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***Continuous update project 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***

**Prepared by Imperial College CUP team**

**Version 5**

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# BACKGROUND

More than 50.5 million adults worldwide are living within five years after cancer diagnosis, from which more than 7.7 million are women with breast cancer (Ferlay J et al., 2020). Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women worldwide. Breast cancer accounts for 25% of all cancer cases and 15% of all cancer deaths among women, with an estimated 2.3 million new breast cancer cases and 684,996 breast cancer deaths occurring in 2020 (Ferlay et al., 2020; available from: https://gco.iarc.fr/today, accessed 30/12/2020).

The incidence rates of breast cancer have increased in the past decades in high-income countries and are increasing in other countries (Bray et al., 2018). In contrast, breast cancer mortality rates have been stable or decreasing since around 1990, possibly due to better treatment and early detection in high income countries (Torre et al., 2015; Plevritis et al., 2018; Marmot et al., 2013). Overall, the U.S. relative survival rates of breast cancer are 91% at 5 years, 84% at 10 years and 80% at 15 years after diagnosis (ACS Breast Cancer Facts & Figures 2019-2020). Survival rates in the U.S. are higher for earlier stages at diagnosis (5-year relative survival: about 100% for ductal carcinoma in-situ (DCIS); 99% for localised, 86% for regional and 27% for metastatic breast cancers). Breast cancer survival differs between countries, in a large population registry-based survival study in 66 countries, 5-years net breast cancer survival was 85% or higher in 25 countries for women diagnosed during 2010–14. However, international differences remain very wide, with levels as low as 66% in India (Allemani et al., 2018).

There is evidence that physical activity, body weight control and adequate diet may improve survival after cancer diagnosis. A systematic literature review of randomised controlled trials and observational longitudinal studies on food, nutrition, physical activity, and the risk of death and second cancers in breast cancer survivors was published in 2014 as part of the WCRF-AICR Continuous Update Project (CUP), an ongoing programme aimed to analyse global research on how diet, nutrition and physical activity affect cancer risk and prognosis (<https://www.wcrf.org/int/continuous-update-project>). The scientific evidence reviewed suggested that having a [healthy body weight](https://www.wcrf.org/dietandcancer/exposures/body-fatness), being physically active, having a diet rich in fibre and low in fats, in particular trans and saturated fats, and eating foods containing soy may be related to longer survival after breast cancer diagnosis (https://www.wcrf.org/dietandcancer/breast-cancer-survivors; Chan et al., 2014). However, the CUP panel of experts concluded that the scientific evidence was inadequate to make specific recommendations for cancer survivors with confidence. The general recommendation for people living with cancer was to follow the general advice for cancer prevention if appropriate to their circumstances and unless otherwise advised by a health professional: be a healthy weight, physically active, eat more wholegrains, vegetables, fruits and legumes, avoid sugary drinks and limit consumption of “fast foods” and other processed foods high in fat, starches or sugars, limit consumption of red meats, avoid processed meats and alcohol and do not rely on supplements. The expert panel indicated that further research should be conducted on how diet, body fatness, and physical activity influence all-cause and cancer-specific mortality in cancer survivors, the response to and side effects from treatment, the quality of life during and after treatment, as well as the risk of metastasis, recurrence and second primary cancer (<https://www.wcrf.org/dietandcancer/cancer-survivors>).

Women with breast cancer experience physical and/or psychosocial changes as a result of the disease and treatments that may develop late and have long-term effects (Montazeri, 2008). Cancer survivors with impaired physical functioning have reported increased psychological distress and poorer health and quality of life compared with individuals without cancer and limitations (Joshy, 2020). Illness perceptions (the cognitive and emotional responses from the patients on their illness) have been shown to associate with health-related quality of life (HRQoL) and survival (de Rooij, 2018). Assessing HRQoL changes in cancer patients may give insight into patient events beyond tumour response and survival (O’Mara and Denicoff, 2010).

Lifestyle factors may influence HRQoL in breast cancer patients. Several randomised controlled trials have reported beneficial effects of physical activity during or after adjuvant therapy on HRQoL after breast cancer (Lipsett et al., 2017; Cramer et al., 2017, Lahart et al., 2018; Soares Falcetta et al., 2018) and other cancers (Speck et al. 2010; Mishra et al. 2012) with little evidence of adverse effects. The beneficial effects include improvement in symptoms such as fatigue (Cramer et al., 2017; Lipsett et al., 2017) and secondary lymphoedema (Baumann et al., 2018). In a systematic literature review of physical activity interventions after adjuvant therapy in breast cancer survivors, small‐to‐moderate beneficial effects on HRQoL were observed (Lahart et al., 2018).

No systematic literature review of HRQoL in cancer survivors has been conducted in the CUP.

This document is the protocol for conducting the CUP SLR of observational and interventional studies on the link between diet, nutrition, physical activity, body weight control and HRQoL in breast cancer survivors. The CUP SLR will provide information to the WCRF expert panel who will judge the strength of the evidence and if relevant, update the WCRF-AICR recommendations for cancer survivors.

## Definitions

**Cancer survivors**

In the CUP, a “cancer survivor” is anyone who has been diagnosed with breast cancer, from the time of diagnosis through the rest of their life (Centers for Disease Control and Prevention, 2011). Different phases or trajectories have been described that can be resumed in three general phases: living “with”, “through”, and “beyond” cancer. Living “with” cancer refers to the experience of receiving a cancer diagnosis and any treatment that may follow, living “through” cancer refers to the extended stage following treatment, and living “beyond” cancer refers to post-treatment and long-term survivorship. The phases may not be clearly delineated (Centers for Disease Control and Prevention, 2004).

**Health related quality of life**

Quality of Life (QoL) has been defined by the World Health Organization as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”. QoL is a multidimensional concept incorporating the individual’s perception of “the person’s physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment” (<https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/>).

Health-related quality of life (HRQoL) includes those aspects of QoL that can be clearly shown to be related to and affect health—either physical or mental (Centers for Disease Control and Prevention, United States (<https://www.cdc.gov/hrqol/concept.htm>).

In CUP, HRQoL will refer to any instrument, including its domains or subscales, that was designed to assess the patient’s self-reported health-related experience (‘‘patient-reported outcomes’’ or PRO).

**Theoretical framework of health**

Different dimensions with multiple interrelated elements affect health and QoL. The theoretical framework of health has been conceptualised in three dimensions: physical health, social health and mental health, with multiple indicators that reflect primarily one, two or three dimensions (Table 1) (van Leeuwen et al., 2018). A framework for breast cancer (Table 2) was proposed by Ferrell and further adapted by Chopra and Kamal (Chopra and Kamal, 2012).

Table 1.Three-dimensional theoretical framework of health (from van Leeuwen et al., 2018).

X indicates the dimensions reflected by each indicator.

|  |  |  |  |
| --- | --- | --- | --- |
| Health indicators | Dimension | | |
|  | Physical health | Mental health | Social health |
| Physical condition | x |  |  |
| Physical functioning | x |  |  |
| Mobility | x |  |  |
| Satisfaction with physical functioning | x |  |  |
| Prior health | x |  |  |
| Energy/fatigue | x | x |  |
| Sleep problems | x | x |  |
| Health perceptions | x | x |  |
| Physical symptoms | x | x |  |
| Health distress | x | x |  |
| Health outlook | x | x |  |
| Pain | x | x |  |
| Mental illness |  | x |  |
| Anxiety |  | x |  |
| Depression |  | x |  |
| Psychological distress |  | x |  |
| Psychological wellbeing |  | x |  |
| Positive affect |  | x |  |
| Cognitive functioning |  | x |  |
| Role limitations due to emotional problems |  | x | x |
| Feelings of belonging |  | x | x |
| Role limitations due to health | x | x | x |
| Sexual functioning | x | x | x |
| Social activities limitations due to health | x | x | x |
| Family functioning |  |  | x |
| Marital functioning |  |  | x |
| Role limitations due to physical problems | x |  | x |

The importance of the elements or domains that determine the HRQoL may vary depending on the phase of cancer survivorship. Physical and social functioning generally improve in the first year after acute treatment completion; side effects such as pain, insomnia, fatigue, fear of recurrence may affect cancer survivors during a longer post-treatment phase (van Leeuwen et al., 2018).

Table 2. Conceptual framework on quality of life in breast cancer survivors (adapted from Ferrell et al. by Chopra and Kamal, 2012). All domains are interconnected in the model.

|  |  |
| --- | --- |
| Domain | Element |
| Physical well being | Functional ability  Overall physical health  Fatigue/vitality  Fertility/bone loss  Swelling of arms (lymphedema)  Pain/aches  Weight gain  Sleep |
| Psychological well being | Interpersonal factors  Uncertainty  Anxiety/depression  Fear of recurrence  Cognition/attention  Pain distress  Distress from diagnosis/treatment  Emotional support |
| Spiritual well being | Meaning of illness  Religiosity  Transcendence  Hope  Inner strength |
| Social well being | Family  Roles and relationships  Affection/sexual function  Self-concept/appearance  Enjoyment/leisure  Isolation/abandonment  Social support  Financial concerns/ employment |

The framework of the International Classification of Functioning, Disability and Health developed by the WHO in 2001 (WHO-ICF) is a comprehensive and universally applicable health classification that serves as a platform to clarify and specify health-related concepts such as well-being, health state, health status, QoL and HRQoL. The WHO-ICF provides a system for organising the components of the biological aspects of health (body structure and function), health-related functioning (activity and participation), and the non-health-related environmental aspects. There are several studies linking the domains of QoL tools with the ICF framework. For example, Tucker et al, 2014 mapped the PROMIS tool and the ICF conceptual framework. The mapping is summarised in Table 3. No similar mapping for cancer survivors has been identified in the literature.

