# Global Cancer Update Programme (CUP Global)\*: Protocol for the data collection and systematic literature reviews on the role of diet, nutrition and physical activity on outcomes after diagnosis of breast cancer

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

# Modifications to the review protocol

# 8 July 2020

The protocol is developed for the systematic literature review and meta-analysis of epidemiological studies on lifestyle factors – nutrition, diet, body size and physical activity – before and after breast cancer diagnosis and their relationships with survival and disease recurrence.

The first systematic literature review focuses on the role of the lifestyle factors after cancer diagnosis.

Intervention/exposures:

An overview of the findings will be conducted for each post-diagnosis lifestyle factor that met the review criteria. All post-diagnosis results will be pooled in a meta-analysis when enough studies have reported data sufficient for analysis. When possible, subgroup meta-analysis will be conducted to restrict the studies by exposure timing respective to cancer treatment (before, during, and/or after neoadjuvant/adjuvant treatment is completed). The purpose is to separate the studies in which participants may have changed lifestyle factors due to the treatment.

Outcomes:

The outcomes to investigate are overall survival (all-cause mortality or total mortality), breast cancer-specific survival, other causes of death, breast cancer recurrence, and second primary cancer.

Breast cancer recurrence is defined differently in the studies. In some studies, the term “recurrence/relapse-free survival” or “breast cancer recurrence” is used; while in others, the terms “disease-free survival”, “event-free survival”, “progression-free survival”, or “additional breast cancer events” is used. In some studies, the events included in the definition of recurrence are local, regional and/or distant recurrence (metastasis). Other studies include second primary cancer, breast cancer-related death, any cause of death, or any combination of these as events. For each factor to review, all the studies will be reviewed under “recurrence” because of the generally limited number of studies with recurrence as outcome. For BMI, the number of studies is likely large, and will likely allow additional analysis by recurrence type, mainly whether non breast cancer-related deaths or any cause of death are included.

Evidence quality/risk of bias assessment:

The main issues in the identified studies that can affect the quality of the review, including selection bias, study power, measurement error, outcome assessment, losses to follow-up, and residual confounding, rather than an individual assessment of study quality, will be evaluated.

The results of the tests for publication bias and heterogeneity statistics will be indicated in tables and figures. In general, there may not be enough studies to formally explore heterogeneity sources.

Evidence synthesis:

Linear-dose response meta-analysis will be conducted when there are at least three comparable observational studies with the required data to do the analysis. Meta-analysis of randomised controlled trials will be conducted when there are at least two studies reporting comparable data. Highest versus lowest forest plots showing the relative risk estimates for the highest category compared with the reference category in each study will be produced to aid results interpretation, in particular for when a dose-response meta-analysis is not possible and the evidence is narratively synthesised. The overall summary estimate will not be calculated, except for the studies of physical activity that often do not report the data required for conducting the linear dose-response meta-analysis. To examine potential impact from cancer treatment, subgroup analysis will be conducted when possible to separate the studies by year 2000 when there was a shift in breast cancer chemotherapy regimens to include doxorubicin/cyclophosphamide, and year 2005 when anthracycline use began to decline with increase in taxane use and the use of human epidermal growth factor receptor 2 (HER2) targeted therapy - trastuzumab. Studies with diagnosis/treatment period spanning over the year will be excluded. Further, studies that reported results according to adjuvant treatment (received treatment or not) will also be examined.