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Meta-Analyses Including Observational Studies in the Field of Nutrition: a Methodological Systematic Review

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Abstract

Objective: To systematically assess the methods used and the reporting quality in the systematic reviews with meta-analyses (MA) including at least one observational study focusing on the impact of nutritional intervention on cancer.

Design: Methodological systematic review.

Data sources: Medline via PubMed, searched from 20 February 2010 to 21 February 2015, on 5th March 2015.

Review methods: All meta-analyses including at least one observational study evaluating nutritional intervention that focused on cancer were included in the review. We assessed general characteristics and the reporting and conduct of key methodological components for systematic reviews and meta-analyses.

Results: 115 MA were included. Grey literature was searched in 2.6% MA. Methodological quality/risk of bias was assessed in 44.3% MA. Reporting bias was assessed in 92.1% MA. 74.8% MA used adjusted estimates (of primary included studies) on confounding in the MA. Heterogeneity was assessed in 98.2% MA, and explored by subgroup and sensitivity analysis in 94.7% MA.

Conclusion: In total, we assessed 115 MA including observational studies in a variety of medical areas for key methodological components. Our results highlight some important methodological deficiencies. We found that in more than half of the MA, the methodological quality/risk of bias was not assessed. The most of the MA did not search for grey literature. Future development and standardization of the methods for conducting MA including observational studies are necessary.

Key words: “observational”, “non-randomized”, “systematic review”, “meta-analyses”, “diet”, “dietary”, “nutrition”, “food”, “daily intake”.

Résumé

Objectif : Evaluer systématiquement les méthodes utilisées et la qualité de rapport dans les revues systématiques avec méta-analyses (MA), incluant au moins une étude observationnelle sur l’impact de l’intervention nutritionnelle sur le cancer.

Design : Revue systématique méthodologique.

Données: Medline via PubMed, recherché du 20 février 2010 au 11 février 2015, le 5 mars 2015.

Méthodes : Toutes les méta-analyses incluant au moins une étude observationnelle évaluant l’intervention nutritionnelle sur le cancer ont été incluses dans la revue. Nous avons évalué les caractéristiques générales, les rapports et la conduite des composantes méthodologiques essentielles pour les revues systématiques et les méta-analyses.

Résultats : 115 MA ont été incluses. La littérature grise a été recherchée dans les 2.6% méta-analyses. La qualité méthodologique / risque de biais, a été évalué dans les 44.3% de MA. Le rapport de bias a été évalué dans les 92.1% de MA. Les 74.8% de MA a utilisé l’estimations ajustées (de première revue inclue) sur le confondant dans le MA. L’hétérogénéité a été évaluée dans les 98.2% de MA, et exploré par le subgroup et l’analyses de sensibilité dans les 94.7 % de MA.

Conclusion : Au total, nous avons évalué 115 MA incluant les études observationnelles dans une variété de domaines médicaux pour les composants méthodologiques clés. Nos résultats mettent en évidence certaines déficiences méthodologiques importantes. Nous avons constaté que dans plus de la moitié de méta-analyses, la qualité méthodologiques /risque de bias n’a pas été évaluée. La plupart des MA n’a pas recherché pour la littérature grise. Le développement futur et la standardisation des méthodes de réalisation de méta-analyses incluant des études observationnelles sont nécessaires.

Mots clés: “observational”, “non-randomized”, “systematic review”, “meta-analyses”, “diet”, “dietary”, “nutrition”, “food”, “daily intake”.

List of abbreviations

BOUTRON Isabelle	IB
FAB Timor	TF
GU Linaer	GL
Meta-analyses	MA
Randomized controlled trial	RCT

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1. Introduction

In the field of Evidence Based Medicine (EBM), a hierarchy of grades of evidence exists based on the research design, with internal validity being the overarching criterion for this hierarchy [1]. Systematic reviews (SRs) have become increasingly popular in medicine. Clinical practice guideline developers use them as a starting point for guideline development. Granting agencies require them as an evidence base for the need to conduct new research [2] [3], and healthcare journals are moving in the same direction [4].