Table 3. Summary of mapping of PROMIS items and corresponding ICF concepts

(From Tucker et al, 2014)

|  |  |
| --- | --- |
| **PROMIS items** | **Related ICF concepts** |
| Physical health—functioning and symptoms | |
| Physical function | Mobility (D4) |
|  | Self-care (D5) |
| Physical function—mobility aids | Domestic life (D6) |
|  | Major life areas (D8) |
|  | Community, social, and civic life (D9) |
| Sexual function and satisfaction | Sexual functions (b640) |
| Sensations associated with genital and reproductive functions (b670) |
| Sleep disturbance | Sleep functions (b134) |
| Sleep-related impairment | Energy and drive functions (b130) |
| Fatigue | Energy and drive functions (b130) |
| Pain intensity | Sensation of pain (b280) |
| Pain behavior | Sensation of pain (b280) |
| Communicating–producing (d330–349) |
| Pain interference | Sensation of pain (b280) |
| Mental functions (b1) |
| Mobility (D4) |
| Self-care (D5) |
| Domestic life (D6) |
| Community, civic, and social life (D9) |
| Pain quality | Sensation of pain (b280) |
| Pain intensity | Sensation of pain (b280) |
| GI symptoms | Functions related to the digestive system (b510–b539) |
| Mental health—affect, behaviors, and cognition | |
| Emotional distress—anxiety | Emotional functions (b152) |
| Emotional distress—depression | Emotional functions (b152) |
| Emotional distress—anger | Emotional functions (b152) |
| Psychosocial illness impact (positive and negative) | Temperament and personality functions (b126) |
| Cognitive function | Global mental functions (b110–139) |
| Specific mental functions (b140–189) |
| Alcohol use—problem drinking | Energy and drive functions (b130) |
| Emotional functions (b152) |
| Alcohol use—consequences (positive and negative) | Energy and drive functions (b130) |
| Emotional functions (b152) |
| Alcohol use—expectancies (positive and negative) | Energy and drive functions (b130) |
| Emotional functions (b152) |
| Social health—relationships and function | |
| Ability to participate in roles and activities | Self-care (D5) |
| Domestic life (D6) |
| Interpersonal interactions and relationships (D7) |
| Major life areas (D8) |
| Satisfaction with roles and activities | Community, social and civic life (D9) |
| Companionship | Interpersonal interactions and relationships (D7) |
| Emotional support | Support and relationships (E3) |
| Attitudes (E4) |
| Instrumental support | Support and relationships (E3) |
| Informational support | Support and relationships (E3) |

# Aims of the CUP systematic literature review on diet, nutrition, physical activity and health-related quality of life after breast cancer

The main aim is to summarise, evaluate and interpret the scientific evidence on the role of diet, nutrition, body fatness and physical activity on health-related quality of life after breast cancer.

# Research Question

The research question is:

The associations between diet, body fatness and physical activity and health-related quality of life after breast cancer.

The PICOS statements are:

**P**opulation: Women who had a diagnosis of breast cancer, with any stage of the disease at cancer diagnosis.

**I**ntervention/exposures: Diet or nutrient intervention, physical activity intervention or a combination of both interventions. In observational studies, the exposures may be diet, foods, nutrients including supplements, biomarkers of dietary intake, physical activity, sedentary behaviour and measures of body fatness after diagnosis, including changes of any of the exposures.

**C**omparison population: In randomised controlled trials, there will not be restriction of the comparison treatment. In observational studies, exposed and non-exposed groups should be from the same study population.

**O**utcomes: Patient-reported health-related quality of life, overall and by specific domains.

**S**tudy design: Randomised controlled trials (RCT) with nutrition, diet or physical activity as intervention, ancillary analyses of therapeutic RCT and observational longitudinal studies in breast cancer survivors.

# Review Team

**IMPERIAL COLLEGE LONDON**

|  |  |
| --- | --- |
| **CUP team member** | **Role** |
| Doris Chan, PhD  Acting Senior Research Fellow, Nutritional epidemiologist | Co-Principal Investigator |
| Kostas Tsilidis, PhD  Senior Lecturer in Cancer Epidemiology | Co-Principal Investigator |
| Dagfinn Aune  Research Associate, Cancer Epidemiology | Data analyst |
| Georgios Markozannes  Research Associate, Cancer Epidemiology | Data analyst |
| Leila Abar  Research Assistant, Clinical Nutritionist | Reviewer |
| Katia Balducci  Research Assistant, Public Health Nutritionist | Reviewer |
| Margarita Cariolou, MSc  Research Assistant, Public Health Nutritionist | Reviewer |
| Neesha Nanu, MSc  Research Assistant, Epidemiologist | Reviewer |
| Rita Vieira, MSc  Research Assistant, Public Health Nutritionist | Reviewer |
| Lekan Anifowoshe, MSc | Database manager |

**EXTERNAL COLLABORATORS**

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**PROTOCOL EXPERT SUB GROUP (PEG)**

**WCRF Outcome After Cancer Diagnosis (OACD) Workstream Committee members**

## Timeline. Imperial College Team

|  |  |
| --- | --- |
| **Task** | **Date /Time required** |
| Preparation and submission of the protocol Version 1 | 1st April, 2019 |
| First meeting with Protocol Expert Subgroup (PEG) | First week April, 2019 |
| Revision of the protocol and submission of version 2 and version 3 | One month after receiving PEG comments (12th December2019)  Further revision (6th February 2020) |
| Preparation of data extraction forms | From April, 2019 |
| Search of relevant articles | November 2019 |
| Select articles | November-December 2019 |
| Data extraction | January-June 2020 |
| Revision of the protocol and submission of Version 4 | 20th August 2020 |
| Analytical summary | August-September 2020 |
| Preparation of SLR report Version 1 | September-October 2020 |
| Submission of SLR report Version 1 | October 2020 |
| Presentation of SLR report Version 1 to the Expert Panel | November 2020 |
| Preparation of SLR report Version 2 | December 2020-January 2021 |
| Submission of SLR report Version 2 | 1st February 2021 |

# Search Strategy

The search for primary studies will be conducted in PubMed and Cochrane Library. The full search strategy for PubMed is in Annex 1. Equivalent search strategy will be used to search in Cochrane Library.

The reviewers will hand search the references of the meta-analyses, reviews and pooled projects identified in the searches in PubMed, and the Cochrane Database. This process should allow identification of all relevant published research.

# Selection of Articles

## Inclusion Criteria

The studies relevant to the CUP and that will be included in the review have the following characteristics:

* Referenced in PubMed or Cochrane Library since database inception up to 31st August 2019 (end date of the search).
* The study design is:
* Randomised controlled trials with diet, nutrition, physical activity1 as intervention.
* Longitudinal observational studies (cohorts) of cancer survivors. The breast cancer patients in the longitudinal observational studies (cohorts) may have been identified from cancer registries, hospital registries, clinical settings, or can be incident breast cancer cases identified during the follow-up of cohorts of “healthy” individuals or in extended follow-up of randomised controlled trials, or may have participated in previous case-control studies of breast cancer risk factors.
* The study participants are women who have been diagnosed with breast cancer as first cancer during adulthood, at any stage at diagnosis.
* For randomised controlled trials, the intervention is dietary modification, or diet supplements, or exercise, or a combined intervention of diet, supplements or exercise of any duration with any comparison group, before treatment (prehabilitation), during or after treatment.
* For observational studies, the exposure is any dietary patterns, foods, nutrients including supplements, beverages, biomarkers of dietary intake, body fatness measures, physical activities, measures of sedentary behaviour, or changes of these factors. The exposure refers to a time period after diagnosis (post-diagnosis) and could have been assessed before, during treatment or after treatment.
* The instrument or tool assessing health-related quality of life is patient-reported and validated.
* The primary or secondary study outcome is overall health-related quality of life, any health-related quality of life domains relevant to breast cancer patients, or treatment-related side-effect such as fatigue.
* Health-related quality of life is assessed - but not limited to - by one or several ones of the following tools2 (Annex 2):
* Cancer Rehabilitation Evaluation System (CARES)
* European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30-item (EORTC QLQ-C30), Breast Cancer Module 23-item (EORTC QLQ-BR23)
* EuroQOL Five Dimension Scale (EQ-5D)
* Fatigue Symptom Inventory (FSI)
* Functional Assessment of Cancer Therapy-General (FACT-G), FACT-Breast (FACT-B)
* Functional Living Index: Cancer (FLIC)
* International Breast Cancer Study Group Quality of Life Core Form (IBCSG-QLC)
* Medical Outcomes Study 36-item Short Form Health Survey (MOS SF-36)
* Rotterdam Symptom Checklist (RSCL)
* Are original articles published in peer-reviewed journals.

1Physical activity is bodily movement produced by skeletal muscles that results in energy expenditure. This included all types, intensities, and domains of physical activities. Exercise is physical activity that is planned, structured, repetitive, and designed to improve or maintain physical fitness, physical performance, or health (https://health.gov/sites/default/files/2019-09/04\_C\_Background\_and\_Key\_Physical\_Activity\_Concepts.pdf).

2Based in the review by O’Mara and Denicoff, 2010

## Exclusion Criteria

The articles to be excluded from the CUP are:

* The number of total participants in the study is less than 203.
* Population-level studies, cross-sectional studies, or case-control studies.
* Studies in which the comparison group is not from the same study population.
* Studies in which the exposure or intervention is:
  + “Non-dietary” supplement use (e.g. shark cartilage)
  + Physical therapy aided by a physiotherapist or equivalent
  + Combined with a mindfulness-based cognitive therapy programme or meditation - with the exception of yoga, which may combine meditation with exercise, and will be included in the review.
* Studies in which the interventions/exposures combine diet or physical activity with an intervention/exposure that is not diet, nutrient, supplements, physical activity or body fatness (e.g. multimodal rehabilitation programme and the comparison group is not the non-dietary or physical activity group) with the exception of yoga (see above).
* Pilot studies exploring the feasibility or validity of QOL assessment.
* Outcomes that are not patient reported such as measures of VO2 peak, grip strength, strength testing, 6-minute walk test, arm circumferences (to assess lymphoedema), neuropsychological tests (Trail Making Test or d2 Test of Attention), clinician-reported outcomes.
* Articles published as comments, reviews, news, conference abstracts.
* Studies with mixed cancer sites where breast cancer is not evaluated separately.

3Excluded studies with less than 20 total participants, as smaller studies will be unlikely to affect inference.

## Endnote Files

The references of articles retrieved in the searches in the different databases will be merged in Endnote databases. The duplicates will be eliminated by the deduplication tool of Endnote and deduplication verified by the database manager.

**4.3.1 File names**

During the continuous process, the Endnote files will be named using the code of the cancer site and the publication date range of the retrieved references. For example, QoLBR01Jan2010\_31Dec2010 will be the name of the Endnote file containing the references on breast cancer included in PubMed or Cochrane Library during the period January 1st 2010 to December 31st 2010 (edate).

**4.3.2 Selection process**

The titles and abstracts will be visually screened by a reviewer and articles satisfying the inclusion criteria will be selected. The full text will be reviewed in case of doubts. The article selection will be double checked by a second reviewer. The articles with inclusion criteria and without exclusion criteria will be indicated as “included”. All other articles will be excluded from the CUP.

