# Global Cancer Update Programme (CUP Global)\* on diet and cancer: Protocol for the data collection and systematic literature reviews on the role of diet, body fatness and physical activity on health-related quality of life after diagnosis of breast cancer

# \*Formerly known as World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project

# Modifications to the review protocol

# 28 August 2021

The first systematic literature review focuses on physical activity and overall health-related quality of life (HRQoL) and its main functional domains (physical, emotional or mental health) in women with breast cancer.

Physical activity is defined as bodily movement produced by skeletal muscles that results in energy expenditure. This includes all types, intensities, and domains of physical activity. Exercise is physical activity that is planned, structured, repetitive, and designed to improve or maintain physical fitness, physical performance, or health (2018 Physical Activity Guidelines Advisory Committee Scientific Report https://health.gov/sites/default/files/2019-09/04\_C\_Background\_and\_Key\_Physical\_Activity\_Concepts.pdf).

HRQoL measures include global or overall HRQoL, general health perceptions, physical functioning or well-being, emotional functioning or well-being, mental health and the summary scores of these, assessed by but not limited to the following scales: Functional Assessment of Cancer Therapy-General (FACT-G) (Cella, 1993) or when used with the Breast (FACT-B) (Brady, 1997), Fatigue (FACT-F or Functional Assessment of Chronic Illness Therapy (FACIT)-F) (Yellen, 1997), or other FACT modules, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Aaronson, 1993) or when used with the Breast module (-BR23) (Sprangers, 1996), and the Medical Outcomes Study Short Form instruments (MOS SF-36 (Ware, 1992) or SF-12 (Ware, 1996), and RAND 36-Item Short Form Health Survey (Hays, 1993)) (Table 1). List of items and range of scores for these scales and sub-scales are shown in table 2. Reference values for minimal important differences and effect sizes are shown in table 3.

Other specific QoL domains, such as role functioning and social functioning, or breast cancer-related symptoms, such as fatigue and pain, assessed by these or other instruments are not reviewed in this first systematic literature review.

We are interested in the effect of assignment to intervention (the intention-to-treat effect). We will use the results from the intention-to-treat analysis or the per-protocol analysis if this was the only analysis conducted in the studies. In randomised controlled trials, any types of comparison group will be included. In trials with a usual care control group, participants received no physical activity intervention but care as per usual practice. In trials with a waitlist control group, participants received the same treatment as those in the physical activity intervention group but at a later time. In trials with an attention control group, equivalent or similar attention to those in the physical activity group, but without physical activity content, was provided.

The procedures for the systematic literature review are described in the study protocol. Meta-analysis will be conducted when there are at least three comparable studies. Studies are considered “comparable” when the HRQoL outcome measure was assessed by the same instrument. The following inclusion and exclusion criteria will be applied when conducting the meta-analyses.

Studies to include in the meta-analysis:

* Randomised controlled trials (RCTs) with more than 20 participants that evaluated the effects of physical activity interventions on HRQoL compared with a usual care, attention control, or wait-list control.
* Physical activity of any type or intensity, but not for therapeutic purposes (see below), will be analysed together. These included, for instance, aerobic or resistance exercises, strength training, yoga, stretching exercises, and Pilates.

Studies or results to exclude from the meta-analysis:

* RCTs comparing different doses (e.g. frequency, intensity) of the same or different exercise regimen without a control group
* Dietary or multimodal lifestyle interventions, unless the effects of physical activity can be evaluated, e.g. by comparing with the dietary or non-exercise lifestyle intervention group.
* Studies that investigated therapeutic exercises, such as gentle shoulder range of motion exercises.
* Studies that involved only metastatic breast cancer patients.

Inverse variance DerSimonian-Laird random effects meta-analyses will be conducted separately for each HRQoL instrument because of different constructs in their scales and sub-scales (table 2). We will calculate weighted mean difference and weighted mean change difference as summary effect estimates since the HRQoL values in the intervention and control groups may be different at study baseline. There may be small variations between the different versions of the same instruments, but this is often not clear in the studies; as a sensitivity analysis, we will estimate standardised weighted mean difference and standardised weighted mean change difference (Hedges’ g).

