Acta Oncologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

# Is it safe to exercise during oncological treatment? A study of adverse events during endurance and resistance training – data from the Phys-Can study

Anna Henriksson, Birgitta Johansson, Calin Radu, Sveinung Berntsen, Helena Igelström & Karin Nordin

**To cite this article:** Anna Henriksson, Birgitta Johansson, Calin Radu, Sveinung Berntsen, Helena Igelström & Karin Nordin (2021) Is it safe to exercise during oncological treatment? A study of adverse events during endurance and resistance training – data from the Phys-Can study, Acta Oncologica, 60:1, 96-105, DOI: 10.1080/0284186X.2020.1851046

**To link to this article:** https://doi.org/10.1080/0284186X.2020.1851046

ACTA ONCOLOGICA
2021, VOL. 60, NO. 1, 96–105
https://doi.org/10.1080/0284186X.2020.1851046

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE



# Is it safe to exercise during oncological treatment? A study of adverse events during endurance and resistance training – data from the Phys-Can study

Anna Henriksson[a], Birgitta Johansson[b], Calin Radu[b], Sveinung Berntsen[a,c], Helena Igelström[d] and Karin Nordin[a]

[a]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; [b]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; [c]Department of Sport Science and Physical Education, University of Agder, Kristiansand, Norway; [d]Department of Neuroscience, Uppsala University, Uppsala, Sweden

**ABSTRACT**

**Introduction:** Few studies have systematically evaluated the risk of adverse events (AEs) among persons exercising during oncological treatment. We aimed to describe incidence and types of AEs during exercise for persons undergoing oncological treatment, and associations to exercise intensity, exercise adherence, chemotherapy treatment, initial aerobic fitness. A second aim was to compare incidence of lymphedema, periphery inserted central catheter (PICC) complications, and other new medical conditions (any illness or injury occurred during the exercise trial) between high-intensity vs low-to-moderate exercise and usual care (UC).

**Methods:** This descriptive, comparative study was based on data from an observational study including patients in an UC setting ($n = 90$) and a randomized exercise trial ($n = 577$) in which participants exercised at high-intensity (HI) or low-moderate intensity (LMI). Persons with breast, prostate, or colorectal cancer undergoing neo/adjuvant treatment were included. AEs were reported by exercise coaches, participants, and identified in medical records, as were lymphedema, PICC-complications, and new medical conditions.

**Results:** Coaches reported AEs for 20% of the participants, while 28% of participants self-reported AEs. The most common coach- and participant reported AEs were musculoskeletal and the majority (97%) were considered minor. HI had higher likelihood of AEs than LMI, according to both coaches (OR: 1.9 [95%CI 1.16–3.21], $p$=.011) and participants (OR: 3.36 [95%CI 2.00–5.62], ≤.001). Lymphedema rates were low (4-9%) and PICC complications ranged from 15% in LMI to 23% in UC and there were no statistically significant differences between HI, LMI, and UC. There were no statistically significant differences between HI and LMI regarding new medical conditions.

**Conclusions:** Exercise during treatment is safe for these patient groups in this setting, even HI exercise can be recommended if no medical contraindications are present. Similar to healthy populations, a higher risk of having minor AEs when exercising at HI in comparison to LMI may exist.

**ARTICLE HISTORY**
Received 11 July 2020
Accepted 6 November 2020

**KEYWORDS**
Physical exercise; adverse events; oncology; peripherally inserted central catheter; lymphedema

## Introduction

The benefits of exercise (i.e., structured, planned physical activity aimed to maintain or improve physical function and fitness [1]) for persons living with and beyond cancer have proven to be many. Exercise may improve or maintain aerobic and muscular fitness, counteract cancer-related fatigue, and improve health-related quality of life both during and after oncological treatment [2–4].

However, exercising during oncological treatment is challenging, and patients often reduce their physical activity level during treatment [5]. One barrier, experienced by both patients and clinicians, is uncertainty regarding the safety of exercise during treatment. This may prevent clinicians from advising patients to exercise and, ultimately, prevent patients from exercising [6–8]. Knowledge is needed about the risks of exercise-related adverse events (ex-AEs). AEs are defined as undesirable events that occur during or after an intervention but are not necessarily caused by it [9].

In reviews of exercise trials for persons with cancer, it has repeatedly been stated that exercise is safe during treatment for most individuals [4,10–12] and reports of exercise related serious AEs (ex-SAEs) due to exercise during are rare. However, it has also been recognized that ex-AE reporting is neither systematic nor standardized across studies (e.g., definition of AEs and information on data collection methods are lacking) [10,11,13]. This causes difficulties in determining if persons with cancer engaging in exercise experience more ex-AEs than individuals without cancer, and if there are any treatment or exercise-related factors associated to occurrence of ex-AEs.

A systematic review of randomized controlled exercise trials (RCTs) [13] including persons with cancer (and other

CONTACT Anna Henriksson anna.henriksson@pubcare.uu.se Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
Supplemental data for this article can be accessed here.

diagnostic groups) did not find evidence for increased risk of ex-SAEs leading to hospitalization, severe impairment or death, in intervention groups compared to non-exercising controls. However, the authors found a 19% increased risk of non-serious ex-AEs (e.g., pain, fatigue, bursitis). A limitation in the reviewed RCTs was a lack of systematic assessments of ex-AEs, and 51% did not report ex-AEs at all.

Studies in healthy adult populations have indicated that exercise mode may influence the risk of injury. Walking seems safe, while HI exercise, like running and contact sports, increase risks of musculoskeletal injuries, pain, or other discomforts [14–16]. Also, increasing time of physical activity at a higher intensity, especially in persons not previously physically active [14,16,17]. An RCT including healthy women at risk for breast cancer found that higher volumes of aerobic exercise increased risk of musculoskeletal injuries compared to controls. However, injuries impairing daily activities did not increase with higher volumes of aerobic exercise [17].

One dreaded side effect of breast cancer surgery and oncological treatment is lymphedema, affecting approximately 20% of patients [18]. Previously, resistance training (RT) was believed to increase lymph fluid production and trigger or worsen lymphedema [19]. Historically, RT has therefore not been advised for patients with breast cancer at risk of or already suffering from lymphedema. Nonetheless, research has demonstrated that slowly progressive RT is safe, and there have even been indications that exercise can improve lymphedema [10,20]. However, few studies comparing RT with different intensities have been conducted regarding incidence of lymphedema [20,21]. More information could help guide recommendations for patients at risk of developing lymphedema.