During the selection process the reviewer will indicate in four user-defined fields the inclusion/exclusion status for each article and if the article was selected upon reading the title and abstract or the entire article, the reasons for article exclusion, the study design of articles relevant to the review; the status of data extraction and the WCRF code assigned to the studies in the WCRF database.

The user-defined fields will be the following:

1. User-defined field 1 (inclusion): indicate inclusion/exclusion status.

* Code “included”, when the article is deemed relevant
* Code “excludedtiab”, when the article is not relevant to the CUP based on the title and abstract.
* Code “excluded”, when the article is deemed not relevant after reading the full text.

1. User-defined field 2 (exclusion reason): indicate reason for exclusion
2. User-defined field 3 (study design of included studies):

* Codes of study design:
* Randomised controlled trials
* Longitudinal observational studies of cancer survivors (see PICOS)
* Pooled analyses of observational studies of cancer survivors

1. User-defined field 4 (article labelling, indicate that the data is extracted in the WCRF database)

# Data Extraction

The data will be extracted into a MariaDB database using an in-house application (under development).

For feasibility reasons, the authors of the articles will not be contacted during the process of data extraction. Only the data provided in the article (text, tables and supplementary information) will be extracted.Extractions will be double checked by a second reviewer.

The data of each article with inclusion criteria should be extracted, even if there is more than one article of the same study on a particular topic.

## 5.1 Information to be extracted

The full bibliographic reference (author, title, journal details, year) and study design will be extracted first. The data indicated in 5.1.1 and 5.1.2 will be extracted as mean, ranges, percentages, categories, etc. as reported in the articles. A list of variables to extract is provided in Annex 3.

**5.1.1 For randomised controlled trials, the data to be extracted are:**

* Study characteristics: study type (parallel, factorial, crossover, other design), study name, number of study centres, calendar years, country.
* Participant characteristics: age, race/ethnic group, menopausal status at cancer diagnosis, body mass index (BMI); smoking status, comorbidities (e.g. hypertension, cardiovascular disease and diabetes mellitus), or other specific characteristics such as BRCA1/2 mutation carriers, women who were sedentary or exercise regularly, overweight or obesity, or had cancer-related lymphoedema or fatigue.
* Disease characteristics: ductal carcinoma in situ (DCIS), invasive breast cancer, local, regional or distant breast cancer, metastatic breast cancer, TNM classification, grade, or other stage described in the article, molecular characteristics (luminal A/B, human epidermal growth factor receptor-2 (HER2) enrich and basal-like; based on oestrogen receptor (ER), progesterone receptor (PR) and HER2/neu tumour status), year of cancer diagnosis, time since breast cancer diagnosis.
* Breast cancer treatment: surgery (breast-conserving surgery or mastectomy), radiation therapy, systemic treatment including cytotoxic chemotherapy and other agents, e.g. targeted agents (anti-HER 2 agents for HER2-positive breast cancer), hormone therapy (selective oestrogen receptor modulator/degrader, aromatase inhibitors), and modality (neoadjuvant, adjuvant and palliative).
* Interventions: description of intervention and comparison arms including modality, frequency, intensity, duration of intervention, number of participants allocated to each arm, randomisation method, blinding (for supplements: patients, researchers, and/or data analysts; other interventions: data analysts), allocation method and adherence to the interventions.
* HRQoL assessment: instrument/tool, validation including cultural validation if applicable
* Outcome: overall or domain-specific health-related quality of life description, assessment time, number and modality of assessment and for each outcome: whether primary or secondary outcome, outcome measure (mean scores, mean differences, standard errors, , proportions, confidence intervals, p-values), analysis (intention-to-treat or per protocol), number of patients randomised in each arm, drop out number/percentage of missing outcome data, whether the difference or change is of clinical significance as reported in the paper .
* Adverse effects from the intervention

**5.1.2 For observational studies, the data to be extracted are:**

* Study characteristics: study design (see inclusion criteria), study name, size and calendar years, country.
* Participant characteristics: age, race/ethnic group, menopausal status at diagnosis, body mass index (BMI); smoking status, comorbidities (e.g. hypertension, cardiovascular disease and diabetes mellitus), or other specific characteristics such as BRCA1/2 mutation carriers, women who were sedentary or exercise regularly, overweight or obesity, or had cancer-related lymphoedema or fatigue.
* Disease characteristics: ductal carcinoma in situ (DCIS), invasive breast cancer, local, regional or distant breast cancer, metastatic breast cancer, TNM classification, grade, or other stage described in the article, molecular characteristics (luminal A/B, human epidermal growth factor receptor-2 (HER2) enrich and basal-like; based on oestrogen receptor (ER), progesterone receptor (PR) and HER2/neu tumour status), mode of detection of the cancer (through mammography screening or not), year of cancer diagnosis, time since breast cancer diagnosis.
* Breast cancer treatment: surgery (breast-conserving surgery or mastectomy), radiation therapy, systemic treatment including cytotoxic chemotherapy and other agents, e.g. targeted agents (anti-HER 2 agents for HER2-positive breast cancer), hormone therapy (selective oestrogen receptor modulator/degrader, aromatase inhibitors), and modality (neoadjuvant, adjuvant and palliative).
* Exposure: exposure name and details, assessment method and whether it is at baseline or repeated, time between cancer diagnosis and exposure assessment, exposure levels.
* HRQoL assessment: instrument/tool and its assessment of validation including cultural validation if applicable.
* Outcome: overall or domain-specific health-related quality of life description, assessment time, number and modality of assessment and for each outcome: outcome measure (mean scores, mean score changes, mean differences, regression coefficients, standard deviations, standard error, confidence intervals, p values), assessment time (baseline, follow-up), losses to follow-up/percentage of missing outcome data, clinical significant difference.
* Adjustment factors: age, alcohol intake, smoking, body mass index, energy intake, disease characteristics at diagnosis (e.g. stage, grade), treatment (type and completion), comorbidity conditions, other factors adjusted for in the studies.

## Labels of exposures/interventions in the CUP database

Interventions/exposures will be labelled using the codes listed in the Guidelines for the Search Literature Reviews of the 2007 WCRF/AICR Expert Report. Biomarkers of exposure will be listed under the heading/subheading of the corresponding exposure.

The main headings for codification of the exposure groups are:

1) **Patterns of diet**, including regionally defined diets such as Mediterranean diet, socio-economically defined diets, culturally defined diets, individual level dietary patterns, other dietary patterns, and other issues.

2) **Foods**, including starchy foods; fruit and (non-starchy) vegetables; pulses (legumes); nuts and seeds; meat, poultry, fish and eggs; fats, oils and sugars; milk and dairy products; and herbs, spices, and condiments, and composite foods.

3) **Beverages**, including total fluid intake, water, milk, soft drinks, fruit juices, hot drinks and alcoholic drinks.

4) **Food production**, including traditional methods and chemical contaminants, food preservation, processing and preparation.

5) **Dietary constituents**, including carbohydrate, lipids, protein, alcohol (as ethanol), vitamins, minerals, phytochemicals, nutrient supplements and other bioactive compounds.

6) **Physical activity**, including total physical activity and domain-specific physical activity (e.g. total leisure time activity, vigorous physical activity, moderate physical activity, exercise, walking, cycling, gardening, yoga, tai chi, qi gong) and sedentary behaviours (e.g. sitting time or other similar).

7) **Energy balance**, including energy intake, energy density and energy expenditure.

8) **Anthropometry**, including markers of body composition, markers of body fat distribution, weight change, height and other skeletal measures at any moment of life.

The details of exposure/intervention codes are in Annex 4.

## Labelling of Outcomes

The outcomes will be recorded using the name of the instrument (see inclusion criteria) and the name of the subscale or domain. The tool names will be initially programmed in the data entry application (on development) by the database manager, using the list provided in 4.1 Inclusion criteria. Any new code needed during the review will be assigned by the review coordinator in liaison with the database manager.

## Quality Control

Article selection and data extraction will be double checked by a second reviewer. Any disagreement between reviewers will be solved with the review coordinator. When discrepancies are detected, the protocol may be revised and clarifications added.

# Systematic Literature Reviews

The process of data search and collection in the CUP is continuous during time. A systematic literature review and data synthesis is conducted by the Imperial College CUP team at least once during the next ten years. The SLR is presented to the Expert Panel for their judgement on causality and if pertinent, for the revision of the recommendations for cancer survivors.

## 6.1 Data Synthesis

The high level of heterogeneity in study designs, quality of life tools, domains of quality of life investigated, study participant characteristics and presentation of study results makes comparison between studies difficult.

A narrative synthesis will be conducted (Ryan R; Cochrane Consumers and Communication Review Group, 2013). This will be followed by a meta-analysis when possible (see 6.1.2 meta-analysis). Randomised controlled trials and observational studies will be analysed separately.

***Multiple articles of the same study***

The data should be extracted for each article, even if there is more than one article of the same study on a particular topic. The most adjusted set of data among the articles of the same study will be selected for the narrative synthesis and meta-analysis, and if the adjustment is the same, the set with higher number of patients with complete data will be used. The reviewers will ensure that data of the same study is not included as two different studies. Pilot studies of a subsequent full-scaled RCT will be excluded.

***Unit of analysis***

The unit of analysis will be the study. For studies with multiple outcome time points, the outcome measures from the final assessment will be included in the overall analysis. Interim time points and extended follow-up assessments will be excluded from the overall analysis. If a RCT included multiple intervention or control arms, these will be combined together in order to create a single intervention and control arm per study to be included in the overall meta-analysis when appropriate. If an observational study reported results only based on subgroups/stratified results, these will also be combined together. The combination of study arms or subgroups/strata will be performed using the formulas illustrated in Annex 5.

***Missing data***

Study results are expected to be presented in different formats and levels of completeness in the included studies, such as numbers of participants, means and standard deviations (SD) per group (“raw” values), and/or as effect measures: between-group mean difference (MD) and its measure of variance (standard errors (SE) or 95% confidence intervals (CI)) or P-value, or between-group effect size (MD/pooled SD). Several transformations and computations will be performed based on the reported data in order for the analyses to be as inclusive as possible. Data presented as, median scores or in another format instead of mean scores will be excluded from the analyses.