It is known that dietary food intake is associated with human health, such as meat intake, fruit and vegetable intake, dietary fiber intake, and dietary supplements (calcium, folic acid, magnesium, etc). Cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 [5]. There is evidence pointing to a possible role of diet on cancer etiology [6]. For example, previous studies suggested a potential link between a high intakes of meat, in particular red meat and processed meat, and the risk of several types of cancer including colorectal, stomach, breast, and prostate cancers [7]. An example for supplements, high vitamin D status is weakly associated with low breast cancer risk but strongly associated with better breast cancer survival [8].

Systematic reviews and meta-analyses are essential tools for summarizing evidence accurately and reliably. They help clinicians keep up-to-date; provide evidence for policy makers to judge risks, benefits, and harms of health care behaviors and interventions; gather together and summarize related research for patients and their careers; provide a starting point for clinical practice guideline developers; provide summaries of previous research for funders wishing to support new research [9].

Systematic reviews of randomized controlled trials are considered to be the highest quality scientific evidence regarding the effectiveness of healthcare interventions [8], because this study design minimizes bias [11] [12].However, in some situations RCTs are not feasible due to ethical concerns or due to strong patients' preferences and the results may not be applicable to everyday practice [13] [14], and only data from observational studies are available [15] [16]. Some nonrandomized studies are designed to evaluate effectiveness and may show that interventions will work under every day circumstances, for example in a general practice [14] [17]. Observational studies are the overarching term for all non-experimental non-randomized studies including cohort, case-control, and cross-sectional studies [18]. Observational studies have several advantages over randomized, controlled

trials, including lower cost, greater timeliness, and a broader range of patients [19] [20], and they are used primarily to identify risk factors and prognostic indicators and in situations in which randomized, controlled trials would be impossible or unethical [21].

Due to this lack of consensus and guidance on how to conduct systematic reviews with meta-analyses including observational studies, it is unknown whether such reviews that are published indeed use the best available methods. If observational studies with poor quality are included, or if the methods conducting the meta-analysis are inadequate, this has serious implications in the use of these systematic reviews for decision-making. Therefore, it is important to explore and review the methods used in systematic reviews with meta-analyses that include observational studies that focusing on the impact of nutritional intervention on cancer.

2. Methods

1) Study design

We performed a methodological systematic review to assess whether the key methodological components of meta-analyses of including observational studies have been reported adequately.

2) Search strategy

The electronic database that was used to conduct the search was MEDLINE (accessed via PubMed). Sample of systematic reviews and meta-analysis indexed in PubMed.

We are interested in the systematic reviews of nutrition evaluation that have conducted a meta-analysis including data from at least one observational study. This means that both meta-analyses of only observational studies and a mixture of observational studies and RCTs will be considered.

The actual search strategy included the key words alone or in combination for design of the included studies (“observational”, “non-randomized”, “non-randomised”, “cohort”, “case-control”, “cross-sectional ”, and Mesh terms “cohort studies”, “case-control studies”, “cross-sectional studies”) with keywords for systematic reviews and meta-analyses (“Systematic review”, “Systematic reviews” , “meta-analysis”, “meta-analyses”) with keywords for in the field of nutrition (“diet”, “dietary”, “nutrition”, “food”, “foods”, “nourishment”, “meal”, “daily intake”, “eating behavior”, “feeding behavior”, and Mesh terms “diet”, “dietary supplements”, “diet therapy”, “nutritional requirements”, “food, formulated”) (Appendix 1) on 5 March 2015,

we conducted the search on Medline via PubMed and restricted the search between 20 February 2010 and 21 February 2015 published in English.

As only published systematic reviews were of interest for this study, no actions were taken to identify unpublished reviews.

3) Eligibility criteria

Systematic reviews published between 20 February 2010 and 21 February 2015 with meta-analyses that included data from at least one observational study in the field of nutrition and the outcome is cancer/carcinoma were eligible for inclusion.

A systematic review was defined as the authors refer to article as “systematic review” either in title, abstract, or in the main text. Otherwise, the authors seek to identify all relevant evidences by systematically search the databases. A meta-analysis was defined as the statistical pooling of results from more than one study. The exposure is nutrition that included food and supplements, the outcome is cancer/carcinoma.

