Protocol *Version 2*

Continuous Update and Systematic Literature Review of Randomised Controlled Trials and Prospective Studies on Food, Nutrition, Physical Activity and the Risk of Lung Cancer.

Reviewed by: CUP Team, Imperial College London, July 2013

INTRODUCTION

The World Cancer Research Fund/ American Institute for Cancer Research: (WCRF/AICR) has been a global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The First and Second Expert Reports (1;2) represent the most extensive analyses of the existing science on the subject to date.

The Second Expert Report features eight general and two special recommendations based on solid evidence (**Figure 1**) which, when followed, will be expected to reduce the incidence of cancer. More recently, empirical evidence from a large European cohort study showed that people with lifestyle in agreement with the WCRF/AICR recommendations experienced decreased risk of cancer after an average follow-up time of ten years (3). The main risk reductions were for cancers of the colon and rectum, and lung cancer, and significant associations were observed for cancers of the breast, endometrium, lung, kidney, upper aerodigestive tract, liver, and oesophagus.

The Second Expert Report was informed by a process of seventeen systematic literature reviews (SLRs) all of the evidence published. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP) in collaboration with Imperial College London (ICL). The CUP [http://www.wcrf.org/cancer_research/cup/index.php] is an on-going systematic literature review on food, nutrition, physical activity and body fatness, and cancer risk. The project ensures that the evidence, on which the WCRF/AICR recommendations are based, continues to be the most-up-to-date and comprehensive available.

WCRF/AICR has convened a panel of experts for the CUP consisting of leading scientists in the field of diet, physical activity, obesity and cancer, who will consider the evidence produced by the systematic literature reviews conducted by the research team at ICL. The CUP Panel will judge the evidence, draw conclusions and make recommendations for cancer prevention. The entire CUP process will provide a transparent analysis and interpretation of the data as a basis for reviewing and where necessary revising the 2007 WCRF/AICR's cancer prevention recommendations (**Figure 2**).

Figure 1. 2007 World Cancer Research Fund/ American Institute for Cancer Research recommendations for cancer prevention.

RECOMMENDATIONS
BODY FATNESS Be as lean as possible within the normal range of body weight
PHYSICAL ACTIVITY Be physically active as part of everyday life
FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN Limit consumption of energy-dense foods Avoid sugary drinks
PLANT FOODS Eat mostly foods of plant origin
ANIMAL FOODS Limit intake of red meat and avoid processed meat
ALCOHOLIC DRINKS Limit alcoholic drinks
PRESERVATION, PROCESSING, PREPARATION Limit consumption of salt Avoid mouldy cereals (grains) or pulses (legumes)
DIETARY SUPPLEMENTS Aim to meet nutritional needs through diet alone
BREASTFEEDING Mothers to breastfeed; children to be breastfed
CANCER SURVIVORS Follow the recommendations for cancer prevention

Source: WCRF/AICR Second Expert Report (2)

Figure 2. The Continuous Update Process
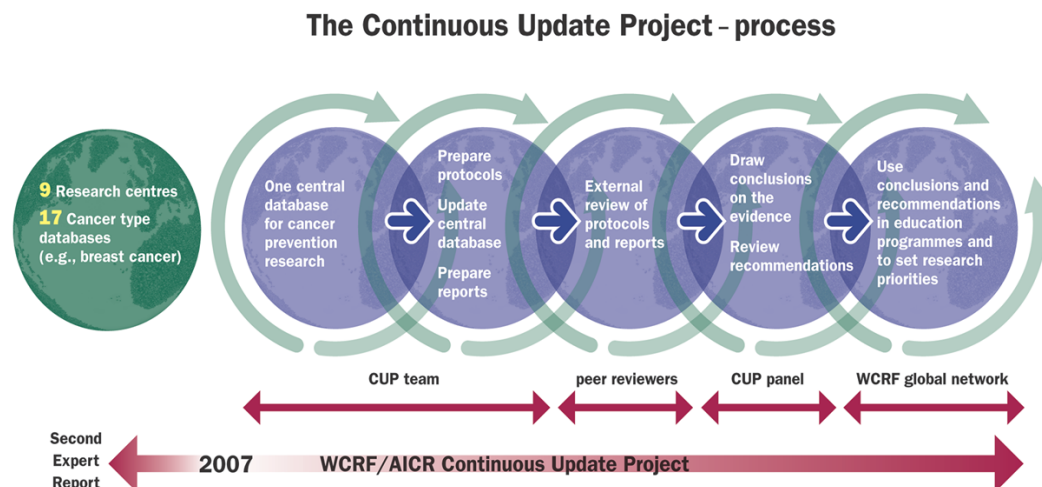
The CUP builds on the foundations of the Second Expert Report to ensure a consistent approach to reviewing the evidence SLR (4). A key step of the CUP is the update of the central database with the results of randomised controlled trials and prospective studies. The CUP Expert Panel advised that these are the study designs that should be prioritized for update because the 2007 WCRF recommendations had been mainly based on the results of randomised controlled trials and prospective cohort studies. A team at ICL conducts the CUP SLRs, where a central database has been created by merging the cancer-specific databases generated in the 2007 SLR's.

The WCRF database is being updated at ICL in a rolling programme. The CUP started in 2007 and breast cancer was the first cancer to be updated, followed by prostate and colorectal cancers. When a cancer site is included in the CUP, the team at ICL keeps updating the database for that cancer and all the other cancers already included in the CUP (**Figure 3**). Currently, the central database is continuously updated for cancers of the breast, prostate, colon and rectum, pancreas, ovary, endometrium, bladder, kidney, gallbladder, liver, stomach and oesophageal cancers.