Final group means and changes from baseline scores with their measures of variability such as standard deviations (SDs) or confidence intervals (CIs) and number of participants per group will be used to estimate the between-group mean difference and mean change difference. Missing data will be imputed when possible following the standard approaches as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2021). When imputing the SDs, we will assume that they were the same in both intervention and control groups. We will not use an external estimate of SD or use a correlation coefficient to impute the missing SD for the mean changes, to avoid making further assumptions. When the studies reported between-group mean differences or mean change differences with measures of uncertainty such as standard errors (SEs), 95% CIs or exact P-values, these will be pooled directly with the other studies in the meta-analysis. We will not pool the reported effect sizes (i.e. the between-group mean difference or mean change difference, divided by the pooled SD at study baseline (Cohen, 1988) directly in the meta-analysis of standardised mean difference, as often their measures of uncertainty are not reported. Studies could not be included in the meta-analysis will be narratively synthesised.

For RCTs with multiple exercise or control groups, we will combine the exercise groups or the control groups but not the exercise with the active control group or other interventions including cognitive therapy, unless the effects of physical activity can be evaluated through the comparison, for the purpose of retaining as much information as possible from a study and including such a study as one unit in the meta-analysis. The mixed exercise groups will then be separated in the analysis by type of physical activity.

Subgroup and meta-regression analysis will be conducted when there are at least two comparable studies in more than one of the subgroups in the analysis. *A priori* defined subgroups include: intervention time frame (during or after primary adjuvant treatment), mode of intervention (group-based, individual-based, or mixed), type of control group (attention control or other non-intervention control such as usual care, wait-list controls) and type (aerobic, resistance, aerobic and resistance, yoga, or others), frequency (1-3 or >3 days/week), duration (<60 or ≥60 minutes/session) and total duration (<120, 120 to 180, or ≥180 minutes/week) (or as appropriate based on the data) of physical activity. Additional analysis restricting to the studies with outcomes assessed immediately post-intervention or at the follow-up closely after the end of the intervention (minimum follow-up) will be conducted to examine short-term intervention effects. *A posteriori* defined subgroups by any other characteristic that could support the results interpretation will also be analysed when the numbers allow it.

**Table 1 Domains assessed in the health-related quality of life (HRQoL) instruments\***

\*Domains reviewed in the present SLR are in bold font. Domains of a similar concept are aligned for presentation. It does not reflect the mapping of the construct.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Instrument/**  **domains** | **FACT-G** | **FACT-B**  **FACT-B+4** | **FACT-F/FACIT-F** | **EORTC QLQ-C30** | **EORTC QLQ-BR23** | **SF-36 (MOS/RAND)** |
| **Functional**  **scales** | **Physical well-being (PWB)** | **Physical well-being (PWB)** | **Physical well-being (PWB)** | **Physical functioning (PF)** | **Physical functioning (PF) when used with C30** | **Physical functioning (PF)** |
| Functional well-being (FWB) | Functional well-being (FWB) | Functional well-being (FWB) | Role functioning (RF) | Role functioning (RF) when used with C30 | Role limitations due to physical health (RP) |
| Social/family well-being (SWB) | Social/family well-being (SWB) | Social/family well-being (SWB) | Social functioning (SF) | Social functioning (SF) when used with C30 | Social functioning (SF) |
| **Emotional well-being (EWB)** | **Emotional well-being (EWB)** | **Emotional well-being (EWB)** | **Emotional functioning (EF)** | **Emotional functioning (EF) when used with C30** | Role limitations due to emotional problems (RE) |
|  |  |  | Cognitive functioning (CF) | Cognitive functioning (CF) when used with C30 | **Mental health (MH)** |
|  |  |  |  | Body image |  |
|  |  |  |  | -Sexual functioning  -Sexual enjoyment |  |
|  |  |  |  | Future perspective |  |
| Symptom scales/items |  |  | Additional concerns: fatigue subscale | Fatigue |  | Vitality (VT) |
|  |  |  | Nausea and vomiting |  |  |
|  |  |  | Pain |  | Bodily pain (BP) |
|  |  |  |  | Systemic therapy side-effects |  |
|  | Additional concerns: breast cancer subscale (BCS) |  |  | Breast symptoms |  |
|  | Arm symptoms (FACT-B+4) |  |  | Arm symptoms |  |
| Other outcome measures |  |  |  | Dyspnea |  |  |
|  |  |  | Sleep disturbance |  |  |
|  |  |  | Appetite loss |  |  |
|  |  |  | Constipation |  |  |
|  |  |  | Diarrhoea |  |  |
|  |  |  | Financial impact |  |  |
|  |  |  |  | Upset by hair loss |  |
|  |  |  |  |  |  |
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|  |  |  |  |  |  |
| **Component scores** |  |  |  |  |  | **Physical component scale (PCS)** |
|  |  |  |  |  | **Mental component scale (MCS)** |
| **Global/**  **total score** | **Total QoL** | **Total FACT-Breast** | **Total FACT-Fatigue** | **Global QoL** | **Global QoL when used with C30** | **General health perceptions (GH)** |

