adjuvant period [19]. Excluding studies that met less than five quality criteria [26, 46] led to similar results in our meta-analysis, except that significance was not reached anymore for fatigue; summary effect size was $-0.20$ (95% CI $-0.42$ to $0.01$), $P = 0.07$. Methodological weaknesses of included studies, especially small sample size and few intent-to-treat analyses, as well as the relatively young median age of participants (50.5 years) compared with the median age of in situ breast cancer diagnosis observed in the USA (58 years) [47] limit the generalizability of intervention effects.

Regarding dose–response analyses, inverse relationships were consistently observed between prescribed exercise and fatigue and QoL based on weekly and total exercise doses as well as longer duration interventions analyses for QoL and fair quality studies for fatigue. It suggests that relatively low targeted doses of exercise (<12 MET h/week) would lead to better improvements of fatigue and QoL in patients receiving adjuvant breast cancer therapy than higher targeted doses. More robust associations were generally found with total exercise dose than weekly exercise dose except with anxiety, implying that the duration of intervention explained some variance in effect sizes. In a meta-analysis investigating the relationship between targeted aerobic METs and QoL in cancer survivors, a trend was only observed among longer duration trials [16]. The authors observed a positive relationship, meaning that larger amounts of targeted aerobic activity were associated with substantial QoL improvements [16] but studies included various cancer sites, both controlled and uncontrolled trials and mixed intervention periods with most of the studies involving postadjuvant therapy interventions. Being aware of the immediate deleterious impact of adjuvant cancer therapy on fatigue and QoL [3, 4, 48], the pattern of their relationship with exercise could differ according to the intervention period, i.e. during versus after adjuvant therapy. The pattern of fatigue evolves through adjuvant therapy, increasing with consecutive chemotherapy.

### Table 4. Relationships of weekly and total exercise dose with psychological outcomes

<table>
<thead>
<tr>
<th></th>
<th>No. of SMDs</th>
<th>$F$</th>
<th>$P$ ($F$)</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly exercise dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>4.73$^b$</td>
<td>0.04</td>
<td>0.19</td>
</tr>
<tr>
<td>Quality of life</td>
<td>12</td>
<td>9.96$^a$</td>
<td>0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10</td>
<td>9.05$^b$</td>
<td>0.01</td>
<td>0.21</td>
</tr>
<tr>
<td>Depression</td>
<td>11</td>
<td>0.52$^b$</td>
<td>0.61</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Total exercise dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>9.95$^a$</td>
<td>0.009</td>
<td>0.26</td>
</tr>
<tr>
<td>Quality of life</td>
<td>12</td>
<td>7.13$^a$</td>
<td>0.02</td>
<td>0.29</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10</td>
<td>3.55$^a$</td>
<td>0.10</td>
<td>0.21</td>
</tr>
<tr>
<td>Depression</td>
<td>11</td>
<td>8.76$^b$</td>
<td>0.01</td>
<td>0.46</td>
</tr>
</tbody>
</table>

$^a$F-statistic obtained from linear regression.

$^b$F-statistic obtained from quadratic regression.

SMDs, standardized mean differences

Figure 1. Linear or quadratic trends of psychological factors change in function of weekly targeted exercise METs. Note: Y-axis has been reversed on QoL graph. Quadratic trend representations were used for fatigue, anxiety, and depression; linear trend representation was used for QoL.
cycles and presenting a peak level ~5 days after chemotherapy administration [49, 50]. Therefore, exercise programs that proposed progressively low-to-moderate doses of exercise across chemotherapy cycles, e.g. 2–5 MET h/week within the first 10 days after chemotherapy administration and 5–10 MET h/week during the following days, could be well adapted to reduce fatigue and improve QoL.

Inconsistent and mostly nonlinear relationships were observed between prescribed exercise dose and anxiety and depression effect sizes. The lack and the nonlinear nature of associations could result from confounding variables. Indeed, sensitivity analyses of longer duration trials revealed a significant and inverse linear relationship of prescribed exercise dose with anxiety whereas a nonlinear U-shaped trend was

---

**Figure 2.** Linear or quadratic trends of psychological factors change in function of total targeted exercise METs. Note: Y-axis has been reversed on QoL graph. Quadratic trend representation was used for depression; linear trend representations were used for fatigue, anxiety, and QoL.