Periodically, the CUP team at ICL prepares SLR reports with updated meta-analyses by request of the CUP Panel and Secretariat. The protocols and reports of systematic literature reviews by the IC team are available at http://www.dietandcancerreport.org/cancer_resource_center/continuous_update_project.php).

The present document is the protocol for the continuous update and the SLR on food, nutrition, physical activity and the risk of lung cancer. The peer-reviewed protocol will represent the agreed plan. Should departure from the agreed plan be considered necessary at a later stage, the CUP Expert Panel must agree with the modifications and the reasons be documented.

**Figure 3. The Continuous Update Project- rolling programme**
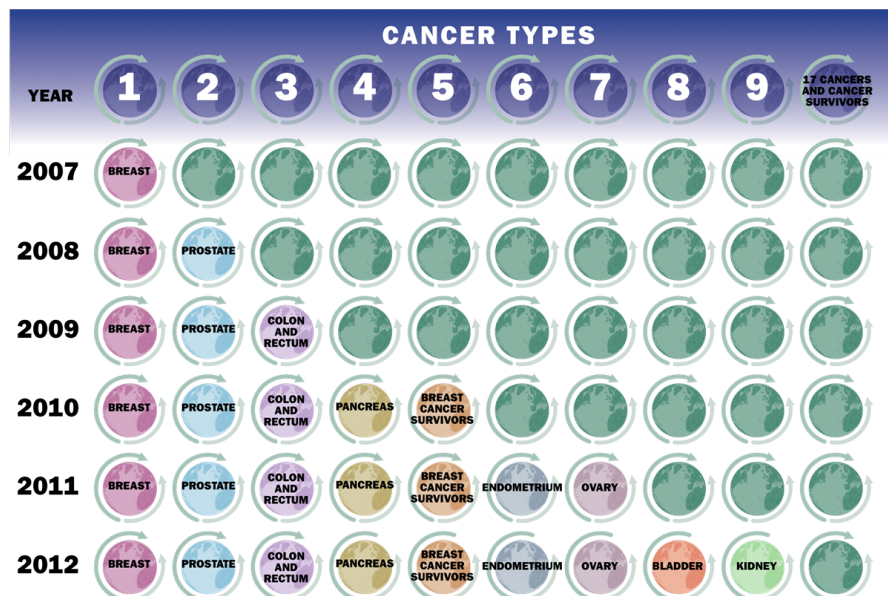
LUNG CANCER: EPIDEMIOLOGY AND RISK FACTORS.

Lung cancer is the most common cause of cancer and the leading cause of cancer death in males worldwide, and the fourth most commonly diagnosed cancer and second leading cause of cancer death in women. Most lung cancers are diagnosed at an advanced stage due to the relative lack of clinical symptoms during early stages. The 5-year survival of lung cancer is only 16% (5). In 2008, lung cancer accounted for 13% (1.6 million) of the total cases and 18% (1.4 million) of the cancer deaths (**Figure 4**).

Tobacco is the main risk factor of lung cancer. Tobacco smoking accounts for 80% of the worldwide lung cancer burden in males and at least 50% of the burden in females (6;7). The geographic variation on lung cancer rates and trends across countries or between males and females within each country mainly reflects differences in tobacco smoking prevalence (**Figure 5**) (8). Male lung cancer death rates are declining in North America, some European countries, and Australia, where smoking prevalence is decreasing, but lung cancer rates are increasing in other countries, such as China and several other countries in Asia and Africa, where the smoking prevalence continues to either increase or show signs of stability (9).