Meta-analyses were excluded if the study is an updated systematic review with meta-analyses. Meta-analyses were excluded if the exposure is not food or vitamin intake, but just the circulating levels in the body. We also excluded network meta-analysis and economical meta-analysis. Meta-analyses published in any languages other than English, and meta-analyses for which the full-text not available were excluded.

The reviewers decided to include the studies that when exposures are nutrition intake and circulating levels of nutrition. We just analyzed the meta-analyses that describe the association between the nutrition intake and the outcomes. To illustrate: Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis (ID: 37).

4) Study selection

The selection of meta-analyses was conducted in two steps which are screening based on titles and abstracts at the same time and screening by full-text.
In the first step, one reviewer (GL) screened the studies based on titles and abstracts through ReSyWeb (A unique web service to facilitate the study selection process in systematic reviews from Cochrane). If it is unclear based on the titles and abstracts whether the paper should be included, the full paper were retrieved and screened for full-text review.
In the second step, one reviewer (GL) screened all the studies by full text, another reviewer (TF) independently screed 40 (30%) MA. Any discrepancies or ambiguity in inclusion

discussed and resolved among the authors (IB, TF, and GL).

5) Data extraction

To systematically assess the methodology of the included papers, a data extraction form was developed for the purpose of the review. This data extraction form contained items for the general characteristics of the paper, introduction of the paper, items of the methods for conducting the systematic review and meta-analysis. The items for the methods was taken from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement) and as well as the AMSTAR measurement tool for assessing the methodological quality of systematic reviews, as well MOOSE guidelines for meta-analyses and systematic reviews of observational studies.
The data extraction form was piloted by two reviewers (TF, GL) on five papers to test for the consistency.

The following characteristics were extracted from the full text of the each meta-analysis:

- *General information:*
  We collected the publication year, whether the journal was a specialized journal or a general journal, the medical area (type of cancer), type of the intervention. We assessed whether the authors reported the funding sources.

- *Introduction of MA:*
  We assessed whether the meta-analyses have a protocol, and whether the study registered in PROSPERO. We assessed whether the author clearly define the intervention, and primary outcomes. We assessed whether the authors justified the inclusion of observational studies. Number of studies included: We collected the number of total included studies, the median number of the total included studies, the number of observational studies, and the number of RCTs in the meta-analysis. We collected the number of studies included only observational studies, and both observational studies and RCTs. We also collected the design type of observational studies.

- *Systematic review methods:*
  - Search strategy:
    We assessed the number and the type of electronic databases were searched, (e.g. MEDLINE (via PubMed), EMBASE, CENTRAL, DARE, Google Scholar). We also collected whether the authors searched for grey literature, and if yes, we

collected the type of grey literature search of registries, conference abstracts, contacting experts, or contacting with the authors of unpublished studies. We assessed whether the authors reported on date (or time period) of the search done in their search strategy. We also assess whether the search strategy available.

- Study selection process:
  We assessed whether study selection was conducted in duplicate. We assessed whether the meta-analysis included a table of characteristics of the included studies and a study selection flow chart (or clear description) with excluded reasons. We also assessed whether the study have a language restriction (in the search and selection), for example, no restriction and all languages are included for inclusion or only English papers are included.

- Data extraction:
  We assessed whether the data extraction was done in duplicate. We also assessed whether the authors attempt to contact the authors of the included studies for clarification or additional results.

- Methodological quality/ risk of bias assessment:
  We assessed whether methodological quality/risk of bias assessment was conducted, and we collected information on the tools used for this assessment. (e.g. ROB, Newcastle-Ottawa Scale (NOS), RTI item bank, and Downs&Black). We assessed whether the results of the risk assessment reported for each study. We also assessed whether the authors discussed the methodological quality/risk of bias assessment.

- *Meta-analysis methods:*
  - Meta-analysis model:
    We collected whether the estimates were reported to be crude or adjusted, both crude and adjusted separately, or the authors combined crude and adjusted estimates. We also collected whether the confounding factors adjustment reported.

  - Studies combined:

We assessed whether the meta-analysis combine the results of observational studies and RCTs, and whether combined the results of observational studies of different design type.