Since intravenous chemotherapy commonly requires central venous access, e.g., a peripherally inserted intravenous catheter (PICC), risk evaluation of exercise during treatment should include access complications. PICC is associated with several complications such as thrombosis, dislocations, and infections [22–24]. Observational studies have identified risk factors for PICC-related thromboembolism such as 5-florouracil and oxaliplatin chemotherapy, higher age, overweight, and diabetes [24–30]. Two small studies found that being less active with the PICC-inserted arm may also be a risk factor for PICC-related thromboembolism [25,31], however, exercise studies reporting PICC safety are lacking. To our knowledge, only Mijwel et al. [32] have studied this, stating that there were no PICC-related AEs during an exercise RCT including women receiving chemotherapy against breast cancer.

In summary, exercise during oncological treatment has many benefits and is an important part of cancer rehabilitation, but studies systematically evaluating risk of ex-AE are lacking. Knowledge regarding ex-AEs can assist clinicians when prescribing, referring, and discussing exercise with patients. Therefore, this study aimed to describe incidence and types of AEs during exercise for persons undergoing oncological treatment, and associations to exercise intensity, exercise adherence, chemotherapy treatment, and initial aerobic fitness. A second aim was to compare incidence of lymphedema, PICC-complications between low-to-moderate (LMI) vs HI exercise and usual care, and other new medical conditions (any illness, disease or injury occurring during the trial) between LMI vs HI.

## Methods

### Study design

This was a descriptive and comparative study based on secondary data from the Phys-Can observational study and exercise RCT. The design and outcomes have previously been described in detail [33].

### Study participants

Participants were recruited at oncology and surgery clinics at three university hospitals in Sweden and were included in the observational study ($n = 90$) or the RCT ($n = 577$). The observational study preceded the RCT and recruitment ran from September 2014 to March 2015. The recruitment to the RCT started in March 2015 (after enrollment in the observation study had ended) and was completed in May 2018. Participants in the observational study received usual care (UC), including advice about being physically active during treatment, but were not offered to participate in an exercise intervention.

Eligible for the Phys-Can project were a) women with breast cancer planned to receive neo/adjuvant chemotherapy (with or without antibody treatment) and/or adjuvant radiotherapy and/or adjuvant endocrine treatment, b) men with prostate cancer planned to receive curative brachy- and/or external radiotherapy with or without neo/adjuvant endocrine treatment, c) women and men with colorectal cancer planned to receive adjuvant chemotherapy. Persons were excluded if they did not speak Swedish, had co-morbid conditions that prevented HI exercise (e.g., severe heart failure, severe chronic obstructive pulmonary disorder, orthopedic or neurological conditions), severe emotional instability, cognitive disorders, or could not perform basic activities in daily life.

Only participants with breast- and colorectal cancer were included from the observational study, as the men with prostate cancer did not undergo chemotherapy and had no central venous access.

### Procedure

All participants were assessed for eligibility by an oncologist or oncology surgeon before receiving information about the study. If eligible, patients received verbal and written information before signing a consent form.

### Exercise intervention

Participants in the RCT were randomized to six months of either HI or LMI exercise, with or without behavior change support (BCS) (Table 1). Exercise was initiated before or at the start of oncological treatment. The exercise consisted of group-

**Table 1.** Description of the exercise intervention performed at high intensity or low-moderate intensity during oncological neo/adjuvant treatment.

| | Resistance training | Endurance training |
|---|---|---|
| 6-months[a] exercise intervention | Seated leg press, leg extension, seated leg curl, seated row, chest press performed in machines seated or standing shoulder press with dumbbells.<br>Body weight exercises: sit-ups, the plank, bird-dog, and pelvic floor exercises. | Intensity based on participant's HRR calculated from measured heart peak rate. Recommended frequency of endurance exercise was two to four times a week for all participants.<br>Type of activity was based on individual preferences, e.g., walking, bicycling, running. Participants used a heartrate monitor to control intensity. |
| Warm-up | 5–10 min warm-up on a treadmill (or other machine) at a moderate intensity. Specific warm-up consisted of one set at 50% RM for each resistance exercise. | HI: 5–10 min warm-up at a moderate intensity. LMI: No warm-up required. |
| HI | Two sessions/week, alternating between:<br>3 set × 6 RM with 2 min set rest.<br>3 set × 10 RM with 1 min set rest.<br>Last set to failure.<br>Last set Omni scale: 9–10. | Intervals of two minutes with a 1:1 work-to-rest ratio at 80–90% of HRR and RPE 15–17 at the end of the last interval. The interval exercise was progressed: 5 work intervals at the start, increasing to six after week 6 and adding one interval every fourth week until a maximum of 10 intervals was reached.<br>Recommended exercise frequency two to four times a week. |
| LMI | Two sessions/week, alternating between:<br>3 set × 12 repetitions at 50% of 6 RM with 2 min set rest.<br>3 set × 20 repetitions at 50% of 10 RM with 1 min set rest.<br>Last set Omni scale: 5–7. | 150 min per week at 40–50% of HRR. RPE: 12–13<br>Recommended exercise frequency two to four times a week. |
| Familiarization and tailoring | Resistance training started at low intensity consisting of 1 set of 20 reps at 30 RM in week 1 and progressed for 6 weeks, including learning how to use the Omni scale.<br>Testing of 6 and 10 RM in all exercises.<br>Exercises that caused pain were substituted with other exercises activating the same muscle groups. Weights were lowered temporarily for patients struggling with severe side effects, and then successively increased. | Four endurance exercise sessions with the coach, including learning how to use a heartrate monitor and RPE. |
| Specific safety measures | For participants receiving intravenous chemotherapy, no resistance training or HI endurance training was conducted for 24 h after administration [34]. | |

[a]For participants with neo/adjuvant chemotherapy the exercise intervention was approximately 4 months.
HI: High intensity; LMI: Low-moderate intensity; HRR: Heartrate reserve (calculated as: peak heartrate – resting heartrate); RM: repetition maximum, i.e., the weight a person can maximally lift × times; Omni scale: a scale for perceived exertion during resistance training (0–10) [35]; RPE: Borg's Ratings of Perceived Exertion (6–20) [36].

based RT, twice a week, at a public gym, and home-based ET. The exercise was supervised by coaches (physiotherapists or personal trainers) who had received study-specific education regarding exercise for persons with cancer [33]. Analysis regarding adherence to exercise showed no difference between groups randomized to BCS or not, [37] why we did not expect any differences in ex-AEs depending on the BCS. Therefore, comparisons were made between participants randomized to HI and LMI, regardless of whether they received BCS or not.

## Data collection

### Medical and sociodemographic data

Age was gathered with study-specific questionnaires at baseline. Baseline physical activity was measured for 7 days with SenseWear™ Mini Armband, for further details see Berntsen et al. [33]. Weight and height were measured at baseline by study personnel and used to calculate body mass index (kg/m$^2$). Data regarding oncological treatment and central venous access (e.g., type of access, insertion and removal date) were gathered from medical records. Data regarding surgery for participants with breast cancer and colorectal cancer were gathered from the Swedish National Quality Registers for Breast Cancer and Colorectal Cancer.