Figure 4. Estimated age (world)-standardized incidence and mortality rates by sex of selected cancers (per 100 000). World. 2008
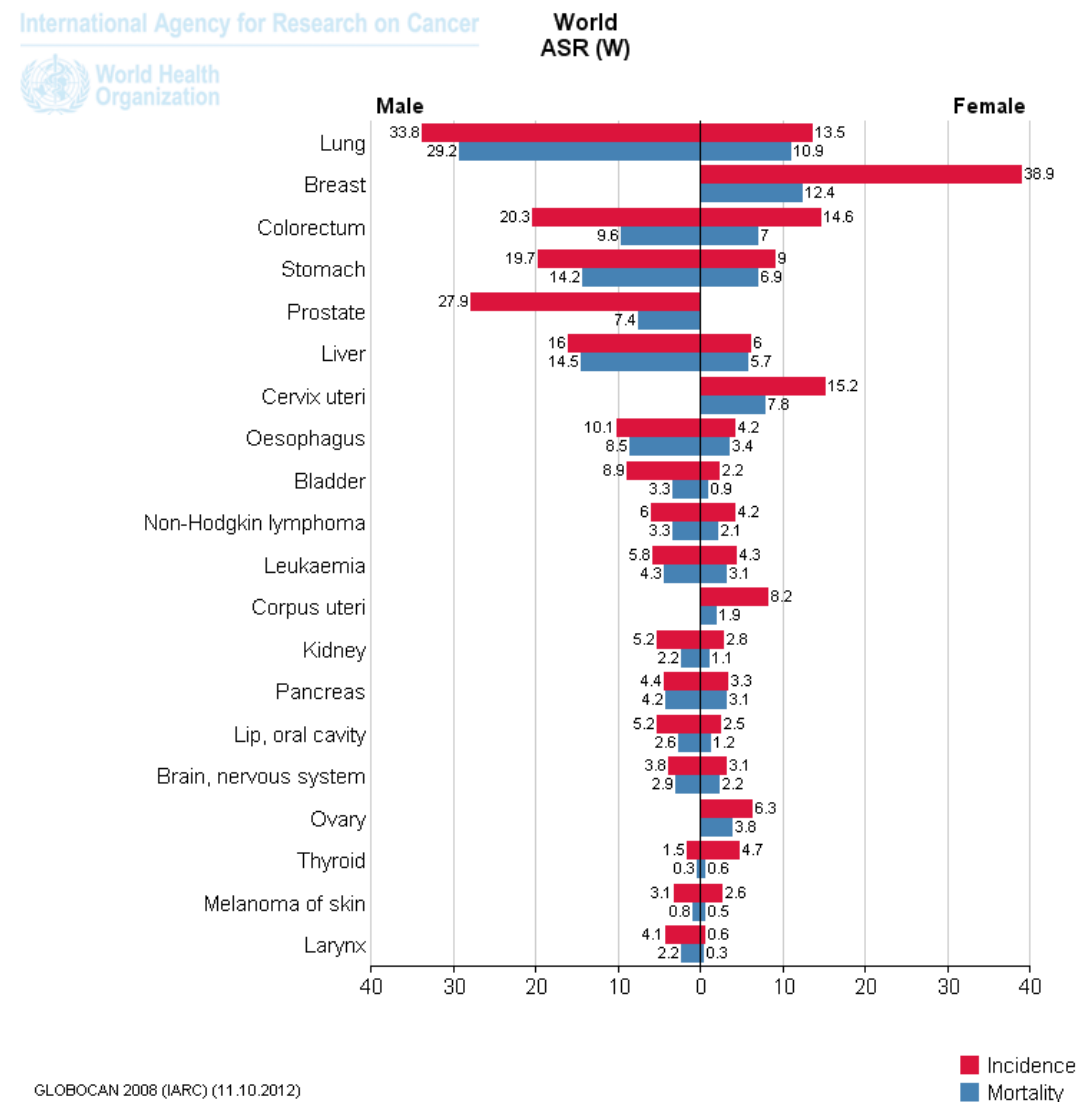
Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 20/03/2013

Figure 5. Estimated age-standardized incidence of lung cancer (per 100 000).
World 2008
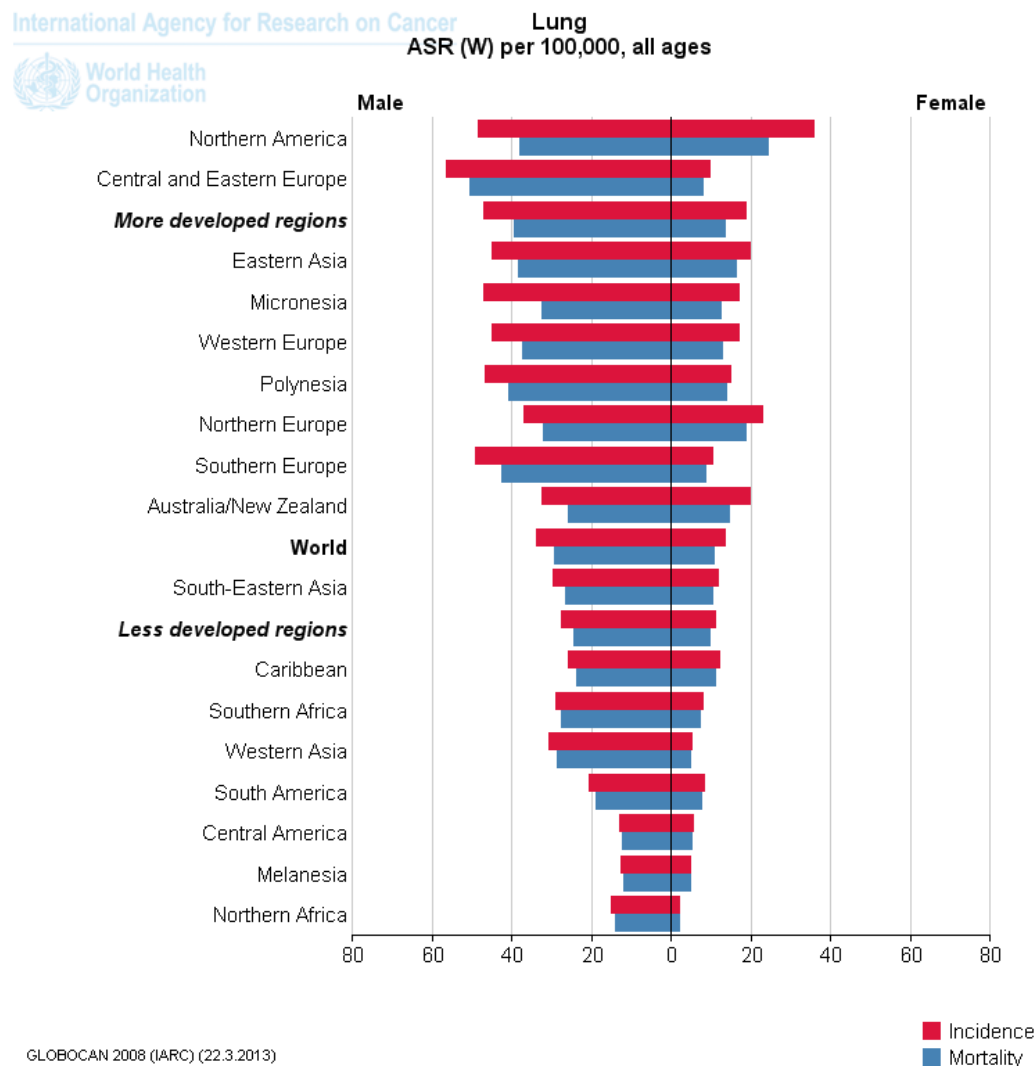
Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM.
GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC
CancerBase No. 10 [Internet].Lyon, France: International Agency for Research on
Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 20/03/2013

Non-smokers exposed to environmental tobacco smoke have an increased risk for developing lung cancer and there is also evidence that air pollution is a risk factor of lung cancer (10). Known risk factors for lung cancer include exposure to several occupational and environmental carcinogens such as asbestos, arsenic, radon, and polycyclic aromatic hydrocarbons (11;12).