EORTC: European Organization for Research and Treatment of Cancer; FACT: Functional Assessment of Cancer Therapy; MOS: Medical Outcome Study; SF: short form

**Table 2** **List of items in the global, physical and emotional domains of the health-related quality of life (HRQoL) instruments**

|  |  |  |  |
| --- | --- | --- | --- |
| **Instrument/**  **domains** | **FACT-G**  **Version 4.0:**  **27 items, 4 domains**  **5-point Likert-rating scale**  **Total score range 0-108**  **Higher scores – better QoL** | **EORTC QLQ-C30**  **Version 3.0:**  **30 items, 9 domains, 6 single items**  **4 and 7-point Likert rating scale**  **Score range for each domain 0-100**  **Higher scores – better QoL** | **SF-36 (MOS/RAND)**  **36 items, 8 domains**  **3, 5 and 6-point Likert rating scale**  **Score range for each domain 0-100**  **Higher scores – better QoL** |
| **Physical function** | Physical well-being (PWB)  (7 items, score range 0-28)  Symptoms:  -Have nausea  -Have pain  -Bothered by side effects of treatment  Impact:  -Trouble meeting the needs of family  -Lack of energy  -Feel ill  -Spend time in bed | Physical functioning (PF)  (5 items, score range 0-100)  -Strenuous activities  -Short walk  -Long walk  -Stay in bed or chair during the day  -Help with eating, dressing, washing yourself or using toilet | Physical functioning (PF)  (10 items, score range 0-100)  -Vigorous activities  -Moderate activities  -Lifting or carrying groceries  -Climbing several flights of stairs  -Climbing one flight of stairs  -Bending, kneeling, or stooping  -Walking more than a mile  -Walking several blocks  -Walking one block  -Bathing or dressing |
| **Emotional function** | Emotional well-being (EWB)  (6 items, score range 0-24):  -Feel sad  -Coping with illness  -Losing hope in the fight against illness  -Feel nervous  -Worry about dying  -Worry that condition will get worse | Emotional functioning (EF)  (4 items, score range 0-100):  -Felt tense  -Worry  -Felt irritable  -Felt depressed | Mental Health/emotional well-being scale (5 items, score range 0-100)  -Been nervous  -Felt down in the dumps  -Felt calm and peaceful  -Felt downhearted and blue  -Been happy |
| **Component scores** |  |  | Physical component scale (PCS)  (4 scales, 21 items, score range 0-100):  -Physical functioning  -Physical role limitations  -Pain  -General health |
|  |  | Mental component scale (MCS)  (4 scales, 14 items, score range 0-100):  -Mental health  -Emotional role limitations  -Vitality  -Social functioning |
| **Global/total score** | Total FACT-G: sum of all items (physical, emotional, functional\*, and social and family† well-being) (27 items, score range 0-108)  Total FACT-B: sum of all items in FACT-G and B‡ (37 items, score range 0-148)  Total FACT-B+4: sum of all items in FACT-G and B+4§ (41 items, score range 0-148) | Global QoL  (2 items, score range 0-100):  -Self-rated overall health  -Self-rated overall QoL | General health  (5 items, score range 0-100):  -Self-perceived health in general  -Easily get sick than others  -Healthy as others  -Expect health to get worse  -Excellent health |

\*FACT-G: (FWB) Functional well-being (7 items, score range 0-28): able to work and is fulfilling; enjoy life and enjoy things for fun; accepted illness; sleep well; content with quality of life.

†FACT-G (SWB) Social and family well-being (7 items, score range 0-28): feel close to friends; get emotional support from family; get support from friends; family accepted illness; satisfied with family communication about illness; feel close to partner; satisfied with sex life.

‡FACT-B: Breast cancer subscale (10 items, score range 0-40): short of breath; self-conscious about the way I dress; have swollen or tender arm(s); feel sexually attractive; bothered by hair loss; worry that other family members might get breast cancer; worry about the effect of stress on illness; bothered by weight change; able to feel like a woman; experience pain in body.

§FACT-B+4: Breast cancer subscale + arm subscale (4 items): movement is painful; have poor movements; feels numb; have stiffness; is/are swollen or tender.