**Table 5.** Sensitivity analyses in linear relationships of weekly and total exercise dose with psychological outcomes

<table>
<thead>
<tr>
<th>Study subgroup a</th>
<th>Outcome</th>
<th>Exercise dose b</th>
<th>No. of SMDs</th>
<th>P</th>
<th>P (F)</th>
<th>$R^2$</th>
<th>Relationship pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair quality studies (score ≥ 5)</td>
<td>Fatigue</td>
<td>Total</td>
<td>12</td>
<td>7.43</td>
<td>0.02</td>
<td>0.47</td>
<td>Inverse</td>
</tr>
<tr>
<td>Longer duration interventions (≥ 18 weeks)</td>
<td>QoL</td>
<td>Weekly</td>
<td>8</td>
<td>10.2</td>
<td>0.02</td>
<td>0.19</td>
<td>Inverse</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Weekly</td>
<td>7</td>
<td>10.0</td>
<td>0.025</td>
<td>0.36</td>
<td>Inverse</td>
<td></td>
</tr>
<tr>
<td>Exercise-focused interventions</td>
<td>Depression</td>
<td>Weekly</td>
<td>10</td>
<td>5.24</td>
<td>0.05</td>
<td>0.18</td>
<td>Inverse</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>10</td>
<td>10.5</td>
<td>0.01</td>
<td>0.37</td>
<td>Inverse</td>
<td></td>
</tr>
</tbody>
</table>

*aFair quality studies subgroup analyses were carried out for fatigue and anxiety as two studies scored <5, one assessed fatigue [26], one assessed anxiety [46]; longer duration intervention subgroup analyses were tested in fatigue, QoL, anxiety and depression; exercise focused interventions subgroup analyses were tested in QoL, anxiety and depression (only one study involved a mixed exercise and diet intervention [30]); only significant relationships are reported in the table.

*bFair quality studies and exercise focused interventions linear regression subgroup analyses were tested with both weekly and total exercise doses; longer duration intervention subgroup analyze were tested with weekly dose; only significant relationships are reported in the table.

SMDs, standardized mean differences; QoL, quality of life.
observed when all studies were included. Regarding depression, excluding mixed exercise and diet intervention also led to obtain significant and inverse linear dose–response relationship. Other confounders that cannot be tested may introduce bias, e.g. unbalanced groups in included studies regarding the proportion of subjects diagnosed for clinical depression or anxiety and treated with antidepressant or anxiolytic drugs. Indeed, only two studies checked homogeneity of groups for psychiatric history [43, 51] and medication [29, 43] and none adjusted for it in statistical analyses while large-scale cohorts of patients with breast cancer reported 25–30% of antidepressant users [52, 53]. Although randomization is intended to create balanced groups, the probability that two treatment groups differ on confounding factors in small sample RCTs is not negligible [54]. The inconsistent findings regarding anxiety and depression also suggest that these psychological outcomes may not be directly related to targeted dose of exercise; beneficial effect of exercise on these outcomes can primarily be mediated by others factors such as enhanced self-esteem, improved body image, increased sense of mastery [55] and increased personal control over treatment [56]. The dose–response relationship between exercise and depression has been investigated in a meta-analysis including 12 RCTs of both general population and clinically depressed subjects and revealed a nonsignificant association [57]. Wipfli et al. [58] who evaluated the dose–response relationship of exercise with anxiety in a meta-analysis including both clinical anxious and nonclinical population, reported a nonsignificant and nonlinear U-shaped relationship, similar trend that was observed with weekly exercise dose in our meta-analysis. However, the authors did not explore sensitivity analyses according to potential confounders.