There are two main classes of lung cancer: small cell lung cancer (SCLC) and non-SCLC. Non-SCLC accounts for approximately more than 85% of all lung cancer cases and includes two major types: nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types) and squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most frequently occurring cell type in non-smokers. Small-cell lung cancer is an aggressive form of lung cancer, strongly associated with cigarette smoking (13).

There is evidence that nutritional factors play a role in lung cancer development. The expert panel of the 2007 WCRF/AICR Second Report concluded that the evidence that arsenic in drinking water and beta-carotene supplements (high doses in smokers) increases the risk of lung cancer was convincing; fruits and foods containing carotenoids probably decrease the risk of lung cancer. The evidence suggesting a protective effect of non-starchy vegetables, foods containing selenium, foods containing quercitin, selenium (supplements) and physical activity was limited. There was limited evidence suggesting that red meat, processed meat, total fat intake, butter and retinol supplements and low body fatness increase the risk of lung cancer. There was not enough evidence to allow conclusions on other nutritional factors investigated (**Figure 6**).

Figure 6. Summary of judgements of the 2007 Second Expert Report on lung cancer 2007

Source: WCRF/AICR Second Expert report world (2)

SYSTEMATIC LITERATURE REVIEW ON LUNG CANCER

1. RESEARCH QUESTION

The research topic is:

The associations between food, nutrition and physical activity and the risk of lung cancer.

The main objective is:

To summarize the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of lung cancer in men and women.

2. REVIEW TEAM

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Doris Chan	Research Assistant	Supervisor of data extraction. Data analyst, SLR report preparation
Ana Rita Vieira	Research Assistant	Data analyst, SLR report preparation
Leila Abar	Research Assistant	Systematic search, article selection, data extraction
Deborah Navarro	Research Assistant	Systematic search, article selection, data extraction
Snieguole Vingeliene	Research Assistant	Systematic search, article selection, data extraction

Review coordinator, WCRF: Rachel Thompson
Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

All the reviewers are trained in the procedures for literature search, data selection and extraction for systematic literature reviews. The reviewers that will conduct the data analyses have experience in meta-analyses. Selected CUP SLRs published by members of the ICL team are in the References Section (14-22).

3. TIMELINE

The SLRs for the Second Expert Report ended in December 30th 2005. The SLR centre extracted all the data from relevant articles published up to this date for the Second Expert Report.

The CUP team at IC will search and extract data of the articles from prospective studies and randomised controlled trials published from January 1st 2006. The reviewers will verify that there are not duplicities in the database using a module for article search implemented in the interface for data entry.

List of tasks and deadlines for the continuous update on lung cancer:

Task	Deadline
Start Medline search of relevant articles published from January 1st 2006	1st October 2013
Start review of title and abstracts of articles identified in electronic search and select papers for complete review	1st November 2013
Download papers and select relevant papers for data extraction	1st December 2013
Start data extraction	6th January 2014
Start hand search of references	6th January 2014
Start quantitative analysis of articles included in PubMed up to 30th March 2015*	1st April 2015
Start writing SLR report	1st July 2015
Send SLR report for review to CUP secretariat	30th September 2015
Review and modify SLR report according to reviewer's comments	December 2015
Send reviewed SLR report to CUP secretariat	21st December
Transfer Endnote files to SLR CUP Secretariat	21st December
Panel meeting	April 2016

*End date of the intermediate systematic literature review to the CUP Panel

4. SEARCH STRATEGY

4.1. Search database

The Medline database (includes coverage from 70 countries) will be searched using PubMed as platform. The rationale for searching only in Medline is the results of the SLR's for the Second Expert Report indicated that searching reports of prospective studies in databases other than Medline was not cost effective (23). Central and ClinialTrials.gov will be searched for evidence of trials relevant to this review. A study comparing different electronic databases concluded that "The publications found in only one database were not unique with regard to access by the other databases to each reference, but rather to our particular search strategy" (24). We conducted a test using two published systematic literature reviews randomly selected from reviews on oesophageal cancer and diet (25;26). Although the authors reported searching in several electronic databases, all the articles included in the reviews were identified in PubMed if the CUP search strategy was used. Therefore, the inclusion of

other electronic databases does not appear to confer further advantage to our specific search strategy.

4.2. Hand searching for cited references

The review team will also hand search the references of reviews and meta-analyses identified during the search.

4.3 Search strategy for PubMed

The CUP review team will use the search strategy established in the SLR Guidelines for the WCRF-AICR Second Expert Report. The full search strategy is in **Annex** 1.

A first search will be conducted using as date limits January 1st 2006 to September 30th 2013 and subsequent searches will be conducted every month. The relevant articles published before January 2006 were identified and the data extracted into the WCRF database during the SLR for the Second Expert Report.