**6.1.1 Narrative synthesis**

The narrative synthesis will include:

* Textual description of study results, main potential sources of bias and any other key data needed for interpretation. A standard format will be developed to ensure consistency of presentation across reviewers.
* Tables: to facilitate the study comparison
* Forest plots: to aid the overall interpretation of results and vote counting based on direction and size of effect or association.
* Groupings and clusters: to identify and describe patterns across the studies in terms of the direction and size of effects or associations and to consider the factors that might explain any differences in results across the included studies.
* The clusters will be defined by clinical characteristics of the patients, study characteristics, and exposure/intervention and outcome characteristics:
  + Same HRQoL instrument, similar domains of different HRQoL instruments
  + Phase of survivorship (before, during, or after primary treatment, or post-diagnosis if unclear; 1-5 years or >5 years after primary treatment)
  + Calendar years of diagnosis or treatment (≤2000 or >20001)
  + Tumour stage at diagnosis (DCIS, stages, or metastatic)
  + Age groups (<65 or ≥65 years)
  + Study size (≤ or > median size of included studies in the review)
  + Outcome assessment time points (minimum follow-up either immediately after the intervention or from the follow-up closest to the completion of the intervention)
  + “A posteriori” by any other characteristic common to several studies that could support the results interpretation.
* Comparison with other reviews: to assess whether the conclusions of the CUP and other reviews differ depending on the difference of articles included or the methods used.

**6.1.2 Meta-analysis**

Meta-analysis will be conducted when there are at least three comparable studies. Studies will be considered “comparable” if the HRQoL outcome measure is assessed by the same instrument. RCTs using a parallel or crossover design, and cluster-randomised trials will be included in the meta-analysis. Specifically, regarding RCTs using a crossover design, unless they provide the necessary data to be included as such in the meta-analyses, only the parallel part will be kept.

*Summary effect measures*

The effect measures of interest are the mean score difference at the end of follow-up and the mean change score difference between the intervention (or exposed group) and the control (or unexposed). The unstandardised mean score difference and mean change score difference – traditionally known as weighted mean difference (WMD) – will be analysed separately. The effect measures will be meta-analytically summarised using inverse variance random effect models (DerSimonian and Laird, 1986).

*Subgroup and sensitivity analyses*

If the number of studies allows it, heterogeneity will be explored by I2 test (Higgins and Thompson, 2002). Subgroup analyses will be performed as illustrated above for narrative synthesis. Sensitivity analysis will be performed by omitting each included study, one by one, to explore their influence on the overall estimate (Tobias, 1999). Publication bias will be visually examined by funnel plot and using the Egger’s regression asymmetry test (Egger, 1997) when at least 10 studies are included in the meta-analysis. The meta-analytical results will be summarised in forest plots and tables. The analysis will be conducted in Stata version 13. A two-tailed P-value of <0.05, or P-value of <0.10 in the generally low-powered Egger’s test, is considered as statistical significant.

## 6.2 Interpretation of the results

In the synthesis, the reviewers will describe the results for each tool and its HRQoL domain, and conduct the risk of bias assessment. Since there is evidence that the study results may depend on the tool used, the reviewers will indicate if the use of the HRQoL tool in each study followed a rationale or was guided by a previous hypothesis. For instance, in a randomised controlled trial on the effect of an exercise program started early during breast cancer treatment, there were significant improvements for the intervention group using the SF-36 but not for the EORTC-QLQ-C30 questionnaire (Travier et al., 2015). Also, the selection of the HRQoL tool or domain reported may depend on the phase of cancer survivorship of study participants (Patient-reported Outcome Measurement Group, 2009).

The reviewers will describe the clinical significance of the results as indicated by the study authors, or for FACT-G (King, 2010) and EORTC QLQ-C30 (Cocks, 2010), use available established effect sizes. However, a meta-review including six systematic reviews and 70,403 patients found that only 30% of RCTs reported clinical significance (Smith et al., 2014).

# Assessment of risk of bias of the studies

The risk of bias of the individual studies will be assessed by two independent reviewers.

# 7.1 Risk of bias of randomised controlled trials

The risk of bias will be assessed using the Cochrane risk-of-bias tool for randomized trials, version 2 (RoB 2) (Sterne, 2019).

The dimensions of quality and susceptibility to bias in the tool are:

* Bias arising from the randomisation process: systematic differences between baseline characteristics of the groups that are compared
* Bias due to deviations from intended intervention: Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.
* Bias due to missing outcome data: Systematic differences between groups in withdrawals from a study.
* Bias in measurement of the outcome: Systematic differences between groups in how outcomes are determined (see HRQoL outcome measures under risk of bias in observational studies, below).
* Bias in selection of the reported result: Systematic differences between reported and unreported findings.

# 7.2 Risk of bias in observational studies

The reviewers will discuss the risk of bias of observational studies focusing on a few of the most likely influential sources of bias. The risk of bias will be discussed for each study using the factors outlined below. Guidance to reviewers is in Annex 5.

The criteria that will be considered in the risk of bias assessment are:

* Exposures: measurement error.
* Outcome: validity and adequacy of HRQoL
* Selection bias
* Control for confounding.
* Losses to follow-up

Representativeness of the exposed cohort and selection of the non-exposed cohort will not be included because non-representativeness will not affect interval validity and the study results will be synthesised according to phases of survivorship. Also, studies will be included in the review only if the non-exposed cohort is drawn from the same source as the exposed cohort.

The discussion of potential study biases will be used to inform the interpretation of the panel. The Criteria will not be “scored”

# Systematic literature reviews report

The process of data collection in the CUP is continuous. A systematic literature review report is prepared by the Imperial College CUP team when there is scientific evidence accumulated in the CUP database and by request of the CUP Expert Panel.

The SLR report will include:

1. Changes to the agreed protocol. A change log will be implemented during the CUP.
2. Flow chart of study identification and selection.
3. Table with number of articles by intervention/exposure.
4. Table with description of HRQoL tools used in the studies
5. Table of number of RCT and observational studies by HRQoL tool used by intervention/exposure grouped as diet or supplement, physical activity, body fatness, and combined interventions/exposures.

The narrative and analytical syntheses will be presented in four sections according to exposure/intervention groups: diet or supplements, body fatness, physical activity and combined interventions/exposures. Within each section, the syntheses will be presented for each outcome (overall HRQoL, and specific domains). Depending on the number of studies, specific components of HRQoL, e.g. fatigue, or specific intervention/exposures may be described separately in specific subsections.

Each section of the SLR report will include:

1. Tables of study description including study design and its implementation, study population, completeness of recruitment into the study from the population of interest, length of follow-up, losses to follow-up, exposure ascertainment method, HRQoL tool, ascertainment of potential confounding, study results for overall global HRQoL and for the different dimensions.
2. Table of risk of bias assessment for each study by exposure and outcome.
3. Table of summary of main study results

* by intervention/exposure of randomised controlled trials and observational studies
* for overall HRQOL and by domain
* by clusters of study and patients characteristics (see data synthesis)

The meta-analytical results will be included in each section, supplemented by the summary table of the results and tables of the main characteristics of studies (Annex 7).

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# Annexes

# Annex 1. Search Strategy For PubMed

**a. Searching for health-related quality of life**

(Search not tested, based in published systematic literature reviews)

“Quality of Life”[Mesh] OR “quality of life” OR "Patient Reported Outcome Measures"[Mesh] OR “patient-reported outcomes” OR “health-related quality of life” OR “Life Quality” OR “wellbeing” OR “well-being” OR “Mental Health”[Major] OR “Physical Fitness/psychology”[Major] OR “Physical Fitness/physiology”[Major] OR “Health Status”[Mesh] OR “health status” OR “late effects” OR “self-rated health” OR “self-reported health” OR fatigue OR anxiety OR depression OR lymphedema OR Edema[mesh] OR “edema” OR cognition[Mesh] OR “cognitive” OR Sleep[Mesh] OR sleep\* OR Pain[Mesh] OR “pain”

**b. Searching for studies on breast cancer**

(Search terms are those tested in the SLR for the WCRF Second Expert Report and the CUP)

#1 Breast Neoplasms [MeSH Terms]

#2 Breast AND (cancer\* OR neoplasm\* OR tumor\* OR tumor\* OR carcinoma\* OR adenocarcinoma\*)

#3 mammary AND (cancer\* OR neoplasm\* OR tumor\* OR tumor\* OR carcinoma\* OR adenocarcinoma\*)

#4 #1 OR #2 OR #3

**c.** **Search for all studies relating to diet, body fatness and physical activity**

#1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]

#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR

intake[tiab] OR nutrient\*[tiab] OR nutrition[tiab] OR vegetarian\*[tiab] OR vegan\*[tiab]

OR "seventh day adventist"[tiab] OR macrobiotic[tiab]

#3 “food and beverages” [MeSH Terms]

#4 food\*[tiab] OR cereal\*[tiab] OR grain\*[tiab] OR granary[tiab] OR

wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain\*[tiab] OR tuber[tiab]

OR tubers[tiab] OR vegetable\*[tiab] OR fruit\*[tiab] OR pulses[tiab] OR beans[tiab] OR

lentils[tiab] OR chickpeas[tiab] OR legume\*[tiab] OR soy[tiab] OR soya[tiab] OR

nut[tiab] OR nuts[tiab] OR peanut\*[tiab] OR groundnut\*[tiab] OR (seeds[tiab] AND (diet\*[tiab] OR food\*[tiab])) OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR (fish[tiab] AND (diet\*[tiab] OR food\*[tiab])) OR ((fat[tiab] OR fats[tiab] OR fatty[tiab]) AND (diet\*[tiab] OR food\*[tiab] OR adipose[tiab] OR blood[tiab] OR serum[tiab] OR plasma[tiab])) OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR (oils[tiab] AND (diet\*[tiab] OR food\*[tiab] OR adipose[tiab] OR blood[tiab] OR serum[tiab] OR plasma[tiab])) OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper\*[tiab] OR condiments[tiab] OR tomato\*[tiab]

#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR

liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage\*[tiab] OR

(ethanol[tiab] AND (drink\*[tiab] OR intake[tiab] OR consumption[tiab])) OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]

#7 pesticide\*[tiab] OR herbicide\*[tiab] OR DDT[tiab] OR fertiliser\*[tiab] OR

fertilizer\*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate\*[tiab] OR

veterinary drug\*[tiab] OR polychlorinated dibenzofuran\*[tiab] OR PCDF\*[tiab] OR

polychlorinated dibenzodioxin\*[tiab] OR PCDD\*[tiab] OR polychlorinated

biphenyl\*[tiab] OR PCB\*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated

hydrocarbon\*[tiab] OR microbial contamination\*[tiab]

#8 food preservation[MeSH Terms]

#9 (mycotoxin\*[tiab] OR aflatoxin\*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack\*[tiab] OR refrigerate\*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive\*[tiab] OR colouring\*[tiab] OR coloring\*[tiab] OR flavouring\*[tiab] OR flavoring\*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment\*[tiab] OR processed[tiab] OR antioxidant\*[tiab] OR genetic modif\*[tiab] OR genetically modif\*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]) AND (diet\*[tiab] OR food\*[tiab] OR adipose[tiab] OR blood[tiab] OR serum[tiab] OR plasma[tiab])