### Adherence to the exercise program and aerobic fitness

Exercise adherence was calculated as performed exercise/prescribed exercise, in accordance with previous research [38], as described in Table 1, for RT and ET combined. Before the start of the exercise program, aerobic fitness was measured with a maximal oxygen uptake ($VO_2$max) test, using a modified Balke test-protocol. The participants walked/ran on a treadmill until exhaustion. For further details see Berntsen et al. [33].

### Coach-reported adverse events

Coach-reported ex-AEs were registered as soon as possible when they occurred or became known by the coach (ex-AEs occurring at home was reported to the coach by the participant by phone or at the RT sessions), in a study-specific checklist for each participant. Only events deemed to be caused by the exercise were reported. The severity of an ex-AE was graded depending on whether the participant had to stop the specific exercise (grade 1) or had to end the entire training session (grade 2). The coaches described the ex-AE and whether it occurred during ET or RT. All eventual ex-AEs for a participant were summarized when the participant had completed the exercise program.

The ex-AEs were categorized as musculoskeletal/connective tissue, accidents/injuries, cardiovascular symptoms/conditions, or 'other'. 'Other' were symptoms/conditions occurring at a low frequency (Table 2). Ex-SAEs were defined as an ex-

Table 2. Description of adverse events categories of coach- and participant reported AE, PICC- complications and other new medical conditions.

| | |
|---|---|
| Description of coach- and participant-reported exercise-related AE | |
| Musculoskeletal and connective tissue | muscle strains, joint pain and muscular pain |
| Accidents/injuries | falling/tripping resulting in fractures, bruising, and swelling |
| Cardiovascular symptoms/conditions | feelings of lightheadedness, dizziness, fainting, and heart palpitations |
| Other | fatigue, hernia, and eczema from heartrate monitor |
| Description of PICC complications | |
| *Medical record* | arm swelling, occlusion/no back flow, leakage, pain at the insertion site, not being able to remove PICC, and too narrow blood vessel |
| *Participant-reported* | feelings of discomfort in the arm with PICC inserted, PICC chafed during exercise, and discomfort in the arm during chest press |
| Description of other new medical conditions[a] | |
| Musculoskeletal and connective tissue | arthritis, swollen ankle, back pain, knee pain, impingement of shoulder, and herniated disk |
| Accidents/injuries | tripping/falling resulting in fractures, and spraining of ankle |
| Cardiovascular symptoms conditions | nose bleeding, atrial fibrillation, fainting, and chest pain during interval training. Atrial fibrillation was treated with anticoagulant medication and in one instance cardioversion therapy. Chest pain was further investigated by physician without finding an underlying cause and the patient continued exercising without experiencing pain. |
| Pulmonary symptoms/conditions | asthma, coughing, and shortness of breath |
| Other | migraine, myomas, inguinal hernia, skin cancer, infections, psychiatric conditions and colon polyps, hyperlipidemia, endometriosis, and gastritis |

AE: adverse events; PICC: Peripherally inserted central catheter.
[a]All new medical conditions occurring during the exercise trial period.

AE requiring immediate hospital care and were as soon as possible reported to the principal investigator.

### Participant-reported adverse events

Participant-reported ex-AEs and PICC-related complications were gathered through a study-specific questionnaire at the end of the exercise program. The questions concerned whether they had experienced any injuries or discomfort during the six-month exercise intervention (yes/no). Participants who answered yes were asked to describe the injury/discomfort in free text. Participant-reported ex-AE were categorized as musculoskeletal/connective tissue, accidents/injuries, cardiovascular symptoms/conditions, or 'other'. PICC-related complications were categorized as thrombosis, infection, dislocation, thrombophlebitis, or 'other' (Table 2).

### Medical record review – lymphedema, PICC complications and other new medical conditions

The oncological medical records were reviewed regarding lymphedema, PICC-related complications, and other new medical conditions (any illness, disease or injury) that had occurred from the time of inclusion in the RCT until the 6-month follow-up. Lymphedema was categorized as present or absent. PICC-related complications were categorized as thrombosis, infections, dislocations, thrombophlebitis, or 'other'. New medical conditions were categorized as musculoskeletal/connective tissue, accidents/injuries, pulmonary symptoms/conditions, cardiovascular symptoms/conditions, or 'other' (Table 2). Lymphedema and PICC-related complications were collected for all participants (UC and RCT). New medical conditions were collected for RCT participants only.

### Analysis

Multiple logistic regression analyses were used to explore if coach-reported ex-AEs (no = 0, yes = 1) or participant-reported ex-AEs (no = 0, yes = 1) were associated with exercise intensity (LMI = 0, HI = 1), chemotherapy (no = 0, yes = 1), adherence to exercise (continuous variable) or baseline aerobic fitness (continuous variable). Only participants from the RCT were included in the multiple logistic regression analyses because this data was not available in the UC. Odds ratios with 95% confidence intervals (CI) were calculated for all variables. Differences between UC, HI, and LMI groups regarding the presence (no/yes) of lymphedema and PICC-related complications, and differences between HI and LMI groups regarding the presence (no/yes) of new medical condition were analyzed with the chi-square test. Participant-reported discomfort or injuries regarding PICC were presented descriptively only, due to few events. All available data were used in the chi-square tests and complete cases in the multiple logistic analyses. All analyses were carried out in IBM SPSS Statistics version 25.

### Ethical approval

The study was approved by the Swedish Ethical Review Authority (Dnr 2014/249).

## Results

The most common diagnosis in all groups was breast cancer (UC: 84%, HI: 79%, LMI: 79%). Fewer women with breast cancer in UC (41%) received chemotherapy than in HI (60%) or LMI (61%). Mean age was 58 years in UC and 59 years in HI and LMI (Table 3).