- Heterogeneity assessment:
  We assessed whether the authors assessed heterogeneity and if yes, whether the authors conducted subgroup, or sensitivity analysis. We also assessed how the authors assessed subgroup or sensitivity analysis, for example by study design, risk of bias, type of intervention, type of outcomes, or by leave-one-out method.

- Reporting bias assessment:
  We assessed whether the authors assessed reporting bias, and how the assessed by Funnel plot, Egger regression test, Hedges-Olken, or Begg's rank correlation test. We also assessed whether the authors discussed the likelihood of publication bias

6) Analysis

The analysis of the data consisted of descriptive statistics, mostly only for qualitative variable, providing with the numbers and percentages for qualitative variables. For quantitative variables, we did not do that much analysis, just one variable (the number of included studies in the MA) provided the median number. The statistical analysis was performed on STATA version 12.

3. Results

1) Study selection (Figure 1)

The study selection process is reported in **Figure 1**. The Medline search resulted in 1266 citations on 5 March 2015.

The first step of the study selection resulted in 1215 citations after eliminating 51 citations in the ReSyWeb by deduplication step. In the second step, 353 citations were selected and 862 citations were excluded based on titles and abstracts review, reasons being “Not a meta-analysis” (n=275), “Not in the field of nutrition” (n=528), “No observational studies” (n=46), “Network meta-analysis” (n=1), “Economical meta-analysis” (n=3), and “Exposure is not nutrition intake”(n=1). In the third step, 130 citations were selected and 223 citations were excluded, reasons being “Not in the field of nutrition” (n=2), “Updated meta-analysis” (n=14),

"Not about the cancer" (n=203), "Not in English" (n=2), and "Not available full text" (n=2). In the last step, 115 meta-analysis were included and 15 citations were excluded, reasons being "Not a systematic review" (n=10), "Not a meta-analysis" (n=1), "Exposure is not nutrition intake" (n=2), "No observational studies" (n=1), "Nutrition in the circulating level" (n=1).

In total 115 meta-analyses were included for assessment in this methodological review. The complete list of included studies is in **Appendix 3**.

2) General characteristics (Table 1)

In the 115 included meta-analyses, most of them were published in specialized journals (n=98, 85%). The meta-analyses covered many different medical areas, with (n=51, 44.3%) being gastrointestinal cancer, (n=24, 20.8%) in breast cancer, and (n=11, 9.6%) in prostate cancer.

The type of intervention, the intervention of 102 meta-analyses (82.3%) is food in general, 19 meta-analyses (15.3%) is specific nutrition supplement, and 3 meta-analyses (2.4%) is other in 115 meta-analyses.

Funding sources, more than half meta-analyses (n=63, 54.8%) reported having the funding. 52 meta-analyses (45.2%) were not having the funding or not reported the funding.

3) Introduction (Table 2)

A systematic review protocol was reported to be used in 17 meta-analyses (14.8%) of 115 meta-analyses. Systematic review registered in PROSPERO reported in 1 (0.8%) of all the meta-analyses.

The authors clearly defined the interventions (n=65, 56%), and primary outcomes in 105 (91%) of all the meta-analyses. The authors justified the inclusion of observational studies reported in 14 (12.2%). The number of the included studies reported more than 10 (n=94, 81.7 %) in the meta-analyses. The median number of the total included studies is 16. The number of meta-analyses that included only observational studies reported (n=111, 96.5%), included both RCTs and observational studies reported (n=4, 3.5%). The meta-analyses included cohort studies (n=106, 92.1%), case-control studies (n=77, 66.9%), nested case-control studies (n=16, 13.9%).

4) Systematic reviews (Table 3)

- *Search strategy*

All of the meta-analyses reported have searched at least 1 electronic database, and (n=55, 47.8%) searched more than 2 electronic databases. Medline and Embase were most frequently used (n=112, 97.3 %), (n=73, 63.4%), respectively. Only three of the meta-analyses (n=3, 2.6%) reported to have searched for grey literatures, and all of three is contacting with experts. The most meta-analyses (n=103, 89.5%) reported the date (or the time period) of search strategy for inclusion studies. One-third of the meta-analyses (n=74, 64.3%) reported available search strategy.