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR

fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol\*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR ((microwave[tiab] OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab]) AND (diet\*[tiab] OR food\*[tiab])) OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue\*[tiab] OR chargrill\*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab]

#12 ((carbohydrates[MeSH Terms] OR proteins[MeSH Terms]) AND (diet\*[tiab] OR food\*[tiab])) OR sweetening agents[MeSH Terms]

#13 (salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide\*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate\*[tiab] OR lipid\*[tiab] OR linoleic acid\*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar\*[tiab] OR sweetener\*[tiab] OR saccharin\*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]) AND (diet\*[tiab] OR food\*[tiab] OR adipose[tiab] OR blood[tiab] OR serum[tiab] OR plasma[tiab])

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin\*[tiab] OR retinol[tiab] OR

carotenoid\*[tiab] OR tocopherol[tiab] OR folate\*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral\*[tiab] OR (sodium[tiab] AND (diet\*[tiab] OR food\*[tiab])) OR iron[tiab] OR ((calcium[tiab] AND (diet\*[tiab] OR food\*[tiab] OR supplement\*[tiab])) OR selenium[tiab] OR (iodine[tiab] AND (diet\*[tiab] OR food\*[tiab] OR supplement\*[tiab] OR deficiency)) OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate\*[tiab] OR glucosinolate\*[tiab] OR indoles[tiab] OR polyphenol\*[tiab] OR phytestrogen\*[tiab] OR genistein[tiab] OR saponin\*[tiab] OR coumarin\*[tiab] OR lycopene[tiab]

#16 physical fitness[MeSH Terms] OR physical exertion[MeSH Terms] OR physical endurance[MeSH Terms] OR walking[MeSH Terms] OR exercise[MeSH Terms] OR muscle stretching exercises[MeSH Terms] OR tai ji[MeSH Terms] OR yoga[MeSH Terms] OR sedentary lifestyle[MeSH Terms]

#17 recreational activit\*[tiab] OR household activit\*[tiab] OR occupational activit\*[tiab] OR physical activit\*[tiab] OR physical inactivit\*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab] OR sedentar\*[tiab] OR standing[tiab] OR sitting[tiab] OR television[tiab] OR aerobic activities[tiab] OR aerobic activity[tiab] OR cardiovascular activities[tiab] OR cardiovascular activity[tiab] OR endurance activities[tiab] OR endurance activity[tiab] OR resistance training[tiab] OR strength training[tiab] OR physical conditioning[tiab] OR functional training[tiab] OR leisure-time physical activity[tiab] OR lifestyle activities[tiab] OR lifestyle activity[tiab] OR qi gong[tiab] OR tai chi[tiab] OR tai ji[tiab] OR yoga[tiab] OR free living activities[tiab] OR free living activity[tiab] OR walk[tiab] OR walking[tiab]

#18 body weight[MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms] OR body size[MeSH Terms] OR body size[tiab]

#19 weight loss[tiab] OR weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass index[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement\*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio\*[tiab]

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR

#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

1. **Limiting to human studies:**

#21 animal[MeSH Terms] NOT human[MeSH Terms]

#22 #20 NOT #21

1. **Combining the searches for each cancer**

(a) AND (b) AND (c) AND (d)

# Annex 2. Description of some HRQoL assessment tools identified in SLRs

Note: A full list and clustering of domains by similarities will be conducted after the article selection is completed and before data analysis

|  |  |
| --- | --- |
| **Name of HRQOL Assessment Tool** | **Description of Tool**  (fromhttp://qol.thoracic.org/sections/instruments/ae/index.html) |
| **Bone Metastasis Quality of Life (BOMET-QoL-10)** (Sureda, 2007, https://doi.org/10.3111/200710027039) | Measures QoL in metastatic breast cancer patients with bone metastasis. (Barnadas, 2019, PMID 31865481) |
| **Cancer Rehabilitation Evaluation System (CARES) (**Schag et al., 1990**)**  <https://cancer.ucla.edu/patient-care/survivorship/for-healthcare-providers/cancer-rehabilitation-evaluation-system-cares> | The CARES is a cancer-specific health-related quality of life self-administered questionnaire developed by Schag and Heinrich. It has four forms: a long form in a clinical or research version (139-items) and a short form in a clinical or research version (59-item).  It can be scored to provide a global score or scores for five summary scales (medical interaction, physical, psychosocial, marital and sexual wellbeing) or 31 subscales. Patients rate a minimum of 93 items and a maximum of 132 items. |
| **European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30-item (EORTC QLQ-C30)** (Aaronson et al., 1993)  https://qol.eortc.org/ | The EORTC QLQ-C30 is a self-administered questionnaire developed to assess the quality of life of cancer patients.  It incorporates five functional scales (physical, role, cognitive, emotional, social), three symptom scales (fatigue, pain, nausea/vomiting), a global health status/quality of life scale, single items on symptoms (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea), and perceived financial impact of the disease. Score ranges from 0 to 100. |
| **European Organisation for Research and Treatment of Cancer Quality of Life Breast Cancer Module 23-item (EORTC QLQ-BR23)**  https://qol.eortc.org/ | The EORTC QLQ-BR23 is a supplementary breast cancer-specific module of the EORTC QLQ.  It contains five functional scales (measuring physical, role, emotional, social and cognitive functioning), three symptom scales (measuring pain, fatigue and nausea and vomiting), a global health status/ quality of life scale, and 6 single items measuring dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial impact.  The QLQ-C30 has undergone a number of revisions since its inception as the QLQ-C36 in 1986 |
| **EuroQOL Five Dimension Scale (EQ-5D)** (EuroQol Group, 1990)  https://euroqol.org/ | The EQ-5D is a generic instrument that measures the health-related quality of life of general patients.  It has five subscales (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 3 or 5 levels of severity and a visual analogue scale (EQ VAS) that reflects the patient’s own judgement. The scores on the five domains can be converted to a summary index number. |
| **Functional Assessment of Cancer Therapy-General** (FACT-G) (Cella et al., 1993)  <http://www.facit.org/FACITOrg> | The FACT-G (version 4) is a 27-item self-administered questionnaire developed by Cella to measure the quality of life of general patients.  The tool has four subscales (physical well-being, social/family well-being, emotional well-being, functional well-being) for patients to report on their feelings in the past seven days.  The tool can provide four domain scores or an overall score that ranges from 0 to 108 points, with higher score indicting a better quality of life. |
| **Functional Assessment of Cancer Therapy-Breast** (FACT-B)  <http://www.facit.org/FACITOrg> | The FACT-B (37-item, version 4) is intended for patients with breast cancer.  The tool consists of five subscales: four on well-beings as in FACT-G and a breast cancer-specific subscale (“I have been short of breath”, “I am self-conscious about the way I dress”, “One or both of my arms are swollen or tender”, “I feel sexually attractive”, “I am bothered by hair loss”, “I worry that other members of my family might someday get the same illness I have”, “I worry about the effect of stress on my illness”, “I am bothered by a change in weight”, “I am able to feel like a women”, “I have certain parts of my body where I experience pain”.  The experience of patients affected by specific postoperative problems can be captured using the arm morbidity subscale (FACT-B+4). |
| **Functional Assessment of Cancer Therapy—Cognition (FACT-Cog)** (van Dyk, 2019, PMID32064458) | FACT-Cog measures perceived cognitive impairments (PCI; 18-item); perceived cognitive abilities (7-item); impact of perceived cognitive impairment on QoL (4- item); and comments from others on cognitive function (4-item). |
| **Functional Living Index: Cancer (FLIC)** (Schipper et al., 1984) | The FLIC has 22 specific questions that assess the overall functional quality of a cancer patient undergoing treatment, including pain, stress, and the ability to work and do household chores.  Score ranges from 0 to 154, with higher score indicating better quality of life. |
| **International Breast Cancer Study Group Quality of Life Core Form (IBCSG-QLC)** (Bernhard et al., 1997) | The IBCSG-QLC is developed for assessing the impact of adjuvant therapy on quality of life in breast cancer patients.  The tool consists of self-administered items that give global indicators of well-being, functioning and health perception, and specific indicators of symptoms of disease and treatment. |
| **Medical Outcomes Study 36-item Short Form Health Survey (MOS SF-36)** (Ware et al., 1992)  http://www.outcomes-trust.org/ | The SF-36 is a self-administered 36-item tool that measures health status as well as quality of life.  The generic tool has eight subscales (physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality [energy level and fatigue], general health perceptions). The tool provides eight scores for the domains or overall physical and mental health component summary scores.  There are other versions with different number of items, e.g. SF-8 |
| **Rotterdam Symptom Checklist (RSCL)** (de Haes et al., 2012; de Haes et al., 1990) | The RSCL measures psychological and physical distress in cancer patients.  Cancer patients report on how their feel in the past week, regarding:  23-item on physical symptoms (lack of appetite, tiredness, sore muscles, lack of energy, low back pain, nausea, difficulty sleeping, headaches, vomiting, dizziness, decreased sexual interest, abdominal aches, constipation, diarrhoea, acid indigestion, shivering, tingling hands or feet, difficulty concentrating, sore mouth/pain when swallowing, loss of hair, burning/sore eyes, shortness of breath, dry mouth)  7-item on psychological symptoms (irritability, worrying, depressed mood, nervousness, despairing about the future, tension, anxiety)  8-item on activity level (care for myself, walk about the house, light housework/household jobs, climb stairs, heavy housework/household jobs, walk out of doors, go shopping, go to work)  And a measure of global/overall quality of life |