### Coach- and participant-reported adverse events

One hundred and seven (20%) of 519 participants (26% in HI and 15% in LMI) had at least one coach-reported ex-AE, while 119 (28%) of 420 participants (40% in HI and 17% in LMI) reported at least one self-reported ex-AE (Table 4). The distributions were similar when data are presented by diagnosis (Supplementary Table 1). AEs were more common during RT (coach-reported $n = 115$, participant-reported $n = 105$) than ET (coach-reported $n = 23$, participant-reported $n = 50$)

**Table 3.** Baseline demographic and physical variables, adherence to exercise and oncological treatment in patients receiving care as usual and in patients exercising at high intensity or low-moderate intensity during oncological treatment.

| | Care as usual | HI | LMI |
|---|---|---|---|
| Total, n | 90 | 288 | 289 |
| Age, years, mean (sd) [min–max] | 57.7 (11.2) [28–80] | 58.7 (12.2) [22–85] | 58.8 (11.7) [30–85] |
| Baseline body mass index (BMI), n (sd) | | | |
| BMI $\leq$ 18.4 kg/m$^2$ | 0 (0.0) | 5 (1.7) | 2 (0.7) |
| BMI 18.5–24.9 kg/m$^2$ | 31 (34.4) | 124 (43.1) | 129 (44.6) |
| BMI 25–29.9 kg/m$^2$ | 30 (33.3) | 90 (31.3) | 97(33.6) |
| BMI $\geq$ 30 kg/m$^2$ | 10 (11.1) | 48 (16.7) | 39 (13.5) |
| Missing, n (%) | 19 (21.1) | 21 (7.3) | 22 (7.6) |
| Baseline aerobic fitness, mean (sd) | | | |
| VO2max ml/kg/min | 32.6 (32.4) | 29.9 (7.24) | 30.7 (7.1) |
| Baseline PA measured with SenseWear$^{TM}$, mean (sd) | | | |
| MVPA hrs/day | 1.1 (0.56) | 1.2 (0.87) | 1.2 (0.78) |
| Missing | 20 (22.2) | 34 (11.8) | 25 (8.7) |
| Adherence to exercise intervention (randomized intensity), $n = 469$ | | | |
| Resistance traning[a] % (SD) | | 57.9 (23.7) | 62.8 (22.3) |
| Endurance traning[a] % (SD) | | 38.3 (32.9) | 51.0 (38.6) |
| Combined %[b] (SD) | | 52.7 (24.2) | 63.3 (23.5) |
| Breast cancer, total n (% of group) | 86 (84.3) | 228 (79.2) | 229 (79.2) |
| Oncological treatment breast cancer, n (%) | 70 (81.4) | 212 (93.0) | 213 (93.0) |
| Chemotherapy total | 29 (33.7) | 136 (59.6) | 140 (61.1) |
| Adjuvant chemotherapy[c] | 28 (96.5) | 112 (82.4) | 119 (85.0) |
| Neo-adjuvant chemotherapy[c] | 1 (0.3) | 24 (17.6) | 21 (15.0) |
| Chemotherapy type[c] | | | |
| F/E$^{75}$C$^{600}$ | 15 (51.7) | 46 (33.8) | 45 (32.1) |
| F/E$^{90-100}$C$^{500-600}$ | 14 (42.3) | 75 (55.1) | 85 (60.7) |
| Docetaxcel$^{75-80}$ | 18 (62.0) | 54 (39.7) | 58 (41.4) |
| Docetaxcel$^{90-100}$ | 10 (34.4) | 60 (44.1) | 71 (50.7) |
| Paclitaxcel | 0 (0.0) | 18 (13.2) | 9 (6.4) |
| Docetaxcel Capacetabine | 1 (0.3) | 9 (6.6) | 3 (2.1) |
| CEX | 1 (0.3) | 8 (5.9) | 2 (1.4) |
| Antibody treatment[a] | 6 (8.5) | 39 (28.7) | 40 (28.6) |
| Radiotherapy | 51 (59.3) | 172 (74.6) | 177 (77.3) |
| Endocrine treatment | 54 (77.1) | 147 (64.5) | 163 (71.2) |
| Missing | 16 (18.6) | 16 (7.0) | 16 (7.0) |
| Surgery breast cancer, total n | 69 | 204 | 202 |
| Breast conserving treatment | 38 (55.0) | 136 (66.7) | 129 (63.8) |
| Axillary node dissection only | 4 (5.8) | 24 (11.8) | 25 (12.4) |
| Sentinel node only | 54 (78.3) | 148 (72.5) | 137 (67.8) |
| Both | 10 (14.5) | 26 (12.7) | 32 (15.8) |
| Missing | 17 (19.8) | 24 (10.5) | 27 (11.8) |
| Prostate cancer, total n (% of group) | | 49 (17.0) | 48 (16.6) |
| Oncological treatment prostate cancer, n (%) | | 45 (91.8) | 46 (95.8) |
| Brachytherapy only | | 0 (0.0) | 2 (4.4) |
| External therapy only | | 18 (40.9) | 24 (53.3) |
| Brachy- and external therapy comb. | | 26 (59.1) | 19 (42.2) |
| Neo- and/or adjuvant endocrine treatment | | 26 (53.0) | 25 (52.0) |
| Missing, n (%) | | 4 (8.2) | 2 (4.2) |
| Colorectal cancer, total n (% of group) | 4 (3.9) | 11 (3.8) | 12 (4.2) |
| Oncological treatment colorectal cancer | 4 (100.0) | 11 (100.0) | 11 (91.7) |
| Chemotherapy type, n (%) | | | |
| CAPOX | 1 (25.0) | 7 (63.6) | 6 (50.0) |
| Capecitabine single | 3 (75.0) | 4 (36.4) | 5 (41.6) |
| Pre-operative radiotherapy, n (%) | 0 (0.0) | 3 (27.3) | 0 (0.0) |
| Missing | 0 (0.0) | 0 (0.0) | 1 (8.3) |
| Surgery colorectal cancer, total n (%) | 4 (100.0) | 11 (100.0) | 11 (100.0) |
| Right hemicolectomy | 2 (50.0) | 3 (27.3) | 9 (81.8) |
| Left hemicolectomy | 0 (0.0) | 2 (18.2) | 0 (0.0) |
| Sigmoid resection | 2 (50.0) | 1 (9.0) | 1 (9.9) |
| Rectal excision | 0 (0.0) | 2 (18.2) | 0 (0.0) |
| Frontal resection of rectum | 0 (0.0) | 2 (18.2) | 1 (9.9) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Central venous access | | | |
| Type of access n (%) | | | |
| PICC | 30 (100.0) | 132 (93,6) | 141 (97,9) |
| VAP | 0 (0.0) | 7 (5,0) | 2 (1,4) |
| CVC | 0 (0.0) | 2 (1,4) | 1 (0,7) |
| Days inserted, mean (SD) [Median] | 97.72 (38.57) [110.0] | 101.88 (33.44) [107.0] | 98,48 (29.78) [106.0] |

Missing % is from total N participant in group.

HI: high-intensity exercise group; LMI: Low-moderate intensity exercise group; $VO_2$Max: maximum oxygen uptake; PA: physical activity; MVPA: moderate-to-vigorous intensity physical activity; CEX: Epirubicin-Cyclophosphamide-Capecitabine; CAPOX: Capecitabine-Oxaliplatin; PICC: peripherally inserted central catheter; VAP: venous access port or subcutaneous infusion port; CVC: central venous catheter.

