Continuous update of the epidemiological evidence on food, nutrition, physical activity and the risk of breast cancer.

Protocol: Breast Cancer

Prepared by: Imperial College Team

The current protocol for the continuous update should ensure consistency of approach to the evidence, common approach to the analysis and format for displaying the evidence used as in the literature reviews for the Second Expert Report.

The starting point for this protocol are:

- The judgement of the Panel of the WCRF-AICR Second Expert Report on the evidence of the relationship of food, nutrition, physical activity and breast cancer (Second Expert Report Part 2 Chapter 7.10 pp 289).
- The convention for conducting systematic reviews developed by WCRF International for the Second Expert Report (SLR Specification Manual –version 15).
- The protocol developed by the SLR group on breast cancer for the Second Expert Report (National Cancer Institute, Milan, Version October 29, 2004).

The protocol will represent the agreed plan for the Continuous Update. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed by the Continuous Update Panel (CUP) and the reasons documented.

Judgement of the Panel of the WCRF-AICR Second Expert Report:

The following summary has been extracted from the WCRF-AICR Second Expert Report:

CANCER OF THE BREAST (PREMENOPAUSE)
In the judgement of the Panel, the factors listed below modify the risk of cancer of the breast (premenopause). Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks
Probable	Body fatness	Adult attained height[1] Greater birth weight
Limited –suggestive	Physical activity[2]	
Limited –no conclusion	Cereals (grains) and their products; (grains) and their products; potatoes; vegetables; fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; fats and oils; vegetable fat; sugar; sugary foods and drinks; milk and dairy products; coffee; tea; carbohydrate; starch; dietary fibre; sugars; total fat; fatty acid composition; *trans*-fatty acids; cholesterol; protein; vitamin A; carotenoids; folate; riboflavin; vitamin B6; cobalamin; vitamin C; vitamin D; vitamin E; iron; calcium; selenium; isoflavones; dieldrin; *trans*-nonachlor; dichlorodiphenyltrichloroethane; dichlorodiphenyldichloroethylene; polychlorinated biphenyls; hexachlorocyclohexane; hexachlorobenzene; energy intake; adult weight gain; adult attained height; dietary patterns; culturally defined diets; glycaemic index; and being breastfed.	
Substantial effect on risk unlikely	None identified	

CANCER OF THE BREAST (POSTMENOPAUSE)
In the judgement of the Panel, the factors listed below modify the risk of cancer of the breast (postmenopause). Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks Body fatness Adult attained height[1]
Probable	Physical activity[2]	Abdominal fatness Adult weight gain
Limited –suggestive		Total fat
Limited –no conclusion	Cereals (grains) and their products; potatoes; vegetables and fruits; pulses; soya and soya products; meat; poultry; fish; eggs; fats and oils; sugar; sugary drinks and foods; milk and dairy products; coffee; tea; carbohydrate; starch; dietary fibre; vegetable fat; fatty acid composition; cholesterol; protein; vitamin A and carotenoids; riboflavin; vitamin B6; vitamin B12; folate; vitamin C; vitamin D; vitamin E; isoflavones; iron; calcium; selenium; dieldrin; *trans*-nonachlor; dichlorodiphenyltrichloroethane; dichlorodiphenyldichloroethylene; polychlorinated biphenyls; hexachlorocyclohexane; hexachlorobenzene; energy intake; birth length; culturally defined diets; dietary patterns; glycaemic index; being breastfed; and birth weight.	
Substantial effect on risk unlikely	None identified	

Extent of the continuous update.

The extent of the update has to be adequate to time and resources. The determination of priorities for the update will be based on:

- **Study type**
- **Grade of evidence of the association of exposures with breast cancer**
- **Recommendations from the CUP and the ICL team**

Study type: the study types that will be included in the update are:

- Randomized controlled trial
- Group randomized controlled trial (Community trial)
- Prospective cohort study
- Nested case-control study
- Case-cohort study
- **Population based case-control study with more than 1000 cases**

Factors: In this initial phase the ICL team will update the factors for which the strength of the evidence of association to breast cancer was graded as convincing, probable, limited-suggestive and limited –no conclusion by the Panel of **Second WCRF-AICR Expert Report. :**

- **Lactation**
- **Greater birth weight**
- Adult attained height
- **Alcoholic drinks**
- Body fatness
- Abdominal fatness
- Adult weight gain
- Physical activity
- **Total fat intake**

1. Research question

The research topic is:

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

2. Review team

Name	Current position at ICL	Role within team
Teresa Norat	Research Fellow	Principal investigator
Rui Veira	Data manager	Responsible of the data management, the design and architecture of the database
Doris Chan	Research Assistant	Nutritional epidemiologist, reviewer

3. Timeline

The update will include the articles added to Medline after January 1st 2006. The review for the Second Expert Report ended in December 30th 2005. A pre publication update extended the search to May 30th 2006 for exposures and cancer sites with suggestive, probable, convincing associations with the exposure of interest.