- *Study selection*

Study selection was reported be done in duplicate in 52 meta-analyses (45.2%). About one-third meta-analyses (n=41, 35.6%) reported to have searched with no language restriction, and (n=49, 42.6%) meta-analyses reported only for studies written in English. 19 of meta-analyses (16.6%) are not reported of language restriction. The most of the studies included a table with the study characteristics (n=109, 94.7%), and a study selection flow chart (n=85, 73.9%).

- *Data extraction*

In total, 75 meta-analyses (65.2%) reported to have done data extraction in duplicate, 9 meta-analyses (7.8%) are reported contacted the authors of the included studies for clarification or additional results.

- *Assessing risk of bias*

Methodological quality/risk of bias assessment was reported in 51 of the meta- analyses (44.3%), and for which 33 meta-analyses (64.7%) were reported assessed by Newcastle-Ottawa Scale (NOS), for which 1 meta-analysis (1.9%) were reported assessed by Downs and Black Instrument, for which 15 meta-analyses (29.4%) were reported assessed by Other Scale, and for which 4 meta-analyses (7.8%) were unclear about how they assessed the methodological quality/risk of bias in observational studies. Results of the risk assessment for each included study reported in 35 meta-analyses (68.6%), and the results of the risk assessment discussed in 21 meta-analyses (41.2%).

5) Meta-analysis (Table 4)

- *Meta-analysis model*

In total, the adjusted estimates of primary included studies were performed in 86 meta-analyses (74.8%). 20 meta-analyses (17.4%) did not report or were unclear about whether crude or adjusted estimates were used in the meta-analysis. Crude and adjusted estimates

were combined in 8 meta-analyses (6.9%), and 1 meta-analysis (0.9%) used both crude and adjusted estimates separately in their meta-analyses. No meta-analyses were performed crude estimates used for. Confounding factors mentioned in 100 of these meta-analyses (90%).

- *Meta-analysis combined*

The authors combined results of observational studies and RCTs in 2 of the meta-analyses (50%). The authors combined results of different design types of observational studies and in 66 meta-analyses (85.7%)

.

- *Assessment and exploration of heterogeneity*

Heterogeneity was assessed in 113 meta-analyses (98.2%), and explored by subgroup and sensitivity analysis in 109 meta-analyses (94.7%). Subgroup and sensitivity analyses concerned study design in 51 meta-analyses (46.7%) and risk of bias (ROB) in 23 meta-analyses (21.1%), and type of intervention in 34 meta-analyses (31.1%), and type of outcomes in 32 meta-analyses(29.3%), reported unclear and other is 88 in meta-analyses (80.7%), leave-one-out method used in 59 meta-analyses (54.1%) of all meta-analyses have explored by subgroup and sensitivity analysis (n=109).

- *Reporting bias assessment*

Assessment of reporting bias was reported in 106 meta-analyses (92.1%), of which 76 meta-analyses (71.7%) used a standard funnel plot, and 91 meta-analyses (85.8%) used Egger's linear regression test, and 63 meta-analyses (59.4%) used Begg's rank correlation test. In total, around half of the meta-analyses (n=48, 45.2%) that discussed the likelihood of publication bias.

4. Discussion

1) Methodological quality/risk of bias assessment

The quality of the included studies will determine the quality of the systematic review [22]. In more than half of the meta-analyses the methodological quality/risk of bias was not assessed. It is one of the most important methodological deficiencies in the study.

We found that 44.3% of our meta-analyses assessed methodological quality/risk of bias of the included studies, but that only 68.6 % of our meta-analyses fully reported the results for each study. Also, 55.7 % of our meta-analyses did not conducted and not reported the

methods of methodological quality/risk of bias assessment, indicating there are deficiencies in the reporting of methodological quality/risk of bias assessment.

The Cochrane Collaboration has recognized this and is currently developing a tool to assess the risk of bias of observational studies, which will hopefully improve the methodological quality/risk of bias assessment [23], and none of the meta-analysis uses the Cochrane Collaboration Risk of Bias Tool. In this methodological review, two-third (64.7%) of the meta-analyses used the Newcastle-Ottawa scale. While this is currently the most widely known tool for assessing methodological quality/risk of bias in observational studies, it lacks detailed guidance for systematic reviewers, and needs revision [24].