[a]Number of performed session/number of prescribed sessions $\times$ 100.

[b]Combined adherence calculated as (performed exerciser training)+(prescribed exercise). Participants who dropped out of the study before end of exercise were recorded as 0 adherence to any remaining training sessions.

[c]n (%) of participants with breast cancer receiving chemotherapy. F/EC: Fluorouracil 500–600 mg/m$^2$ and/or only Epirubicin 75–100 mg/m$^2$ cyclophosphamide 500–600 mg/m$^2$.

**Table 4.** Coach- and participant-reported exercise-related adverse events, lymphedema, PICC-related complications and new conditions in the oncology medical record.

| Coach-reported exercise-related AE (randomized intensity) | | | | |
|---|---|---|---|---|
| | | Total $N = 519$ | HI $N = 258$ | LMI $N = 261$ |
| Participants with one or more AE, n (%) | | 107 (20.6) | 68 (26.4) | 39 (14.9) |
| Total number of AE resistance training[a], n | | 115 | 52 | 40 |
| Total number of AE endurance training[a], n | | 23 | 20 | 3 |
| Missing, n (%) | | 51 (8.9) | 28 (9.7) | 23 (8.0) |
| Type of AE resistance training[a] | | | | |
| Musculoskeletal and connective tissue[b], n (%) | | 62 (53.9) | 36 (12.5) | 26 (9.0) |
| Accidents/injuries[c], n (%) | | 3 (2.6) | 2 (0.7) | 1 (0.3) |
| Cardiovascular symptoms/conditions[d], n (%) | | 20 (17.4) | 10 (3.5) | 10 (3.5) |
| Other[e], n (%) | | 7 (6.0) | 4 (1.4) | 3 (1.0) |
| Type of AE endurance training[a] | | | | |
| Musculoskeletal and connective tissue[b], n (%) | | 16 (69.6) | 15 (75.0) | 1 (33.3) |
| Accidents/injuries[c], n (%) | | 2 (8.7) | 2 (10.0) | 0 (0.0) |
| Cardiovascular symptoms/conditions[d], n (%) | | 1 (4.3) | 0 (0.0) | 1 (33.3) |
| Other[e], n (%) | | 4 (17.4) | 3 (15.0) | 1 (33.3) |
| Participant-reported injuries and discomfort (randomized intensity) | | | | |
| | | Total $N = 420$ | HI $N = 208$ | LMI $N = 212$ |
| Participants with one or more injury or discomfort, n (%) | | 119 (28.3) | 83 (39.9) | 36 (17.0) |
| Total number of injury or discomfort, resistance training[a], n | | 105 | 72 | 33 |
| Total number of injury or discomfort, endurance training[a], n | | 50 | 40 | 10 |
| Missing n (%) | | 157 (27.2) | 81 (28.0) | 76 (26.4) |
| Type of injuries or discomfort, resistance training[a] | | | | |
| Musculoskeletal and connective tissue[b], n (%) | | 89 (84.8) | 61 (84.7) | 28 (9.7) |
| Accidents/injuries[c], n (%) | | 4 (3.8) | 4 (5.5) | 0 (0.0) |
| Cardiovascular symptoms/conditions[d], n (%) | | 8 (7.6) | 5 (7.0) | 3 (1.0) |
| Other[e], n (%) | | 4 (3.8) | 2 (2.8) | 2 (0.7) |
| Type of injuries or discomfort, endurance training[a] | | | | |
| Musculoskeletal and connective tissue[b], n (%) | | 41 (82.0) | 32 (80.0) | 9 (90.0) |
| Accidents/injuries[c], n (%) | | 4 (8.0) | 4 (10.0) | 0 (0.0) |
| Cardiovascular symptoms/conditions[d], n (%) | | 2 (4.0) | 1 (2.5) | 1 (10.0) |
| Other[e], n (%) | | 3 (6.0) | 3 (7.5) | 0 (0.0) |
| Lymphedema, PICC-related complications (care as usual and randomized intensity) and new medical conditions (randomized intensity) | | | | |
| Incidence of lymphedema | Total | Care as usual | HI | LMI |
| | $N = 443$ | $N = 50$ | $N = 198$ | $N = 198$ |
| Participants with lymphedema[f] n (%) | 30 (6.8) | 2 (4.0) | 17 (8.6) | 11 (5.6) |
| Missing n (%) | 52 (10.5) | 13 (18.6) | 15 (7.0) | 18 (8.5) |
| Participants with PICC[g] | $N = 303$ | $N = 30$ | $N = 132$ | $N = 141$ |
| Participants with PICC comp. n (%) | 51 (16.5) | 7 (23.3) | 23 (17.4) | 21 (14.9) |
| Missing n (%) | 34 (11.2) | 5 (20.0) | 19 (14.4) | 10 (7.0) |
| Type of complication | | | | |
| Thrombosis, n (%) | 11 (19.6) | 2 (28.6) | 4 (15.4) | 6 (24.0) |
| Infection, n (%) | 13 (23.2) | 1 (14.3) | 6 (23.0) | 6 (24.0) |
| Dislocation, n (%) | 9 (16.0) | 0 (0.0) | 6 (23.0) | 3 (12.0) |
| Thrombophlebitis, n (%) | 4 (7.1) | 0 (0.0) | 2 (7.7) | 2 (8.0) |
| Other[h], n (%) | 19 (33.9) | 3 (42.8) | 8 (30.8) | 8 (32.0) |
| Missing, n (%) | 3 (0.9) | 1 (14.3) | 2 (1.5) | 0 (0.0) |
| Other new medical conditions | $N = 475$ | | $N = 233$ | $N = 242$ |
| Participants with new conditions, n (%) | 61 (11.6) | | 33 (12.6) | 26 (9.9) |
| Type of new condition[i] | | | | |
| Musculoskeletal and connective tissue[j], n (%) | 24 (4.6) | | 14 (5.5) | 10 (3.8) |
| Accidents/injuries[k], n (%) | 5 (0.1) | | 3 (1.1) | 2 (0.8) |
| Pulmonary symptoms/conditions[l], n (%) | 3 (0.5) | | 1 (0.4) | 2 (0.8) |
| Cardiovascular symptoms/conditions[m], n (%) | 9 (1.7) | | 4 (1.5) | 5 (1.9) |
| Other[n], n (%) | 23 (4.4) | | 12 (4.5) | 10 (3.8) |
| Missing total, n (%) | 102 (17.7) | | 55 (19.1) | 47 (16.3) |