Task	Deadline
Preliminary output from search strategy	1st July, 2007
Review abstracts and citations identified in initial electronic search. Select papers for complete review	1st August, 2007
Review relevant papers. Select papers for data extraction*	15 September, 2007
Data extraction	30 December, 2007
Production of preliminary tables	30 January, 2007
Production of tables.	March 30, 2007
Preparation of forrests plot with relevant data	
Preparation of report to WCRF-AICR	April 15, 2007
Transfer copy of database, Endnote files to WCRF	April 15, 2007

** It is intended to continue tasks 1, 2, 3 with a monthly periodicity*

4. Search strategy

The WCRF-PubMed search strategy and search terms used in the SLR for the Second Expert Report will be the core for this literature search.

5. Selection of articles:

5.1 Inclusion criteria

The articles to be included in the review:

- **Have to be included in Medline after January 1st 2006 (closure date of the database for the Second Report).**
- Have to present results from an epidemiologic study of one of the following types:
    - Randomized controlled trial
    - Group randomized controlled trial (Community trial)

- Prospective cohort study
- Nested case-control study
- Case-cohort study
- Population based case-control study with more than 1000 cases
-

- Must have as outcome of interest breast cancer (*in situ*, invasive) incidence or mortality in women.
- Have to present results on the relevant exposures
- Published in English language
- Included in Medline

5.2 Exclusion criteria

The articles to be excluded from the review:

1. Are out of the research topic
2. Do not report measure of relationship
3. The measure of relationship is only the mean difference of exposure
4. Are supplement to the main manuscript (e.g. Authors' Reply).
5. Are in-press
6. Are not in English language

Pooled analysis will be used as support for interpretation, but the data will not be included in the database.

6. Exposures

The continuous update will use the same labels as used in the SLR for the Second Expert Report.

Surrogate exposures of diet at early age, such as attained height at age at menarche and height velocity, have been included as exposures in the database during the SLR for the Second Expert Report and will be included in the continuous update.

Biomarkers of dietary intake was coded under the Main exposure corresponding to the dietary exposure and specified in a sub-exposure. We propose to use the same list of biomarkers used by the SLR teams of Bristol and Leeds (Attachment 1).

7. Outcome

The outcome of interest is breast cancer encompassing incidence and mortality (except for case-control studies, for which the outcome of interest is incidence). Separate analyses for incidence and mortality will be provided.

The information of all the papers reporting outcome for more than one cancer site, will be extracted and the information inputted in the database.

8. Databases

Only the Medline database will be searched. Data provided from the SLR Breast cancer for the Second Expert Report indicates that 95% of the articles included in the review have been retrieved from the Medline database (See Apendix 2).

9. Hand searching for cited references

For feasibility reasons, journals will not be hand searched in the continuous update.

However, hand searching, and searching in other databases should be done when a formal meta-analysis will be done after recommendation of the CUP.

10. Retrieving papers

The abstracts from the initial search results from PubMed will be reviewed by one person to assess each reference as to whether it is relevant and potentially relevant.

Complete papers will be retrieved for all relevant and potentially relevant references, and for references that cannot be excluded upon reading the title and abstracts.

A second assessment will be done after review of the complete papers.

The ICL team uses resources at Imperial College to retrieve the papers identified as satisfying the inclusion criteria. This should cover most of the online journal. For articles not accessible through the ICL library, funds provided by WCRF-AICR will be required.

The assessment of trials and cohort studies will be checked by a second reviewer.

11. Labelling of references

For consistency with the previous data collected during the SLR process for the Second Expert Report, the Imperial College team will use the same labelling of references: the unique identifier for a particular reference will be constructed using a 3-letter code to represent the cancer site (e.g. BRE for breast cancer), followed by a 5-digit number that will be allocated in sequence.

12. Reference Manager files

Reference Manager databases are generated in the continuous update containing the references of the initial search.