5. STUDY SELECTION CRITERIA FOR THE UPDATE

5.1 Inclusion criteria

The articles to be included in the review:

- Must have as exposures/interventions one of the following: dietary patterns, foods, nutrients –dietary, supplemental or both-, diet biomarkers, food contaminants, food additives, indicators of body adiposity in early life, adolescence or adulthood, changes in body adiposity, height, breastfeeding, physical activity.

- Must have as outcome of interest incidence or mortality of lung cancer

- Have to present results from an epidemiologic study in men and/or women of one of the following types:
  - o Randomized controlled trial
  - o Prospective cohort study
  - o Nested case-control study
  - o Case-cohort study
  - o Historical cohort study

- Studies in individuals free of cancer at the moment of exposure assessment or intervention (except non melanoma skin cancer)

5.2 Exclusion criteria

- Studies with designs not listed in the Inclusion criteria (e.g. case-control studies, case-only studies, ecological studies, non-randomized clinical trials, cross-sectional studies, etc.)

- Cohort studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders).
- Articles in foreign language that cannot be translated (members in the review team can read Chinese, French, Italian, Spanish and Portuguese).

6. ARTICLE SELECTION

First, all references obtained with the searches in PubMed will be imported in a Reference Manager Database using the filter Medline.

The article selection will follow three steps:

1. An electronic search will first be undertaken within Reference Manager to facilitate the identification of irrelevant records by using the terms indicated below. Relevance will be assessed upon reading of the titles and abstracts of the articles identified by the electronic search.

List of terms for use within Reference Manager Database

Radiotherapy
Chemotherapy
Cisplatinum
Docetaxel
Cell
Inhibitor
Novel
Model
Receptor
Antibody
Transgenic
Mice
Hamster
Rat
Dog
Cat
In vitro

2. In a second step, two reviewers will assess the titles and abstracts of the remaining articles.

3. In a third step, the reviewers will assess the full manuscripts of all papers for which eligibility could not be determined by reading the title and abstract.

The reviewers will solve any disagreements about the study or exposure relevance by discussion with the principal investigator.

6.1 Reference Manager Files

Five user-defined fields (**Table 1**) will be created in the Reference Manager database where the reviewers will indicate:

1) if the study was selected upon reading of title and abstract, or entire article
2) the study design of articles on exposures/interventions and outcome relevant to the review
3) the status of data extraction of included articles
4) the WCRF code assigned to included studies during data extraction
5) reasons for exclusion of articles on exposures/interventions and outcome relevant to the review

Relevant case-control studies will be labelled in the Reference manager database as Included for the purpose of identification, but the results of case-control studies will not be included in the WCRF database or in the meta-analysis.

Table 1. User-defined fields and terms to be used in the Reference Manager database for identification of the status of articles identified in the searches

Field	Use	Terms	Notes
User Def 1	Indicate result of assessment for inclusion	Excludedabti	Excludedabti: paper exclusion based on abstract and title
		Excluded	Excluded: paper exclusion based on full paper text
		Included	Included: reports of case-control studies, cohort studies, pooled analysis and trials relevant to the review.
User Def 2	Reasons for exclusion	No measure of association No original data Commentary, no original data Foreign article in [*language*] No adequate study design Meta-analysis Already extracted Cancer survivors	No original data uses data from others No adequate study design includes non-controlled trials, cross-sectional analysis, and ecological studies. Already extracted refers to studies identified by another search Cancer survivors for studies that are not in people free of cancer at baseline
User Def 3	Study design	Randomized controlled trial (RCT) Prospective cohort study Retrospective cohort study	Case-control study-other: when the comparison populations are neighbours, friends, and any other case in

		Nested case-control study Case cohort study Population-based case-control study Hospital-based case-control study Case-control study- other Pooled analysis of cohort studies Pooled analysis of case-control studies	which the controls are not population- or hospital- based. Case-control studies and pooled analyses are identified as included but the data are not extracted to the database.
User Def 4	WCRF code	LUN+ consecutive digits	WCRF codes are assigned automatically by the data extraction software when performing the data extraction.
User Def 5	Cancer group	Indicates if the study report aggregative cancer types such as gastro-lung cancer, upper aero-digestive or other	The data should be extracted in the article has inclusion criteria

7. DATA EXTRACTION

The IC team will update the WCRF-AICR central database using an interface created or this purpose **(Figure 6)**. The application will automatically check that the paper has not already been extracted to the database using author name, publication year and journal references. The data extracted will be double-checked by a second reviewer.

The data to be extracted include study design, name, characteristics of study population, mean age, distribution by sex, country, recruitment year, methods of exposure assessment, definition of exposure, definition of outcome, method of outcome assessment, study size, length of follow up, lost to follow-up, analytical methods and whether methods for correction of measurement error were used.

The ranges, means or median values for each level of the exposure will be extracted as reported in the paper.

For each result, the reviewers will extract the covariates included in the analytical models and the matching variables.

Measures of association, number of cases and number of comparison individuals or person years for each category of exposure will be extracted for each model reported in the paper. The reviewer will not do any calculation during this phase. Stratified and subgroup analyses, and results of interaction analyses will be extracted (e.g. by sex, age group, smoking status, BMI category, alcohol intake level, etc.)

The reviewer should extract the results for each type of cancer (non-SCC, SCC, lung cancer site not specified, and indicate histological type if provided), for each gender, for each subgroup, in stratified and interaction analysis.

7.1 Study identifier

The CUP team will use the same labelling of articles used in the SLR process for the Second Expert Report: the unique identifier for an article will be constructed using a 3-letter code to represent the cancer site: LUN (lung cancer), followed by a 5-digit number that will be generated sequentially by the software during data extraction.