HI: high-intensity; LMI: Low-moderate intensity; N = participants with available data. % of participants with available data; AE: adverse events.
[a]Participants could have more than one complaint.
[b]Including muscle strains, joint pain, muscular pain.
[c]Including falling/tripping resulting in fracture, bruising, swollen ankle.
[d]Including feelings of lightheadedness, dizziness, fainting, high pulse.
[e]Fatigue, nausea, hernia, eczema from using heartrate monitor.
[f]Collected from the medical record at 6-month follow-up, only for participants with breast cancer. PICC: peripherally inserted central catheter.
[g]Collected from medical record at 6-month follow-up, only for participants with breast cancer and colorectal cancer having a central venous access. % of participants with available data.
[h]Arm swelling, occlusion/no back flow, leakage, pain at the insertion site, was not able to remove PICC, too narrow blood vessel.
[i]Participants could have more than one complaint.
[j]Arthritis, swollen ankle, back pain, knee pain, impingement of shoulder, herniated disk.
[k]Tripping/falling resulting in fractures, spraining of ankle.
[l]Asthma, coughing.
[m]Nose bleed, atrial fibrillation, fainting, chest pain during interval training.
[n]Migraine, myomas, inguinal hernia, skin cancer, infections, psychiatric conditions and colon polyps, hyperlipidemia, endometriosis, and gastritis.

Table 5. Multiple logistic regression predicting likelihood of coach- and participant-reported exercise-related adverse events.

| Logistic regression predicting likelihood of coach-reported exercise-related AE | | | | |
|---|---|---|---|---|
| Coefficient | B | Odds ratio | 95%CI for odds ratio | *p* value |
| High intensity exercise[a] | 0.657 | 1.930 | 1.161–3.210 | .011 |
| Exercise adherence | −0.004 | 0.996 | 0.985–1.006 | .424 |
| Chemotherapy[b] | −0.170 | 0.844 | 0.517–1.271 | .504 |
| Baseline $VO_2$Max | 0.002 | 1.002 | 0.0967–1.038 | .934 |
| N | | 387 | | |
| **Logistic regression predicting likelihood of participant-reported exercise-related AE** | | | | |
| Coefficient | B | Odds ratio | 95%CI for odds ratio | *p* value |
| High intensity exercise[a] | 1.211 | 3.358 | 2.004–5.626 | <.001 |
| Exercise adherence | 0.004 | 1.005 | 1.005–0.993 | .445 |
| Chemotherapy[b] | −0.047 | 0.954 | 0.575–1.582 | .855 |
| Baseline $VO_2$Max | 0.021 | 1.021 | 0.985–1.059 | .252 |
| N | | 340 | | |

AE: adverse events; $VO_2$Max: maximal oxygen uptake, ml/kg/min; CI: confidence intervals.
[a]Low-moderate intensity vs high-intensity.
[b]No chemotherapy vs chemotherapy.

and AEs of musculoskeletal origin were most common for both RT and ET (Table 4).

Seventy-four (69%) of 107 participants with a coach-reported AE had an AE that prevented them from continuing the specific exercise but not the training session (grade 1). Thirty-one (29%) had an AE that prevented them from finishing the training session (grade 2).

The MLR analysis revealed that the odds of coach-reported AE in the HI group was almost two times the odds in the LMI group (OR: 1.9 [95%CI 1.16–3.21], $p$=.011). For participant-reported AEs the odds in the HI group were more than three times the odds in the LMI group (OR: 3.4 [95%CI 2.00–5.63], $p \leq .001$) (Table 5). There were no associations between AE and chemotherapy, exercise adherence or aerobic fitness in any of the models.

Of 211 participants with a PICC who answered the questionnaire, two reported dislocations (HI), one reported venous thrombosis (HI), and seven (HI $n = 2$, LMI $n = 5$) experienced discomfort in the PICC-inserted arm.

### *Serious adverse events (SAE)*

Three participants had grade 2 AEs that were considered a SAE. The three SAEs occurred in the HI group during RT ($n = 2$) and ET ($n = 1$). Of these, two women with breast cancer had an episode of syncope. Both were taken to hospital for observation and recovered swiftly. After the event, one participant continued the exercise intervention according to protocol. The other participant had just started the exercise intervention and was in the familiarization period, and decided to withdraw from the study. The third participant with a SAE was a man with prostate cancer who tripped over a rowing machine. The accident resulted in a fractured finger that had to be repositioned and sewn. The participant missed three RT sessions before he could continue exercising.

### *Medical record review – Lymphedema, PICC-related complications, and new medical conditions*

According to the oncological medical records, two (4%) participants in UC, 17 (9%) in HI, and 11 (6%) in LMI had developed lymphedema from the time of inclusion until the 6-month follow-up (Table 4). Of participants wearing a PICC (total $n = 303$), 7 (23%) in UC, 23 (17%) in HI, and 21 (15%) in LMI had a PICC-related complication. The most common PICC-related complication was 'other' (34%) (Table 4). There was no statistically significant difference between HI, LMI or UC regarding the incidence of lymphedema ($X^2$ (2, $N = 443$)=2.03 $p$=.36) or PICC-related complications ($X^2$ (2, $N = 269$)=2.20 $p$=.33).

Thirty-three (12%) in HI and 26 (10%) in LMI had a new other medical condition documented in the medical record (Table 4). This difference was not statistically significant ($X^2$ (1, $N = 475$)=1.27, $p$=.26). The most common category for new other med conditions that arose from the time of inclusion in the RCT until the 6-month follow-up was 'other', (e.g., inguinal hernia, infections; see (Table 2) for all other new conditions).

## Discussion

About one-fifth of persons who exercised during oncological treatment had an ex-AE. The most frequent type of ex-AE was minor musculoskeletal injuries and discomfort, commonly occurring also in healthy populations. Ex-SAEs, requiring hospital care, were very rare and there was no indication of an increased risk of lymphedema, PICC-related complication or occurrence of any other medical conditions, due to exercise during oncological treatment. HI exercise was associated with a higher risk of ex-AEs compared to LMI exercise, whereas neither chemotherapy, adherence to exercise nor baseline aerobic fitness were associated to ex-AEs, indicating that intensity may be a more important risk factor for experiencing minor ex-AEs.

The incidence of coach- and participant reported ex-AEs was higher in this study than previously reported in exercise trials for cancer patients [4,13]. The reason for this may be that we included all, even minor ex-AEs, and gathered the data in a systematic way [13] as well as having different definitions of ex-AEs. For instance, other studies including women with breast cancer exercising at HI having reported no ex-AEs when participants reported ex-AEs to the coaches [32], or minor ex-AEs, such as hypotension or dizziness after

maximal treadmill testing while monitored by coaches [39]. However, descriptions of what an AE entailed were lacking in both studies. A trial including men with prostate cancer playing football at local football clubs twice a week, defined safety outcomes as fractures and falls requiring medical assessment and SAEs accordingly to Good Clinical Practice. They reported 60 sport injuries, most of them minor muscle sprain or strains and 11 SAEs in the intervention group vs 22 in usual care. One participant had a fracture in the intervention group and two in usual care [40]

Furthermore, our results could be compared with epidemiological research, describing a similar incidence of exercise-related musculoskeletal injuries in both healthy physically active and inactive adults [16,41]. Minor ex-AEs occur among people both with and without cancer, highlighting the importance of reporting all ex-AEs in a structured way in future studies of persons undergoing oncological treatment.