# 

# Annex 3. List of variables for data entry for the CUP on Cancer Survivors (in preparation for breast, colorectal, prostate cancers)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable/element name** | **Input method** | **Type of data** | **Format of data** | **Purpose** |
| Cancer site | Select pulldown: Breast  Colon, rectum, colorectal Prostate | General | Text | Identification |
| WCRF code | uniquely generated | General | Code | Identification |
| PMID | Manual/copy and paste | Reference details | Number | Identification |
| Author | Automatically retrieved from PubMed | Reference details | Text | Identification |
| Year | Automatically retrieved from PubMed | Reference details | Number | Identification |
| Title | Automatically retrieved from PubMed | Reference details | Text | Identification |
| Journal | Automatically retrieved from PubMed | Reference details | Text | Identification |
| Volume | Automatically retrieved from PubMed | Reference details | Number | Identification |
| Page start | Automatically retrieved from PubMed | Reference details | Number | Identification |
| Page end | Automatically retrieved from PubMed | Reference details | Number | Identification |
| Study type | Select pulldown:  Diet and/or physical activity RCT Cohort of newly diagnosed cancer survivors  Follow-up, "healthy" cohort Follow-up, case-control Follow-up, case-case  Follow-up, diet and/or physical activity RCT Follow-up, other RCTs Pooled analysis of cohort studies | Study characteristics | Code | Tabulation, analysis |
| Study name | Manual or pulldown | Study characteristics | Text | Tabulation, analysis |
| Calendar years | Manual: range | Study characteristics | Text | Tabulation |
| Year of cancer diagnosis | Manual: range | Participant characteristics | Text | Tabulation |
| Region | Manual or pulldown | Study characteristics | Text | Record |
| Country | Manual or pulldown | Study characteristics | Code | Tabulation, analysis |
| Sex | Select pulldown: Men Women Men and women | Participant characteristics | Code | Tabulation, analysis |
| Age start | Manual | Participant characteristics | Number | Tabulation, analysis |
| Age end | Manual | Participant characteristics | Number | Tabulation, analysis |
| Mean age | Manual | Participant characteristics | Number | Tabulation, analysis |
| Ethnicity/race | Manual or pulldown: White African American East Asian  Multi-ethnic Others Not specified | Participant characteristics | Code | Tabulation, analysis |
| Other participant characteristics | Manual or pulldown: Premenopausal Postmenopausal  BRCA1/2 mutation carriers Smokers and ex-smokers Elderly Obese and overweight  Diabetic  Participants of mammography  screening study | Participant characteristics | Code and text | Tabulation, analysis |
| Body mass index | Manual/copy and paste: average | Participant characteristics | Text | Tabulation, analysis |
| Physical activity | Manual/copy and paste: average | Participant characteristics | Text | Tabulation, analysis |
| Smoking status | Manual/copy and paste: percentages | Participant characteristics | Text | Tabulation, analysis |
| Menopausal status | Manual/copy and paste: percentages | Participant characteristics | Text | Tabulation, analysis |
| Disease characteristics | Manual/copy and paste: Cancer site,Percentage by stage or subtypes | Participant characteristics | Text | Tabulation |
| Treatment information | Manual/copy and paste: Percentage by treatment modalities, timing, completion | Participant characteristics | Text | Tabulation |
| Comorbidities | Manual/copy and paste: Percentage of: Hypertension Cardiovascular disease Diabetes mellitus | Participant characteristics | Text | Tabulation |
| Adverse effects from cancer and treatment | Manual: percentages | Participant characteristics | Text | Tabulation |
| Inclusion criteria | Manual/copy and paste | Study characteristics | Text | Tabulation, record |
| Exclusion criteria | Manual/copy and paste | Study characteristics | Text | Tabulation, record |
| **For Randomised controlled trials** | | | | |
| RCT design | Manual or pulldown: Parallel Crossover Factorial | RCT characteristics | Code | Tabulation, analysis |
| Number of study centres | Manual | RCT characteristics | Number | Tabulation |
| Number of arms | Manual | RCT characteristics | Number | Tabulation |
| Blinding | Manual or pulldown: Not blinded/open Researchers  Participants  Outcome assessors  Data analysts  Unknown | RCT characteristics | Code | Tabulation, risk of bias assessment |
| Sampling recruitment procedure | Manual/copy and paste:  Randomisation method  Others… | RCT characteristics | Text | Record |
| Allocation | Manual or pulldown: Concealed Not concealed Unclear | RCT characteristics | Text | Risk of bias assessment |
| Allocation details | Manual/copy and paste | RCT characteristics | Text | Risk of bias assessment |
| Time since intervention to cancer diagnosis | Manual | RCT characteristics | Text | Tabulation, analysis |
| Time since cancer diagnosis to intervention | Manual | RCT characteristics | Text | Tabulation, analysis |
| Sample size | Manual | RCT characteristics | Number | Tabulation |
| **For Randomised controlled trials, results** | | | | |
| Type of intervention | Manual or pulldown: WCRF Code | Intervention | Text | Tabulation, analysis |
| Intervention description | Manual/copy and paste | Intervention | Text | Tabulation |
| Method of intervention | Manual/copy and paste | Intervention | Text | Record |
| Duration of intervention | Manual | Intervention | Text | Tabulation |
| Type of comparison | Manual or pulldown: Placebo Usual medical care Others… | Comparison | Text | Tabulation |
| Comparison description | Manual/copy and paste | Comparison | Text | Tabulation, analysis |
| Compliance | Manual/copy and paste | Intervention/comparison | Text | Tabulation |
| Duration of follow-up after end of intervention | Manual | RCT characteristics | Text | Tabulation, analysis |
| Study endpoint  (QOL tool) | Manual or pulldown: (indicate Quality of life tool or domain) | Endpoint, RCT | Code | Tabulation, analysis |
| Study endpoint description  (tool description including if validated) | Manual/copy and paste | Endpoint, RCT  (for each endpoint) | Text | Tabulation, analysis |
| Endpoint | Select pulldown: Primary Secondary | Endpoint, RCT  (for each endpoint) | Code | Tabulation, analysis |
| Outcome assessment | Manual (interview, at home, etc) | Endpoint, RCT  (for each endpoint) | Code/text | Tabulation, analysis |
| Losses to follow-up\_RCT | Manual | RCT characteristics  (for each endpoint) | Text | Tabulation, risk of bias assessment |
| Intention-to-treat analysis | Select pulldown: Intention-to-treat Per protocol | RCT characteristics  (for each endpoint) | Code | Tabulation |
| Adverse effects | Select pulldown: Yes, describe No Not reported | RCT characteristics  (for each endpoint) | Code | Record |
| Adverse effects description | Manual:  Percentages by effect | RCT characteristics  (for each endpoint) | Text | Record |
| Type of analysis\_RCT | Select pulldown: Mean difference Other | Result, RCT | Code | To indicate what result type should appear in screen, analysis |
| Total number in intervention group | Manual | Result, RCT | Number | Tabulation, analysis |
| Total number in control group | Manual | Result, RCT | Number | Tabulation, analysis |
| Mean difference, SD (intervention vs comparison) | Manual | Result, RCT | Number | Tabulation, analysis |
| Mean, SD at baseline treated | Manual | Result, RCT | Number | Tabulation, analysis |
| Mean, SD at follow-up 1, 2 etc | Manual | Result, RCT | Number | Tabulation, analysis |
| Mean, SD at baseline control | Manual | Result, RCT | Number | Tabulation, analysis |
| Mean, SD at follow-up 1, 2 etc | Manual | Result, RCT | Number | Tabulation, analysis |
| Mean difference of groups | Manual | Result, RCT | Number | Tabulation, analysis |
| P value of group difference | Manual | Result, RCT | Number | Tabulation, analysis |
| Other type of results description | Manual | Result, RCT | Text | Tabulation |
| Other type of results P-value | Manual | Result, RCT | Number | Tabulation |
| Other results not extracted | Manual | Information | Text | Record |
| Subgroup description (participants or endpoint) | Manual or pulldown | Subgroup result, RCT | Code | Tabulation, analysis |
| **FOR FOLLOW-UP STUDIES** | | | | |
| Size of cohort | Manual | Cohort characteristics | Number | Tabulation, analysis |
| Number of men | Manual | Cohort characteristics | Number | Tabulation, analysis |
| Number of women | Manual | Cohort characteristics | Number | Tabulation, analysis |
| Diet assessment method | Manual/copy and paste: FFQ,  Repeated FFQ 24h recall,  Diet history Others... | Exposure | Text | Tabulation, analysis, risk of bias assessment |
| Diet assessment method details | Number of items in FFQ, number of 24-h recalls | Exposure | Text | Tabulation |
| Diet assessment method validated | Select pulldown: Yes No Not reported | Exposure | Code | Risk of bias assessment |
| Anthropometry assessment method | Manual/copy and paste: Measured Self-reported Medical records DEXA, etc Others… | Exposure | Text | Tabulation, analysis, risk of bias assessment |
| Anthropometry assessment method details | Any additional info | Exposure | Text | Tabulation |
| Anthropometry assessment method validated | Select pulldown: Yes No Not reported | Exposure | Code | Risk of bias assessment |
| Physical activity/inactivity assessment method | Manual/copy and paste: Self-reported Medical records Device Others… | Exposure | Text | Tabulation, analysis, risk of bias assessment |
| Physical activity assessment method details | Any additional info | Exposure | Text | Tabulation |
| Physical activity assessment method validated | Select pulldown: Yes No Not reported | Exposure | Code | Risk of bias assessment |
| Length of follow-up | Manual | Cohort characteristics | Number | Tabulation, analysis |
| Time since cancer diagnosis to exposure assessment | Manual | Cohort characteristics, post-diagnosis exposure | Text | Tabulation, analysis |
| Follow-up time after exposure assessment | Manual | Cohort characteristics | Text | Tabulation |
| Follow-up time after cancer diagnosis | Manual | Cohort characteristics | Text | Tabulation |
| Losses to follow-up\_cohort | Manual | Cohort characteristics | Text | Tabulation, risk of bias assessment |
| **FOR FOLLOW-UP STUDIES, RESULTS** | | | | |
| Exposure | Select pulldown (use WCRF exposure code) | Exposure | Code | Tabulation, analysis |
| Exposure description | Manual/copy and paste | Exposure | Text | Tabulation, analysis |
| Timeframe of exposure | Select pulldown: Post-diagnosis | Exposure | Code | Tabulation, analysis |
| Study endpoint  (QOL tool) | Manual or pulldown: (indicate Quality of life tool or domain) | Outcome, cohort | Code | Tabulation, analysis |
| Study endpoint description  (tool description including if validated) | Manual/copy and paste | Outcome, cohort | Text | Tabulation, analysis |
| Study endpoint description  (tool description including if validated) | Manual/copy and paste | Outcome, cohort | Code/text | Tabulation, analysis |
| Subgroup (participants or outcome) | Manual or pulldown | Result, cohort | Code/text | Tabulation, analysis |
| Type of analysis\_cohort | Select pulldown: Mean difference  Other | Result, cohort | Code | To indicate what result type should appear in screen, analysis |
| Number of exposure levels | Manual | Result, cohort | Number/text | Tabulation, analysis |
| Mean of exposure levels | Manual | Result, cohort | Number | Tabulation, analysis |
| Bottom range of exposure levels | Manual | Result, cohort | Number | Tabulation, analysis |
| Top range of exposure levels | Manual | Result, cohort | Number | Tabulation, analysis |
| Reference category | Select checkbox | Result, cohort | Code | Tabulation, analysis |
| Max from reference | Select checkbox | Result, cohort | Code | Tabulation, analysis |
| Mean, SD of outcome by exposure level at baseline | Select checkbox | Result, cohort | Code | Tabulation, analysis |
| Mean, SD of outcome by exposure level at follow-up | Manual | Result, cohort | Number | Tabulation, analysis |
| Adjustments  (covariates) | Manual/select pulldown | Adjustment | Code/text | Tabulation, analysis, risk of bias assessment |
| Best model | Select checkbox | Adjustment | Code | Tabulation, analysis |
| Maximally adjusted | Select checkbox | Adjustment | Code | Tabulation, analysis |
| Intermediately adjusted | Select checkbox | Adjustment | Code | Tabulation, analysis |
| Minimally adjusted | Select checkbox | Adjustment | Code | Tabulation, analysis |
| Unadjusted | Select checkbox | Adjustment | Code | Tabulation, analysis |