Focusing on both adjuvant treatment period and only one localization of cancer may have improved homogeneity between studies compared with previous systematic reviews [13–16, 19], but heterogeneity remains one important limitation of our meta-analysis. It was particularly noticed among included studies that investigated anxiety, fatigue, and QoL. The major percentage of variation was brought by Wang et al. [44] for fatigue (15%) and QoL (21%) and Badger et al. [43] for anxiety (50%) and depression (16%). Differences in population samples of included studies regarding their origins, physical functioning, body mass index, as well as disease severity and treatments represent main sources of heterogeneity. As described in Table 1, various countries and cultures represented in included studies may lead to different cares and interventions. Moreover, few studies only included very early stages (I to II) [39, 44, 59], whereas most of the studies included I to III stage breast cancers. Cancer severity, linked with surgery type, has been shown to be associated with psychological symptoms [60, 61]. Fatigue level is also related to the type of treatment [49]; while most intervention periods involved chemotherapy, a few focused on radiotherapy only [42, 59, 62] and others included a mix of radiation and chemotherapy [26, 39–41, 43, 46, 51, 63, 64]. Other sources of heterogeneity are the type of control condition and the intervention contents. The important part of heterogeneity brought by the study of Badger et al. [43] may be due to the atypical intervention involving women’s partners to increase social support and then exercise motivation. Lastly, the use of motivational approaches explicitly implemented in 7 of 17 studies may have introduced heterogeneity by influencing the adherence rates to exercise programs and then exercise doses achieved, and also by leading to better improvements of psychological factors as it has been shown for fatigue [13].

Estimation of exercise dose represents an important limitation. Targeted aerobic exercise intensity was frequently described within a range such as 50%–80% of the maximal heart rate, which did not enable to consider it precisely; except when it was explicitly stated as light or vigorous, intensity was considered moderate for dose calculation. Although calculation and MET attributions were standardized, only targeted exercise doses were estimated instead of achieved exercise doses. Taking into account the adherence rates was not possible because they were not always reported and if they were, adherence criteria were heterogeneous among included studies, e.g. one study reported phone calls rather than exercise adherence [43]. However, it is important to point out that the exercise doses and the reported adherence rates were significantly and inversely correlated (\( r = -0.62, P = 0.02 \) for weekly dose; \( r = -0.82, P = <0.001 \) for total dose) implying that lower prescribed doses interventions presented greater adherence rates than higher prescribed doses interventions. Therefore, adherence could confound dose–response relationships explored in meta-analyses. Although participants were prescribed higher doses, they may only have been doing similar or even lower amount of exercise as those who were prescribed less. Inverse dose–response relationships observed in our meta-analysis are related to the prescribed exercise dose. The inverse correlation of adherence with prescription suggests the hypothesis that the nature of the relationship of achieved exercise doses with psychological outcomes would be different.

**Conclusions**

The present meta-analysis showed beneficial effects of exercise in psychological factors. Based on current evidence, adapted physical activity programs can be expected to decrease fatigue and depressive symptoms and to increase QoL during chemotherapy and/or radiotherapy for patients with early-stage breast cancer. An anxiety symptoms reduction was also observed but the evidence is still limited. These findings need to be confirmed by higher methodological quality and larger sample sized trials before generalization.

Relationships of targeted exercise dose with psychological factors have emerged. Inverse dose–response relationships were observed for fatigue and QoL, supporting the hypothesis of greater improvements with lower weekly prescribed exercise doses (<12 MET h/week). Exercise interventions that take into account the pattern of fatigue observed during chemotherapy by implementing evolving doses of exercise according to chemotherapy cycles could be well adapted during this particular period. Trials reports should be based on Consolidated Standards of Reporting Trials statement for nonpharmacologic trials [65] and include a proper description of exercise adherence, making possible to explore achieved instead of prescribed doses. Future observational studies and
clinical trials that investigate the nature and the shape of the dose–response relationship taking into account potential confounders as well as the effects of several different exercise doses in terms of the intensity, frequency, and duration on physiological and psychological parameters would be of interest.

funding

This work was supported by a Research Grant from the French Hérault Committee of Cancer League (Ligue contre le cancer); and the French South-West Canceropole (Cancéropole GSO).

disclosure

The authors have declared no conflicts of interest.

references

34. StataCorp. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP 2009.