We gathered data on ex-AEs from three different sources and results indicated that ex-SAEs were uncommon, which is in line with previous research [10,11,13]. Coaches reported only three events that was deemed ex-SAE. Thus, almost all of the ex-AEs were minor, transient, and did not prevent the participants from continuing the intervention. Our participants received supervised exercise, which may have contributed to few ex-SAEs due to the coaches' continuous monitoring and adaption of the exercise if needed

The results from this study indicate that exercise during chemotherapy does not increase the risk of ex-AEs. However, it is unknown how this translates to other patient groups (other diagnoses or more advance stages) or other types of chemotherapy regimens. The sample consisted mainly of persons with breast cancer, and very few participants with colorectal cancer, why future research should endeavor to include risk assessment for the latter. Furthermore, oncological treatments change, making it important that future oncology exercise research continuously assesses the safety and risks of exercise during new oncological treatments, in a standardized and structured way [10]. To enable comparison between studies, intervention characteristics should be described, including preventive strategies used, such as warm-up, progression, etc. [13].

The incidence rates of lymphedema in the present study were similar in the exercise groups and the UC group. However, lymphedema may develop later than six months post-surgery [18]. Therefore, a longer follow-up period is necessary to draw more certain conclusions. For instance, one pre-post study found that 27.5% of women with breast cancer participating in a heavy load exercise intervention ($>$ 80% of 1 RM) were diagnosed with lymphedema after a 14-month median follow-up period [42].

Less than one in ten participants had a PICC-related thromboembolism. This could be compared with an RCT conducted in Sweden where patients with breast cancer or colorectal cancer were randomized to receive a single lumen PICC or a subcutaneous infusion port. Of the participants randomized to PICC, eight percent had a PICC-related deep vein thrombosis [43]. The PICC-related complication rates were comparable or lower than what has been described previously [30,44–46]. While it seems that exercising with a PICC is safe, further research is needed to strengthen this conclusion.

Exercising at HI was not associated with a higher incidence of any other new medical conditions than exercising at LMI, and fewer cases of AE were found in the medical record than reported by coaches and participants. This may be because the information included in the medical record only is of clinical relevance and minor AE may not be recorded.

### *Methodological considerations*

A strength of this study was the systematic and structured collection of coach-reported ex-AEs. In addition, data were gathered from participants and medical records. Since data were gathered from three different sources, the probability of capturing both minor and more serious ex-AEs and different aspects of ex-AEs increased.

There was a lot of missing data, especially from the medical records for participants in UC. Furthermore, participant-reported ex-AEs were gathered retrospectively, and thereby susceptible to memory bias. Unlike coaches, participants were also asked about discomfort, therefore AEs reported may be different from coach reports. The UC group was not randomized and had a much smaller sample size than the groups in the RCT, and in addition, there were differences regarding type of treatment, why interpretations regarding the differences between the UC and randomized groups should be cautious. We also used exclusion criteria in order to reduce risk for participants, a common procedure in exercise studies [3]. Therefor fewer ex-AEs, especially ex-SAEs, are expected in such trials than in the clinical setting, which should be considered when prescribing exercise.

## Conclusions

Supervised exercise during curative oncological treatment is safe and ex-AEs are mostly minor and of musculoskeletal origin. Clinicians can safely recommend exercise during treatment for these patient groups in this setting, even HI exercise can be recommended if no medical contraindications are present. However, similar to healthy populations, there seems to be a higher risk of having minor ex-AEs when exercising at HI in comparison to LMI. This may be taken into consideration when informing, supporting and prescribing exercise for patients. Future research is warranted to strengthen these conclusions for other patient groups and settings.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

This work was supported by the Swedish Cancer Society, The Nordic Cancer Union, The Swedish Research Council, Stiftelsen Onkologiska Klinikens i Uppsala Forskningsfond, and World Cancer Research Fund.

## References

[1] Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep Wash DC. 1974;100:126–131.

[2] Mustian KM, Alfano CM, Heckler C, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol. 2017;3(7):961.

[3] Stout NL, Baima J, Swisher AK, et al. A systematic review of exercise systematic reviews in the cancer literature (2005–2017). PM R. 2017;9(9S2):S347–S384.

[4] Segal R, Zwaal C, Green E, et al. Exercise for people with cancer: a systematic review. Curr Oncol. 2017;24(4):e290–e315.

[5] Huy C, Schmidt ME, Vrieling A, et al. Physical activity in a German breast cancer patient cohort: one-year trends and characteristics associated with change in activity level. Eur J Cancer. 2012;48(3):297–304.

[6] Henriksson A, Arving C, Johansson B, et al. Perceived barriers to and facilitators of being physically active during adjuvant cancer treatment. Patient Educ Couns [Internet]. 2016 [cited 2016 Feb 10]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0738399116300404.

[7] Nadler M, Bainbridge D, Tomasone J, et al. Oncology care provider perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and facilitators. Support Care Cancer. 2017;25(7):2297–2304.

[8] Lavallée JF, Abdin S, Faulkner J, et al. Barriers and facilitators to participating in physical activity for adults with breast cancer receiving adjuvant treatment: a qualitative metasynthesis. Psychooncology [Internet]. 2019. [cited 2019 Jan 30]; Available from: http://doi.wiley.com/10.1002/pon.4980.

[9] Trotti A, Colevas A, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13(3):176–181.

[10] Maltser S, Cristian A, Silver JK, et al. A focused review of safety considerations in cancer rehabilitation. PM R. 2017;9(9S2):S415–S428.

[11] Cave J, Paschalis A, Huang CY, et al. A systematic review of the safety and efficacy of aerobic exercise during cytotoxic chemotherapy treatment. Support Care Cancer. 2018;26(10):3337–3351.

[12] Geidl W, Abu-Omar K, Weege M, et al. German recommendations for physical activity and physical activity promotion in adults with noncommunicable diseases. Int J Behav Nutr Phys Act. 2020;17(1):12.

[13] Niemeijer A, Lund H, Stafne SN, et al. Adverse events of exercise therapy in randomised controlled trials: a systematic review and meta-analysis. Br J Sports Med. 2020;54(18):1073–1080.