**Table 3** **Minimal importance differences and effect sizes for FACT, EORTC QLQ-C30, SF-36 HRQoL measures**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **HRQoL Domain**  **Instrument**  **(scores range)** | **Global HRQoL** | **Physical functioning** | **Physical component summary score** | **Emotional functioning** | **Mental component summary score** |
| **FACT-B**  **(0-148)** | MID: 7 to 8 points1  SMD2:  Trivial effect: 0 to 0.2  Small effect: >0.2 to 0.5  Medium effect: >0.5 to 0.8  Large effect: >0.8 | MDs for final scores/ change scores3:  Trivial effect: -0.09 points/0.5 points  Small effect: 1.9 points/ 0.8 points  Medium effect: 4.1 points/ 1.5 points  Large effect: 8.7points/ 8.2 points  SMDs for final scores/ change scores4:  Trivial effect: -0.10/0.01  Small effect: 0.42/ 0.26  Medium effect: 0.87/ 0.34  Large effect: 1.60/ 1.03 | N/A | MDs for final scores/ change scores3\*:  Trivial effect: -0.16 points/ Omit  Small effect: 1.0 points/ Omit  Medium effect: 1.9 points/ Omit Large effect: NA/ NA  SMDs for final scores/ change scores4\*:  Trivial effect: -0.02/ Omit  Small effect: 0.32/ Omit  Medium effect: 0.40/ Omit  Large effect: NA/ NA | N/A |
| **FACT-G**  **(0-108)** | MDs for final scores/ change scores3:  Trivial effect: -1 point/0.4 points  Small effect: 6 points/ 2.4 points  Medium effect: 11 points/ 3.3 points  Large effect: 22 points/ NA  SMDs4\*:  Trivial effect: -0.14/ Omit  Small effect: 0.46/ Omit  Medium effect: 0.88/ Omit  Large effect: 0.97/ NA |
| **EORTC QLQ- C30**  **(0-100)** | MDs5:  Trivial effect: 0 to 4 points  Small effect: 4 to 10 points  Medium effect: >10 to 15points  Large effect: >15 points  SMDs5:  Trivial effect: 0 to 0.2  Small effect: >0.2-0.4  Medium effect: >0.4-0.6  Large effect: >0.6 | MDs5:  Trivial effect: 0 to 5 points  Small effect: >5 to 14 points  Medium effect: >14 to 22 points  Large effect: >22 points  SMDs5:  Trivial effect: 0 to 0.2  Small effect: 0.2 to 0.6  Medium effect: >0.6 to 1.0  Large effect: >1 | “Significant changes”: 5-10 points6\*  SMD2:  Trivial effect: 0 to 0.2  Small effect: >0.2 to 0.5  Medium effect: >0.5 to 0.8  Large effect: >0.8 |
| **MOS/RAND SF-36**  **(0-100)** | General health perception sub-scale  MID: 3 points7  SMD2:  Trivial effect: 0 to 0.2  Small effect: >0.2 to 0.5  Medium effect: >0.5 to 0.8  Large effect: >0.8 | MID: 3 points8  SMD2:  Trivial effect: 0 to 0.2  Small effect: >0.2 to 0.5  Medium effect: >0.5 to 0.8  Large effect: >0.8 | MID: 4 points9  SMD2:  Trivial effect: 0 to 0.2  Small effect: >0.2 to 0.5  Medium effect: >0.5 to 0.8  Large effect: >0.8 | Mental health sub-scale  MID: 3 points7  SMD2:  Trivial effect: 0 to 0.2  Small effect: >0.2 to 0.5  Medium effect: >0.5 to 0.8  Large effect: >0.8 | MID: 4 points9  SMD2:  Trivial effect: 0 to 0.2  Small effect: >0.2 to 0.5  Medium effect: >0.5 to 0.8  Large effect: >0.8 |

MID: Minimal important difference; MD: mean difference; NA: not applicable; SMD: standardised mean difference

\*The reference values for FACT-G global HRQoL SMD in change scores and FACT-B/G emotional well-being MD and SMD in change scores have been omitted due to the medium estimate being lower than the estimate for small effects, the same for the effect sizes estimations for the EORTC QLQ-C30 emotional functioning (Cocks, 2010). For the EORTC QLQ-C30 emotional functioning sub-scales, between 5 and 10 points change are considered as “significant changes” because as reported such changes are noticeable by patients and are regarded by them as “significant changes” (EORTC Quality of Life Group, 2002).

1Yost, 2005; 2Cohen, 1988; 3King, 2010; 4King, 2010; 5Cocks, 2011; 6EORTC Quality of life group, 2002; 7Ware, 2007; 8Atkinson, 2017; 9Badhiwala, 2018.

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