1) One of the customized fields (custom 1) is named ‘inclusion’ and this field is marked ‘in’, ‘out’ for each paper, thereby indicating which papers are deemed potentially relevant based on an assessment of the title and abstract.
2) One of the customized fields (custom 2) is named ‘reasons’ and this field should include the reason for exclusion for each paper.
3) The study identifier should be entered under the field titled ‘label’.

4) One of the customized fields (custom 3) is named "study design". This field should include a letter (A-Q) representing the study design of each paper.

13. Data extraction

Ideally, data extraction should be performed in duplicate for all papers. This is not feasible with the available resources. Instead, the extracted data of 10% of the prospective cohort studies and trials in the database will be checked by a second reviewer at Imperial College.

The ICL team will update the merged MySQL database using a new interface created at Imperial College. This contains the same fields included in the Access database for the SLR for the Second Expert Report, including quality characteristics and results.

The study design algorithm devised (SLR specification manual –version 15) for use of the SLR centres for the Second Expert Report will be used to allocate study designs to papers. In some cases it will be appropriate to assign more than one design to a particular paper because the methods for assessment of different exposures may vary, because the data analyses correspond to more than one study design (e.g. analyses in the entire cohort and nested case-control).

Important overall aspects of the study that need attention are the strategy of analysis, the variables for which the exposure – disease association was adjusted for, the information given on the validity of the measurements and whether analyses were performed that attempted to correct for the likely effect of measurement error in the exposure variable. These variables were programmed in the Access database and are included in the MySQL database used by the continuous update by the ICL team.

The effect measures estimated with all the models reported in the paper should be extracted. The models should be labelled as not adjusted, minimally adjusted and intermediately adjusted. In addition, the ICL reviewer should indicate a "best model" for inclusion in reports. Where the same exposure was analyzed in more than one way with different levels of adjustment, the best model was taken to be the one with the most appropriate adjustment for confounding. Sometimes, some of the potential risk factors are not kept in the model because its inclusion does not modify the risk estimates. This model should also be considered the "best model". The most appropriate model should adjust for:

- Age
- Socio-economic status, educational attainment
- Alcohol intake
- Anthropometric variables (BMI, weight, height, WHR)
- Total energy intake (if exposure is a dietary variable)
- Menstrual characteristics (including age at menarche, menopausal status, age at menopause, among others)
- Reproductive and hormonal factors (including parity, HRT use, OC use)

- Genetic factors (e.g. family history)
- Previous breast disease
- Factors related to laboratory determinations (e.g. batch)

In relation to effect modification, the ICL team should report whether interaction terms were included in models and extract the results, in particular any statistical tests of heterogeneity across strata.

Data should also be abstracted for sub-groups corresponding to the list of potential effect modifiers. Where the data permit, the following sub-groups must be reported:

- Age
- Obesity
- Physical activity
- Oral contraceptive use
- Menopausal status
- Hormone replacement therapy
- Ethnicity
- Family history
- Smoking
- Genetic polymorphism
- Blood levels of nutrients/hormones

Data should be extracted for each individual paper, even if there is more than one from any one study, unless the information is identical. The extracted information should only be used once per analysis. To facilitate the detection of multiple reports from the same study, the study name in each article should be extracted .

If needed, the CU team should contact the authors to confirm, refute these suspicions. If the matter remains unresolved the coordinator of the continuous update will then seek advice from the CUP if necessary.

14. Reports

14.1 Content of the report:

Results of the search

Information on number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of included relevant papers. The reasons for excluding papers should also be described.

Description of studies identified in the continuous update

Amount of data and study types (i.e. numbers of different types of studies)
Populations studied
Exposures identified
Outcomes identified

Summary of number of studies by exposure and study type, separated on new (studies identified in the continuous update) and total.

14.2. Tabulation of study characteristics

Information on the characteristics (e.g. population, exposure, outcome, study design) and results of the study (e.g. direction and magnitude) of the new studies should be summarised in tables using the same format as for the SLR for the Second Expert Report.

Within this table the studies should be ordered according to design (e.g. trials, cohort studies, case-control studies).

The results will be presented separately for premenopausal and postmenopausal breast cancer. Studies that did not differentiate pre and post menopausal breast cancer will be analyzed separately in the meta-analyses.

14.3 Data analysis

A meta-analysis for a particular exposure and outcome will be conducted when more than 2 trials or 2 cohort studies or 3 case-control studies has been published in the year, and if the new and the previous results totalize more than 3 trials, 5 cohort studies or 5 case-control studies.