Figure 6. CUP interface. Example of screen for data entry.

7.2 Codification of exposures/interventions.

The exposures/interventions will be codified during data extraction as in the Second Expert Report. The main headings and sub-headings codes are in **Annex 2**. Wherever

possible, the reviewer will use the sub-heading codes. Additional codes have been programmed in the database to facilitate the data entry. The reviewer should also extract the description of the exposure/intervention definition in the free text box provided for that purpose in the data entry screen. The definition will be extracted as it appears in the paper.

The main headings for codification of the exposure groups are:

1. **Patterns of diet**, includes regionally defined diets, socio-economically defined diets, culturally defined diets, individual level dietary patterns, other dietary patterns, breastfeeding 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, vitamins, minerals, phytochemicals, nutrient supplements and other bioactive compounds
6. **Physical activity**, including total physical activity, physical inactivity and surrogate markers for physical activity.
7. **Energy balance**, including energy intake, energy density and energy expenditure.
8. **Anthropometry**, including markers of body composition, markers of body fat distribution, height and other skeletal measures, and growth in foetal life, infancy or childhood.

7.3 Codification of biomarkers of exposure

Biomarkers of exposure will be included under the heading and with the code of the corresponding exposure.

During the SLR for the Second Expert Report, some review centres opted for including in the review only biomarkers for which there was strong evidence on reliability or validity whereas other centres opted for including results on all the biomarkers retrieved in the search, independently of their validity. For the evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

However, since the identification and validation of other biomarkers is an expanding area (27), the CUP team will extract the data for all biomarkers of intake reported in the studies, independently of whether validity and reliability had been or not fully documented.

7. 4 Codification of outcomes.

The reviewer will indicate in the field: outcome type, whether the outcome is incidence or mortality and in outcome subtype, if the results are on lung adenocarcinoma, squamous cell carcinoma or lung cancer not specified.

7.5 Extraction and labelling of study results

The reviewer will extract the measures of association (RR estimates and confidence intervals) for the relevant exposures from all the statistical models shown in the paper, including subgroups, stratified analyses, interactions and sensitivity analyses. These results can be shown in tables, in the text or as supplemental information of the paper.

The reviewer should label the results as unadjusted, intermediately adjusted, or most adjusted model, depending on the models:

- Univariate models in the paper will be labelled "unadjusted".

- If the paper shows several multivariable models, the multivariable model with the highest number of covariables in the paper will be labelled "most adjusted".

- Other models in the paper that are not the "unadjusted" or the "most adjusted" model will be labelled "intermediately" adjusted.

In addition, the reviewer will indicate the "best model" for meta-analyses. The "best model" for meta-analysis will be the most adjusted model from the paper. In some papers, the researchers report models that include variables likely to be in the causal pathway of an exposure-outcome relationship. The purpose of these models is the exploration of possible mechanisms. When "mechanistic" models are reported, the "intermediately" adjusted result with the highest number of covariables will be indicated as "best model". The "mechanistic" model will be labelled as "most adjusted" model, but not as "best model" for meta-analysis. If there are enough papers with "mechanistic" models, these results will be meta-analysed independently of the "best models".

If a model is not adjusted for smoking and smokers are included in the study population, the results obtained with this model will not be labelled as "best model".

8. QUALITY CONTROL OF THE ARTICLE SELECTION AND DATA EXTRACTION.

A second reviewer at ICL will check the article selection and the data extraction. If there are discrepancies between the reviewers, the discrepancy will be discussed with the Principal Investigator.

9. DATA ANALYSIS

9.1 Meta-analysis

Dose-response meta-analyses will be conducted, such as in the SLR for the Second Report. The meta-analysis will include studies identified during the 2005 SLR and studies identified during the CUP SLR.

The meta-analyses will be conducted separately for:

- Small cell lung cancer, non- small cell lung cancer, lung cancers any histocytology or non-specified

- Incidence, mortality

- Men, women, both gender

- Smokers, ex-smokers, never smokers (or equivalent groups shown in the papers), smoking status not specified
- Geographic area, race or ethnicity, other sub-groups reported in the papers

When possible, the results of each study from a published pooled analysis will be included individually, instead of using the pooled result reported in the paper. The purpose is to look at heterogeneity across study results. The reviewers will check that the same study is not included twice in the meta-analysis. If this is not possible, meta-analyses will be conducted with and without the overall results of pooled analyses.

The measure of association for the highest vs. the lowest comparison for each study will be displayed graphically in forests plots, but a summary estimate will not be calculated, to avoid pooling exposure levels that are different across studies. However, categorical meta-analyses will be conducted for exposures categorised in two levels (e.g. breastfeeding categorised as yes vs. no, use of multivitamins categorised as yes vs. no).

Linear dose-response meta-analysis will be conducted to express the results of each study in the same increment unit for a given exposure. The results will be shown in a dose-response forest plot with the studies ordered by publication year, the most recent being on the top.

Non-linear dose-response meta-analyses will be conducted as exploratory analysis.

Table 2.Recommended increment units for meta-analyses.