[14] Hootman JM, Macera CA, Ainsworth BE, et al. Association among physical activity level, cardiorespiratory fitness, and risk of musculoskeletal injury. Am J Epidemiol. 2001;154(3):251–258.

[15] Francis P, Whatman C, Sheerin K, et al. The proportion of lower limb running injuries by gender, anatomical location and specific pathology: a systematic review. J Sports Sci Med. 2019;18(1):21–31.

[16] Hootman JM, Macera CA, Ainsworth BE, et al. Epidemiology of musculoskeletal injuries among sedentary and physically active adults. Med Sci Sports Exerc. 2002;34(5):838–844.

[17] Brown JC, Schmitz KH. The dose-response effects of aerobic exercise on musculoskeletal injury: a *post hoc* analysis of a randomized trial. Res Sports Med. 2017;25(3):277–289.

[18] DiSipio T, Rye S, Newman B, et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500–515.

[19] Stuiver MM, ten Tusscher MR, Agasi-Idenburg CS, The Cochrane Collaboration, et al. Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy. Cochrane Database Syst Rev [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2015. [cited 2015 May 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD009765.pub2.

[20] Wanchai A, Armer JM. Effects of weight-lifting or resistance exercise on breast cancer-related lymphedema: a systematic review. Int J Nurs Sci. 2019;6(1):92–98.

[21] Nelson NL. Breast cancer-related lymphedema and resistance exercise: a systematic review. J Strength Cond Res. 2016;30(9):2656–2665.

[22] Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. The Lancet. 2013;382(9889):311–325.

[23] Chopra V, O'Horo JC, Rogers MAM, et al. The risk of bloodstream infection associated with peripherally inserted central catheters compared with central venous catheters in adults: a systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2013;34(9):908–918.

[24] Kang J, Chen W, Sun W, et al. Peripherally inserted central catheter-related complications in cancer patients: a prospective study of over 50,000 catheter days. J Vasc Access. 2017;18(2):153–157.

[25] Gao Y, Liu Y, Chen W, et al. Peripherally inserted central catheter thrombosis incidence and risk factors in cancer patients: a double-center prospective investigation. Ther Clin Risk Manag. 2015;11:153–160.

[26] Fallouh N, McGuirk HM, Flanders SA, et al. Peripherally inserted central catheter-associated deep vein thrombosis: a narrative review. Am J Med. 2015;128(7):722–738.

[27] Leung A, Heal C, Perera M, et al. A systematic review of patient-related risk factors for catheter-related thrombosis. J Thromb Thrombolysis. 2015;40(3):363–373.

[28] Liem TK, Yanit KE, Moseley SE, et al. Peripherally inserted central catheter usage patterns and associated symptomatic upper extremity venous thrombosis. J Vasc Surg. 2012;55(3):761–767.

[29] Jones LW. Evidence-based risk assessment and recommendations for physical activity clearance: cancer. Appl Physiol Nutr Metab. 2011;36(S1):S101–S112.

[30] Bertoglio S, Faccini B, Lalli L, et al. Peripherally inserted central catheters (PICCs) in cancer patients under chemotherapy: a prospective study on the incidence of complications and overall failures: PICC venous access for chemotherapy delivery. J Surg Oncol. 2016;113(6):708–714.

[31] Yi X, Chen J, Li J, et al. Risk factors associated with PICC-related upper extremity venous thrombosis in cancer patients. J Clin Nurs. 2014;23(5-6):837–843.

[32] Mijwel S, Backman M, Bolam KA, et al. Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial. Breast Cancer Res Treat. 2018;168(1):79–93.

[33] Berntsen S, Aaronson NK, Buffart L, et al. Design of a randomized controlled trial of physical training and cancer (Phys-Can) – the impact of exercise intensity on cancer related fatigue, quality of life and disease outcome. BMC Cancer. 2017;17(1):17. [Internet].

[34] Lestuzzi C, Vaccher E, Talamini R, et al. Effort myocardial ischemia during chemotherapy with 5-fluorouracil: an underestimated risk. Annals of Oncology. 2014;25(5):1059–1064. doi:10.1093/annonc/mdu055.

[35] Robertson R J, Goss F L, Dubé J, et al. Validation of the Adult OMNI Scale of Perceived Exertion for Cycle Ergometer Exercise. Med. Sci. Sports Exercise. 2004;36(1):102–108. doi:10.1249/01.MSS.0000106169.35222.8B.

[36] Borg G.Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2(2):92–98.
[37] Mazzoni A-S, Brooke HL, Berntsen S, et al. Exercise adherence and effect of self-regulatory behavior change techniques in patients undergoing curative cancer treatment: secondary analysis from the phys-can randomized controlled trial. Integr Cancer Ther. 2020;19:153473542094683.
[38] Nilsen TS, Scott JM, Michalski M, et al. Novel methods for reporting of exercise dose and adherence: an exploratory analysis. Med Sci Sports Exerc. 2018;50(6):1134–1141.
[39] Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007;25(28):4396–4404.
[40] Bjerre ED, Brasso K, Jørgensen AB, et al. Football compared with usual care in men with prostate cancer (FC Prostate Community Trial): a pragmatic multicentre randomized controlled trial. Sports Med. 2019;49(1):145–158.
[41] Kluitenberg B, van Middelkoop M, Diercks R, et al. What are the differences in injury proportions between different populations of runners? a systematic review and meta-analysis. Sports Med. 2015;45(8):1143–1161.
[42] Bloomquist K, Karlsmark T, Christensen KB, et al. Heavy resistance training and lymphedema: prevalence of breast cancer-related lymphedema in participants of an exercise intervention utilizing heavy load resistance training. Acta Oncol. 2014;53(2):216–225.
[43] Taxbro K, Hammarskjöld F, Thelin B, et al. Clinical impact of peripherally inserted central catheters vs implanted port catheters in patients with cancer: an open-label, randomised, two-centre trial. Br J Anaesth. 2019;122(6):734–741.
[44] Clemons M, Stober C, Kehoe A, et al. A randomized trial comparing vascular access strategies for patients receiving chemotherapy with trastuzumab for early-stage breast cancer. Support Care Cancer [Internet]. 2020 [cited 2020 Feb 5]; Available from: http://link.springer.com/10.1007/s00520-020-05326-y.
[45] Qiu X, Guo Y, Fan H, et al. Incidence, risk factors and clinical outcomes of peripherally inserted central catheter spontaneous dislodgment in oncology patients: a prospective cohort study. Int J Nurs Stud. 2014;51(7):955–963.
[46] Robinson A, Souied O, Bota AB, et al. Optimal vascular access strategies for patients receiving chemotherapy for early-stage breast cancer: a systematic review. Breast Cancer Res Treat. 2018;171(3):607–620.