The meta-analysis will include also the study results extracted during the SLR and included in the merged database. Special care will be taken to avoid including more than once the results of the same study (e.g. previous analyses and re-analyses after a longer follow-up).

Results of pooled analyses will be presented to the CUP to support the evaluation, but they will not be included in the meta-analyses.

The first stage of the analysis will be to investigate whether any variations in estimates of effects exist between studies. Forest plots will be used to assess and display heterogeneity. These should be presented in the report using the standard format for the presentation used in the SLR for the Second Expert Report. Heterogeneity will be formally assessed by using the I^2 statistic.

If sufficient homogeneity exists, an overall summary of effect should be determined. If there is significant heterogeneity, it should be characterised as clearly as possible. If possible meta-regression should be performed to investigate sources of heterogeneity.

The list of characteristics to be explored as possible causes of heterogeneity is:

Method of measurement, assessment of the exposure

Definition of exposure

Exposure range

Adjustment for confounders

Age at recruitment

Duration of follow-up

Geographical region

Outcome

Study design

From this identification, it may be possible for studies to be grouped according to a particular characteristic and separate analysis performed within each sub-group.

Meta-regression analysis will be used when appropriate and possible. In addition, sensitivity analysis and influence analyses could be done when possible and appropriate.

Summary estimates should be prepared for each study design separately but not combined, and these should be displayed on the same forest plot. The studies should be ordered by study design: randomised controlled trials, cohort and then case-control studies.

Formal quality grading should not be performed on an individual study basis. Instead, study characteristics (such as aspects of study design, methods of exposure assessment etc.) will be used to explore potential sources of bias and the robustness of conclusions. This approach has the following uses:

1) To explore the reasons for heterogeneity in study results

2) To guide interpretation of findings and to aid determining the strength of inferences

3) To guide recommendations for future research

The recommended method for presenting the results of the meta-analyses is in terms of *log, per unit increase in exposure*. If it is not possible, the meta-analyses will summarize the comparison of extreme categories. The analyses will be conducted using STATA.

Appendix 2 Search Strategy

WCRF - PUBMED SEARCH STRATEGY (with modifications implemented by the SLR centre Milan)

a) Searching for all studies relating to breast cancer:

#1 Breast Neoplasms [MeSH Terms]

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

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

#4 #1 OR #2 OR #3

b) Searching for all studies relating to food, nutrition and physical activity:

#5 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]

#6 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]

#7 body composition[MeSH Terms] OR body constitution[MeSH Terms] OR growth[MeSH Terms] OR anthropometry[MeSH Terms] OR physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

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

#9 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] OR iron[tiab] OR calcium[tiab] OR selenium[tiab] OR iodine[tiab] 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]

#10 vitamins[MeSH Terms]

#11 salt[tiab] OR salting[tiab] OR salted[tiab] OR fibre[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 diet*protein*[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#12 dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR sweetening agents[MeSH Terms]

#13 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] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab]

#14 cookery[MeSH Terms]

#15 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]

#16 food preservation[MeSH Terms]

#17 diet therapy[MeSH Terms] OR nutrition[MeSH Terms] OR Food Habits[MeSH Terms] OR Micronutrients[MeSH Terms]

#18 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]

#19 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] OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#20 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] 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] OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR oils[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 Potato*[tiab] OR Cabbage*[tiab] OR Brassica[tiab] OR Cruciferous[tiab] OR Radish[tiab] OR Carrot*[tiab] OR Lettuce*[tiab] OR Spinach[tiab] OR Onion*[tiab] OR Tomato*[tiab] OR Soybean[tiab]

#21 food and beverages[MeSH Terms]

#22 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] OR breastfeed*[tiab] OR breast feed*[tiab] OR breastfed[tiab] OR breast fed[tiab] OR breastmilk[tiab] OR breast milk[tiab] OR Lactose[tiab] OR Galactose[tiab] OR Cheese[tiab] OR Sausage[tiab] OR Ham[tiab]

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

#24 #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 OR #20 OR #21 OR #22 OR #23

Combining searches on breast cancer (a) and searches on all studies relating to food, nutrition and physical activity (b):

#4 AND **#24**

Appendix 3 Exposure codes

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 diet diversity, 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 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, lentiles

*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 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.

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

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

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 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

4.2.7.1.1 Cured meats

4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, stomach 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 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

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 eg 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'. 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

*6.1.4.1Duration 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

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