Exposure	Increment unit
Total fruits and vegetables	100 g
Non starchy vegetables	100 g
Fruits	100 g
Citrus fruits	50 g
Red meat	100 g
Processed meat	50 g
Poultry	100 g
Fish	50 g
Eggs	25 g
Salt	1 g
Coffee	1 cup
Tea	1 cup
Alcoholic drinks	1 drink/day
Alcohol (as ethanol)	10 g
Dietary calcium	200 mg
Dietary fibre	10 g
Folate	100 μg
Blood selenium	10 μg/L
Alcohol from beer	10 g/day (approx. one drink)
Alcohol from wine	10 g/day (approx. one drink)
BMI	5 kg/m^2

Waist	2.5 cm (1 inch)
Waist-to-hip	0.1 unit
Height	5 cm
Physical activity	5 MET-h per week

9.2 Selection of exposures for a dose-response meta-analysis

A dose-response meta-analysis will be conducted when at least two new reports of trials or two news reports of cohort studies with enough data for dose-response meta-analysis are identified during the CUP and if there are in total five cohort studies or five randomised controlled trials. The minimum number of two studies was not derived statistically but it is a number of studies that can be reasonable expected to have been published after the Second Expert Report.

Where a particular study has published more than one paper on the same exposure, the analysis using the larger number of cases will be selected but if the most recent paper does not provide enough information for the dose-response meta-analysis, the previous publication will be used. The results section will indicate whether the reports of the same study are similar or not.

For comparability, the increment units for the linear dose-response analyses will be those used in the meta-analyses in the previous SLRs (**Table 2**). If most of the identified studies report servings, times, these will be used as increment unit.

9.3   Selection of results for meta-analyses

The results based on "best" adjusted models will be used in the dose-response meta-analyses. The linear dose-response estimates reported in the article will be used in the CUP dose-response meta-analysis. If the results are presented only for categorical data (quantiles or pre-defined categories), the slope of the dose-response relationship for each study will be derived from the categorical data.

9.4 Derivation of data required for meta-analyses.

The data required to derive the dose-response slope from categorical data are:

1. number of cases for each exposure category

2. person-years -or number of comparison individuals nested case-control analyses- for each exposure category

3. median, mean or cut-offs of exposure categories.

The information provided in the articles is often incomplete and this may result in exclusions of results from meta-analyses. In the SLR on lung and prostate cancers for the Second Expert Report, only 64% of the cohort studies provided enough data to be included in dose-response meta-analysis. There was empirical evidence that studies that showed a significant association were more likely to be usable in dose-response meta-analysis than studies that did not show any evidence of association (28)

The failure to include all available evidence will reduce precision of summary estimates and may lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations. To address the data

incompleteness, a number of approaches will be undertaken to derive the missing data from the available data where possible. The approaches are in **Table 3.**

Table 3. Approaches to derive missing information for meta-analyses in the CUP

Type of data	Problem	Approach
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR
	Standard error missing	Use p value (either exact or the upper bound) to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Confidence interval is missing	Use raw numbers of cases and person years (or controls in nested case-control studies) to calculate confidence interval (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group mean are missing	Estimate using the method of Chêne and Thompson (29) with a normal or lognormal distribution, as appropriate- detailed instructions are in the 2005 SLR Guidelines (30)- or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution (3-4 groups)
	Upper boundary for the highest category not reported	Assume that the boundary had the same amplitude as the nearest category
Category data	Numbers of controls (or the denominator in cohort studies) is missing	Derive these numbers from the numbers of cases and the reported odds ratios (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

Where the units of measurement differ between results, the units would be converted to a common scale. Where assumptions had to be made on portion or serving sizes the assumptions used in the WCRF/AICR Second Expert Report will be applied (4) (**Table 4**). For studies reporting intakes in grams/1000 kcal/day, the intake in grams/day will be approximated using the average energy intake per quantile reported in the article.

Table 4. List of conversion units

Item	Conversion of one unit
Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs	55g serving (1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc. soft & hot drinks	200ml serving
Meat & Fish	120g serving
Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	125ml serving

9.5 Statistical Methods

When not provided, the slopes of a dose-response relationship will be derived from categorical data using generalized least-squares for trend estimation (command GLST in Stata) (31). This method accounts for the correlation between relative risks estimates with respect to the same reference category (32). The dose-response model is forcing the fitted line to go through the origin and whenever the assigned dose corresponding to the reference group (RR=1) is different from zero, this is rescaled to zero and the assigned doses to the other exposure categories are rescaled accordingly.

The study specific log odds ratios per unit increase in exposure will be combined in a random effect model using the method of DerSimonian and Laird (33), with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model.

Publication and related bias (e.g. small study bias) will be explored through visual examination of funnel plots using precision $(1/SE(\beta))$ in the vertical axis and Egger's test egger (34). Funnel plots will be shown when there are at least five studies included in the analysis.

Heterogeneity between studies will be quantified with the I^2 statistic - where cut points I^2 values of 30%, and 50% (35). Mild heterogeneity might account for less than 30 per cent of the variability in point estimates, and notable heterogeneity substantially more than 50 per cent. Heterogeneity will be assessed visually from forest plots and with statistical tests (P value <0.05 will be considered statistically significant) but the interpretation will rely mainly in the I^2 values as the test has low power and the number of studies for some exposures will probably be limited.

Potential sources of heterogeneity will be explored by stratified analyses when the number of studies allows it (at least two studies in each stratum). The variables that will be explored as sources of heterogeneity are gender, smoking status, geographic area, level of control for confounder, publication year, length of follow-up. Meta-regression will be conducted if the number of studies allows it. The interpretation of stratified analysis should be cautious. If a considerable number of study characteristics are investigated in a meta-analysis containing only a small number of studies, then there is a high probability that one or more study characteristics will be found to explain heterogeneity, even in the absence of real associations.