# Annex 4. List of Exposure codes in the cup database

(Note: The database currently contains more items under the main exposures than those listed here)

1 Patterns of diet

1.1 Regionally defined diets

1.1.1 Mediterranean diet

*Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and “western type”.*

1.2 Socio-economically defined diets

*To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).*

1.3 Culturally defined diets

*To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.*

1.4 Individual level dietary patterns

*To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes) that do not fit into the headings above.*

1.5 Other dietary patterns

*Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.*

1.7 Other issues

*For example results related to diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eatin****g*** *should be reported here. Eating out of home should be reported here.*

2 Foods

2.0.1 Plant foods

2.1 Starchy foods

2.1.1 Cereals (grains)

2.1.1.0.1 Rice, pasta, noodles

2.1.1.0.2 Bread

2.1.1.0.3 Cereal

*Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)*

2.1.1.1 Wholegrain cereals and cereal products

2.1.1.1.1 Wholegrain rice, pasta, noodles

2.1.1.1.2 Wholegrain bread

2.1.1.1.3 Wholegrain cereal

2.1.1.2 Refined cereals and cereal products

2.1.1.2.1 Refined rice, pasta, noodles

2.1.1.2.2 Refined bread

2.1.1.2.3 Refined cereal

2.1.2 Starchy roots, tubers and plantains

* + - 1. Potatoes

2.1.3 Other starchy foods

*Report polenta under this heading*

2.2 Fruit and (non-starchy) vegetables

*Results for “fruit and vegetables” and “fruits, vegetables and fruit juices” should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.*

2.2.1 Non-starchy vegetables

*This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported they should be recorded under one of the sub-headings below or if not covered, they should be recorded under ‘2.2.1.5 other’.*

2.2.1.1 Non-starchy root vegetables and tubers

2.2.1.1.1 Carrots

2.2.1.2 Cruciferous vegetables

2.2.1.3 Allium vegetables

2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)

2.2.1.5 Other non-starchy vegetables

2.2.1.5.13 Tomatoes

2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas

*Other non-starchy vegetables’ should include foods that are botanically fruits but are eaten as vegetables, e.g. courgettes. In addition vegetables such as French beans that do not fit into the other categories, above.*

*If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. If in doubt, enter the exposure more than once in this way.*

2.2.1.6 Raw vegetables

*This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 –2.2.1.5.*

2.2.2 Fruits

2.2.2.0.1 Fruit, dried

2.2.2.0.2 Fruit, canned

2.2.2.0.3 Fruit, cooked

2.2.2.1 Citrus fruit

2.2.2.1.1 Oranges

2.2.2.1.2 Other citrus fruits (e.g. grapefruits)

2.2.2.2 Other fruits

2.2.2.2.1 Bananas

2.2.2.2.4 Melon

2.2.2.2.5 Papaya

2.2.2.2.7 Blueberries, strawberries and other berries

2.2.2.2.8 Apples, pears

2.2.2.2.10 Peaches, apricots, plums

2.2.2.2.11 Grapes

*If results are available that consider other groups of fruit or a particular fruit please report under ‘other’, specifying the grouping/fruit used in the literature.*

2.3 Pulses (legumes)

2.3.1 Soya, soya products

2.3.1.1 Miso, soya paste soup

2.3.1.2 Soya juice

2.3.1.4 Soya milk

2.3.1.5 Tofu

2.3.2 Dried beans, chickpeas, lentils

2.3.4 Peanuts, peanut products

*Where results are available for a specific pulse/legume, please report under a separate heading.*

2.4 Nuts and Seeds

*To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts or flaxseed, please report under a separate heading.*

* 1. Meat, poultry, fish and eggs

*Wherever possible please differentiate between farmed and wild meat, poultry and fish.*

* + 1. Meat

*This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.*

*Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.*

2.5.1.1 Fresh Meat

2.5.1.2 Processed meat

2.5.1.2.1 Ham

2.5.1.2.1.7 Burgers

2.5.1.2.8 Bacon

2.5.1.2.9 Hot dogs

2.5.1.2.10 Sausages

*Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of ‘processed meat’ used by each study.*

* + - 1. Red meat

2.5.1.3.1 Beef

2.5.1.3.2 Lamb

2.5.1.3.3 Pork

2.5.1.3.6 Horse, rabbit, wild meat (game)

*Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.*

*Show any data on wild meat (game) under this heading as a separate sub-category.*

* + - 1. Poultry

*Show any data on wild birds under this heading as a separate sub-category.*

2.5.1.5 Offal, offal products (organ meats)

* + 1. Fish

2.5.2.3 Fish, processed (dried, salted, smoked)

2.5.2.5 Fatty Fish

2.5.2.7 Dried Fish

2.5.2.9 White fish, lean fish

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats

2.6.1.1 Butter

2.6.1.2 Lard

2.6.1.3 Gravy

2.6.1.4 Fish oil

2.6.2 Plant oils

2.6.3 Hydrogenated fats and oils

2.6.3.1 Margarine

*Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation*

2.6.4 Sugars

*This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.*

2.7 Milk and dairy products

*Results concerning milk should be reported twice, here and under 3.3 Milk*

2.7.1 Milk, fresh milk, dried milk

2.7.1.1 Whole milk, full-fat milks

2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk

2.7.2 Cheese

2.7.2.1 Cottage cheese

2.7.2.2 Cheese, low fat

2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks

2.7.3.1 Fermented whole milk

2.7.3.2 Fermented skimmed milk

2.7.7 Ice cream

2.8 Herbs, spices, condiments

2.8.1 Ginseng

2.8.2 Chili pepper, green chili pepper, red chili pepper

* 1. Composite foods

*Eg, snacks, crisps, desserts, pizza. Also report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.*

2.9.1 Cakes, biscuits and pastry

2.9.2 Cookies

2.9.3 Confectionery

2.9.4 Soups

2.9.5 Pizza

2.9.6 Chocolate, candy bars

2.9.7 Snacks

3 Beverages

3.1 Total fluid intake

3.2 Water

*(Milk will be reported under 2.7 Milk and Dairy Products)*

* 1. Soft drinks

Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.

3.4.1 Sugary (not carbonated)

3.4.2 Carbonated (not sugary)

*The definition of type of beverage used by the studies should be followed, as definitions of various soft drinks may vary.*

3.5 Fruit and vegetable juices

3.5.1 Citrus fruit juice

3.5.2 Fruit juice

3.5.3 Vegetable juice

3.5.4 Tomato juice

3.6 Hot drinks

3.6.1 Coffee

* + 1. Tea

*Report herbal tea as a sub-category under tea.*

3.6.2.1 Black tea

3.6.2.2 Green tea

3.6.3 Maté

3.6.4 Other hot drinks

3.7 Alcoholic drinks

3.7.1 Total

3.7.1.1 Beers

3.7.1.2 Wines

3.7.1.3 Spirits

3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation

4.1 Production

4.1.1 Traditional methods (*to include ‘organic’)*

4.1.2 Chemical contaminants

*Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:*

4.1.2.1 Pesticides

4.1.2.2 DDT

4.1.2.3 Herbicides

4.1.2.4 Fertilisers

4.1.2.5 Veterinary drugs

4.1.2.6 Other chemicals

4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)

4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)

4.1.2.6.3 Polychlorinated biphenyls (PCBs)

4.1.2.7 Heavy metals

4.1.2.7.1 Cadmium

4.1.2.7.2 Arsenic

4.1.2.8 Waterborne residues

4.1.2.8.1 Chlorinated hydrocarbons

4.1.2.9 Other contaminants

*Please also report any results that cover the cumulative effect of low doses of contaminants in this section.*

4.2 Preservation

4.2.1 Drying

4.2.2 Storage

4.2.2.1 Mycotoxins

4.2.2.1.1 Aflatoxins

4.2.2.1.2 Others

4.2.3 Bottling, canning, vacuum packing

4.2.4 Refrigeration

4.2.5 Salt, salting

4.2.5.1 Salt

4.2.5.2 Salting

4.2.5.3 Salted foods

4.2.5.3.1 Salted animal food

4.2.5.3.2 Salted plant food

4.2.6 Pickling

4.2.7 Curing and smoking

4.2.7.1 Cured foods

4.2.7.1.2 Smoked foods

*Processed meats will be reported under 2.5.1.2*

4.3 Processing

4.3.1 Refining

*Refined cereals and cereal products should be reported under 2.1.1.2.*

4.3.2 Hydrogenation

*Results concerning hydrogenated fats and oils should be reported under 2.6.3 Hydrogenated fats and oils*

4.3.3 Fermenting

4.3.4 Compositional manipulation

4.3.4.1 Fortification

4.3.4.2 Genetic modification

4.3.4.3 Other methods

4.3.5 Food additives

* + - 1. Flavours

*Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.*

4.3.5.2 Sweeteners (non-caloric)

4.3.5.3 Colours

4.3.5.4 Preservatives

4.3.5.4.1 Nitrites and nitrates

4.3.5.5 Solvents

4.3.5.6 Fat substitutes

4.3.5.7 Other food additives

*Please also report any results that cover the cumulative effect of low doses of additives.*