Potential non-linear dose-response relationships will be explored using fractional polynomial models (36). The best fitting second order fractional polynomial regression model defined as the one with the lowest deviance will be determined. Non-linearity will be tested using the likelihood ratio test (37). The non-linear dose-response analyses will be conducted using a program prepared by D. Greenwood, statistical advisor of the project.

All analyses will be conducted in Stata/SE 12.1.

9.6 Sensitivity analyses

Sensitivity analyses will be carried out to investigate how robust the overall findings of the CUP are relative to key decisions and assumptions that were made in the process of conducting the update. The purpose of doing sensitivity analyses is to strengthen the confidence that can be placed in the results.

Sensitivity analyses will be done as a minimum in the following cases:

- Excluding studies that did not adjust for smoking or that did it very crudely (e.g. ever/never).
- Including and excluding studies where exposure level was inferred by the authors (for example assigning a standard portion size when this is not provided) or other missing information was derived from the data.
- Influence-analyses where each individual study will be omitted in turn in order to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies (38)

10. SYSTEMATIC LITERATURE REVIEW REPORT

An updated SLR report will be sent to the CUP Secretariat on January 30, 2015 for discussion in the Expert Panel.

The SLR report will include the following elements:

1. Modifications of the approved protocol
    Any modification required during the review will be described

2. Results of the search
    Flowchart with number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of papers included. The reasons for excluding papers should also be described.

3. Summary tables of studies identified in the continuous update
    Number of studies by study design and publication year.
    Number of studies by exposure (main heading and selected subheadings) and publication year
    Number of studies by exposure and outcome subtype

4. Tabulation of study characteristics

The tables will include study characteristics (e.g. population, exposure, outcome, study design) and main study results.

The tables will include the information required by the Panel to judge the quality of the studies included in the analyses (Newcastle –Ottawa quality assessment scale (39) for cohort studies and the Cochrane Collaboration's tool for assessing risk of bias (40)).

Example of table of study characteristics for cohort studies (in two parts below):

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

Assessment details	Category of exposure	Subgroup	No cat	RR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

5. Graphic presentation of individual studies

Tabular presentation will be complemented with graphic displays when two or more new studies have been published during the CUP. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of ''high versus low'' comparisons for each study. Dose-response graphs will be given for

individual studies for which the information is available. Funnel plots will be shown when there are at least four studies.

6. Results of the dose-response meta-analysis

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.

The results of meta-analysis will be presented in tables and forest plots. The tables will include a comparison with the results of the meta-analyses undertaken during the SLR for the Second Expert Report.

All forest plots in the report will have the same format. Footnotes will provide quantified information (statistical tests and I^2 statistics) on the degree of heterogeneity between the displayed studies.

Meta-regression, stratified analyses and sensitivity analyses results will be presented in tables and, if the number of studies justifies it, in forest plots.

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Annex 1. WCRF - PUBMED SEARCH STRATEGY

1) Searching for all studies relating to food, nutrition 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] 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 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] or bisphenol a[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] and (diet*[tiab] or food*[tiab])) OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[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] OR dietary acrylamide[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]) AND (diet*[tiab] or food*[tiab] or adipose [tiab] or blood[tiab] or serum[tiab] or plasma[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]

#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 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 phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab] OR lycopene[tiab]

#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[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]

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

#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[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] OR weight change [tiab] OR adiposity [tiab] OR abdominal fat [tiab] OR body fat distribution [tiab] OR body size [tiab] OR waist-to-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

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

#22 #20 NOT #21

2) Searching for all studies relating to lung cancer:

#23 lung neoplasm [MeSH Terms] OR (lung AND (carcinoma[tiab] OR neoplasm*[tiab] OR tumor*[tiab]))

3) Searching for all studies relating lung cancer, and food, nutrition and physical activity:

#24   #22 AND #23

Annex 2. LIST OF HEADINGS AND EXPOSURE CODES (minimum list)

Indicates codes added during the CUP

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.

1.6   Breastfeeding

1.6.1   Mother

Include here also age at first lactation, duration of breastfeeding, number of children breast-fed

1.6.2   Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever

possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7 Other issues

For example, results related to meal frequency, frequency of snacking, dessert-eating and breakfast-eating 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

* 2.1.2.1 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, e.g. salted root vegetables (i.e. 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, please report under a separate heading.

2.5   Meat, poultry, fish and eggs

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

2.5.1   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 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.

2.5.1.3 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.

2.5.1.4 Poultry

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

*2.5.1.5 Offals, offal products (organ meats)

2.5.2   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

2.9   Composite foods

E.g., snacks, crisps, desserts, pizza. Also, report any mixed food exposures here i.e. if an exposure is reported as a combination of 2 or more foods that cross categories (e.g. 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

3.3   Milk

For results concerning milk, please report twice, here and under 2.7 Milk and Dairy Products.

3.4   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 precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.

*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
3.6.2   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   Mate
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

4.2.7.1.1 Cured meats
4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, lung and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-*nitrososamines should also be covered here.*

4.3   Processing

4.3.1   Refining

Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.

4.3.2   Hydrogenation

Results concerning hydrogenated fats and oils should be reported twice, here and 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

4.3.5.1 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

4.4.1.1 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 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.

1   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 Glycaemic index, glycaemic load

This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and 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

5.5.2   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 e.g. genistein
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'. E.g. 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

*6.1.4.1Duration of occupational physical activity
*6.1.4.2Duration of recreational physical activity

6.2   Physical inactivity
6.3   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

1.1.1 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 foetal life, infancy or childhood

8.4.1   Birthweight
8.4.2   Weight at one year