*Please also report any results that cover synthetic antioxidants*

4.3.6 Packaging

4.3.6.1 Vinyl chloride

4.3.6.2 Phthalates

4.4 Preparation

4.4.1 Fresh food

* + - 1. Raw

*Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).*

4.4.1.2 Juiced

4.4.2 Cooked food

4.4.2.1 Steaming, boiling, poaching

4.4.2.2 Stewing, casseroling

4.4.2.3 Baking, roasting

4.4.2.4 Microwaving

4.4.2.5 Frying

4.4.2.6 Grilling (broiling) and barbecuing

4.4.2.7 Heating, re-heating

*Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.*

*Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.*

5 Dietary constituents

*Food constituents’ relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.*

5.1 Carbohydrate

5.1.1 Total carbohydrate

5.1.2 Non-starch polysaccharides/dietary fibre

5.1.2.1 Cereal fibre

5.1.2.2 Vegetable fibre

5.1.2.3 Fruit fibre

5.1.3 Starch

5.1.3.1 Resistant starch

5.1.4 Sugars

5.1.5 Glycemic index, glycemic load

*This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for intrinsic and extrinsic sugars should be presented separately. Count honey and sugars in fruit juices as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.*

5.2 Lipids

5.2.1 Total fat

5.2.2 Saturated fatty acids

5.2.3 Monounsaturated fatty acids

5.2.4 Polyunsaturated fatty acids

5.2.4.1 n-3 fatty acids

*Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.*

5.2.4.2 n-6 fatty acids

5.2.4.3 Conjugated linoleic acid

5.2.5 Trans fatty acids

5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

*For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.*

5.3 Protein

5.3.1 Total protein

5.3.2 Plant protein

5.3.3 Animal protein

5.4 Alcohol

*This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.*

5.4.1 Total Alcohol (as ethanol)

5.4.1.1 Alcohol (as ethanol) from beer

5.4.1.2 Alcohol (as ethanol) from wine

5.4.1.3 Alcohol (as ethanol) from spirits

5.4.1.4 Alcohol (as ethanol) from other alcoholic drinks

5.4.1.5 Total alcohol (as ethanol), lifetime exposure

5.4.1.6 Total alcohol (as ethanol), past

5.5 Vitamins

5.5.0 Vitamin supplements

5.5.0.1 Vitamin and mineral supplements

5.5.0.2 Vitamin B supplement

5.5.1 Vitamin A

5.5.1.1 Retinol

5.5.1.2 Provitamin A carotenoids

* + 1. Non-provitamin A carotenoids

*Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.*

5.5.3 Folates and associated compounds

5.5.3.1 Total folate

5.5.3.2 Dietary folate

5.5.3.3 Folate from supplements

*Examples of the associated compounds are lipotropes, methionine and other methyl donors.*

5.5.4 Riboflavin

5.5.5 Thiamin (vitamin B1)

5.5.6 Niacin

5.5.7 Pyridoxine (vitamin B6)

5.5.8 Cobalamin (vitamin B12)

5.5.9 Vitamin C

5.5.10 Vitamin D (and calcium)

5.5.11 Vitamin E

5.5.12 Vitamin K

5.5.13 Other

*If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under ‘other’.*

5.6 Minerals

5.6.1 Sodium

5.6.2 Iron

5.6.3 Calcium (and Vitamin D)

5.6.4 Selenium

5.6.5 Iodine

5.6.6 Other

*Results are likely to be available on other minerals e.g. magnesium, potassium, zinc, copper, phosphorus, manganese and chromium for certain cancers. These should be reported at the end of this section when appropriate under ‘other’.*

5.7 Phytochemicals

5.7.1 Allium compounds

5.7.2 Isothiocyanates

5.7.3 Glucosinolates and indoles

5.7.4 Polyphenols

5.7.5 Phytoestrogens eg genistein, isoflavones, lignans

5.7.6 Caffeine

5.7.7 Other

*Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading ‘other bioactive compounds’.**Eg flavonoids, isoflavonoids, glycoalkaloids, cyanogens, oligosaccharides and anthocyanins should be reported separately under this heading.*

5.8 Other bioactive compounds

6 Physical activity

6.1 Total physical activity (overall summary measures)

6.1.1 Type of activity

6.1.1.1 Occupational

6.1.1.2 Recreational

6.1.1.3 Household

6.1.1.4 Transportation

6.1.2 Frequency of physical activity

6.1.2.1 Frequency of occupational physical activity

6.1.2.2 Frequency of recreational physical activity

6.1.3 Intensity of physical activity

6.1.3.1 Intensity of occupational physical activity

6.1.3.2 Intensity of recreational physical activity

6.1.4 Duration of physical activity

6.1.4.1 Duration of occupational physical activity

6.1.4.2 Duration of recreational physical activity

6.2 Sedentary behaviour (including screen time, sitting time)

* 1. Surrogate markers for physical activity e.g. occupation

7 Energy balance

7.1 Energy intake

7.1.0.1 Energy from fats

7.1.0.2 Energy from protein

7.1.0.3 Energy from carbohydrates

7.1.0.4 Energy from alcohol

7.1.0.5 Energy from all other sources

7.1.1 Energy density of diet

7.2 Energy expenditure

8. Anthropometry

8.1 Markers of body composition

8.1.1 BMI

8.1.2 Other weight adjusted for height measures

8.1.3 Weight

8.1.4 Skinfold measurements

8.1.5 Other (e.g. DEXA, bio- impedance, etc)

8.1.6 Change in body composition (including weight gain)

8.2 Markers of distribution of fat

8.2.1 Waist circumference

8.2.2 Hips circumference

8.2.3 Waist to hip ratio

8.2.4 Skinfolds ratio

8.2.5 Other e.g. CT, ultrasound

8.3 Skeletal size

8.3.1 Height (and proxy measures)

8.3.2 Other (e.g. leg length)

8.4 Growth in fetal life, infancy or childhood

8.4.1 Birthweight,

8.4.2 Weight at one year

# Annex 5. Statistical formulae

The combination of study arms or subgroups will be performed using the following formulas:

Where ***M*** is the combined mean, ***SD*** is the combined standard deviation, N1 is Group 1 sample size, M1 is Group 1 mean, SD1 is Group 1 standard deviation, N2 is Group 2 sample size, M2 is Group 2 mean, SD2 is Group 2 standard deviation.

# Annex 6. Assessment of risk of bias

1. **Criteria to be discussed in risk of bias assessment of observational studies**
2. Ascertainment of exposure

1.1 Anthropometry: lower risk of bias: measured, or self-reported corrected for measurement error.

1.2 Diet: lower risk of bias if validated diet questionnaire, correction for measurement error, high number of items.

1.3 Biomarkers: lower risk of bias if validated test (coefficient of variation), batch and fasting requirements fulfilled.

1.4 Physical activity: lower risk of bias if validated instrument, assessing type, intensity and frequency of activity.

2) Outcome ascertainment

2.1 Lower risk of bias if tool has been validated in similar population (cultural validity) (currently the reviewers do not have criteria to rank different tools by quality)

2.2 Adequacy of the tool/instrument: Lower risk of bias if designed /validated for breast cancer patients

2.3 Relevance of outcome: Lower risk of bias if indicated the difference/minimal significant difference/change, analysed using clinical criteria or not indicated

2.4) Follow up of cohorts of survivors: Lower risk of bias if virtually complete follow up (or <10 % loss)

3) Confounding: A study should control for age, smoking, disease characteristics at diagnosis (e.g. stage, grade), treatment type and completion, comorbidity, alcohol intake, energy intake (for diet)

4) Survivor bias: Lower risk of bias if all incident cases are included in the cohort

1. risk of bias assessment. Randomised controlled trials.

Cochrane risk-of-bias tool for randomized trials , version 2 (RoB 2) (Sterne, 2019)

The results for the assessment will be presented graphically as a summary and for each included study.

| **Bias domain** | **Source of bias** |
| --- | --- |
| Bias arising from the randomisation process | Random sequence generation (were the groups similar at baseline for the measures of quality of life, and if groups were not similar at baseline, this was adjusted for in subsequent analysis) |
| Allocation concealment |
| Baseline differences between intervention groups |
| Bias due to deviations from intended interventions | Blinding of participants and personnel |
| Deviations from the intended intervention that arose because of the trial context |
| Appropriate analysis used to estimate the effect of assignment to  Intervention |
| Bias due to missing outcome data | Availability and missingness of data for the participants randomised |
| Bias in measurement of the outcome | Incomplete outcome data, nature or handling of incomplete outcome |
| Bias in selection of the reported result | Selective outcome reporting |
| Overall bias | Risk-of-bias judgment (low/high/some concerns) |

# Annex 7. Example tables in the systematic literature review

A. Example summary table of the meta-analyses in the systematic literature review

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Intervention Exposure/ | Randomised controlled trials | | | |
| HRQOL domain | No. studies/  participants  I2% | Between group difference in mean scores (95% CI) | No. studies/  participants  I2% | Between group difference in mean change scores (95% CI) |
| HRQoL instrument 1 |  |  |  |  |
| HRQoL instrument 2 |  |  |  |  |
| HRQoL instrument 3 |  |  |  |  |
| ……. |  |  |  |  |

ANNEX 7 (CONT.).

B. Example table of Main Study characteristics and results of the randomised controlled trials included in the review

| **WCRF Code Author Year Study**  **Country** | **Study size**  **Age**  **Menopausal status Disease and other characteristics** | **Intervention Comparison Duration of intervention** | **Outcome assessment** | **Outcome assessment time** | **Baseline mean score (SD)** | **Follow-up mean score (SD)** | **Between group difference in mean scores /mean change scores**  **(SE) (95%CI) (P-value)** | **Summary of findings** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study 1 |  |  |  |  |  |  |  |  |
| Study 2  … |  |  |  |  |  |  |  |  |

C. Example table of Detailed information of the randomised controlled trials included in the review

| **Study**  **Country**  **WCRF Code**  **Author Year** | **RCT design**  **No. of trial arms Intervention Comparison Duration of intervention** | **Study size**  **Time since diagnosis or treatment** | **Intervention description** | **Intervention method** | **Comparison description** | **Intervention timeframe Duration** | **Adherence Adverse effects** | **Blinding Allocation** | **Duration of follow-up Losses to follow-up Outcome time point**  **Assessment tool** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study 1 |  |  |  |  |  |  |  |  |  |
| Study 2  … |  |  |  |  |  |  |  |  |  |

ANNEX 7 (CONT.).

D. Example table of Main Study characteristics and results of observational studies included in the review

| **WCRF Code Author Year Study Country** | **Study type, size**  **Age**  **Menopausal status Other characteristics** | **Time of diagnosis**  **Follow-up**  **Disease characteristics**  **Treatment information** | **Exposure**  **Timeframe relative to treatment** | **Outcome assessment** | **Outcome assessment time** | **Results** | **Adjustment** | **Summary of findings** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study 1 |  |  |  |  |  |  |  |  |
| Study 2  … |  |  |  |  |  |  |  |  |