2) Reporting bias

Assessment of reporting bias was conducted in 92.1% of the meta-analyses. Methods have been developed to assess whether reporting bias may have occurred: the funnel plot and statistical methods to test for asymmetry of the plot. Assessment of reporting bias by funnel plot is expected, but its ability to detect funnel plot asymmetry and corresponding reporting bias is limited by the number of studies, as 10 or more studies should be included [25]. In total, 81.7 % of the meta-analyses included more than 10 studies.

When conducting a systematic review, the only way to minimize the influence of reporting bias is by including all relevant studies, including unpublished studies [25]. It is necessary to search for grey literature when conducting a systematic review because exhaustive and appropriate literature search maximizes the chance of retrieving all relevant published studies [26]. However, unpublished studies (grey literature) will most likely not to be identified in the search, in this methodological review, only 2.6 % of the meta-analyses (n=3) reported to have searched for grey literature.

When including observational studies in a review, retrieving all relevant studies is even more difficult, as there is yet no mandatory registration system for observational studies as there exists one for RCTs. However, 96.5% of the meta-analyses included only observational studies written in English, there is a possible for excluding relevant studies.

3) Heterogeneity

Heterogeneity, it is the differences in study designs, including observational studies may lead to high heterogeneity. Heterogeneity was reported to be assessed in the most meta-analyses (98.2 %), the most of the meta-analyses (94.7%) conducted subgroup analyses or sensitivity

analyses. Exploring the heterogeneity of the results by conducting these analyses (subgroup and sensitivity analyses) help in understanding the heterogeneity, where it comes from, and whether the results are robust to certain changes. In the meta-analysis, is having a high quality of assessing heterogeneity.

4) Confounding

In this methodological review, 90 % of the meta-analyses mentioned adjustment of confounding in primary included studies. When the authors reported to the primary included studies have used adjusted estimates, 74.8 % of the meta-analyses listed all the confounding factors that were adjusted in the meta-analysis, and a small number of the meta-analyses (17.45 %) did report or unclear about estimation were adjusted for confounding factors.

It is well know that the major challenging of observational studies is their risk of confounding, which can be taken into account in multivariate analyses. When including the results of observational studies in a systematic review and meta-analysis, it is important to include all information regarding the methods used to deal with confounding.

5. Study Limitation

This methodological review had some limitations. Firstly, only one electronic database searched by PubMed and the search strategy had language restriction on only in English papers were included for inclusion. We did not search for grey literature. If we searched more databases, search for grey literature, and looked for all language papers that the number of inclusion criteria could be much more than current and decrease the risk of bias.

The second limitation should be lack of extract data details. The intention of this methodological review was to assess the actual conduct of methods, some important essential methodological components of the systematic review and meta-analysis were assessed (**Appendix2**), but not all details of the methods were assessed by the data extraction form.

The third limitation is not all the data that extracted by the data extraction form were analyzed and discussed, we are giving final conclusion by analyzed some of them, not all. This also could subjective and might introduce systematic errors.

The forth limitation in this methodological review was the fact that the study selection done only by one reviewer (GL), and data extraction was not fully conducted in duplicate (TF 30% and GL 100%). It is a problem when some of the items on the data extraction sheet require subjective interpretation of the written texts, and having only one reviewer might introduce random errors or systematic errors. Conducting study selection and data extraction by another reviewer independently would be better for reduce the risk of bias and improve the study quality.

6. Conclusion

In total, we assessed 115 meta-analyses including observational studies in a variety of medical areas for key methodological components. Heterogeneity assessment and exploring of subgroup and sensitivity analysis are frequently reported. (Respectively 98.2% and 94.7%). 86 meta-analyses (74.8%) used adjusted estimates (of primary included studies) on confounding in the MA. However, our results highlight some important methodological deficiencies. We found that in more than half of the meta-analyses (54.8%) did not conduct duplicate the study selection, only two-third of the meta-analyses (65.2%) conducted data extraction duplicate, and in more than half of the meta-analyses (44.3%) the methodological quality/risk of bias was not assessed. The most of the meta-analyses did not search for grey literature. Future development and standardization of the methods for conducting meta-analyses including observational studies are necessary.

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Figure 1. Study selection flow chart

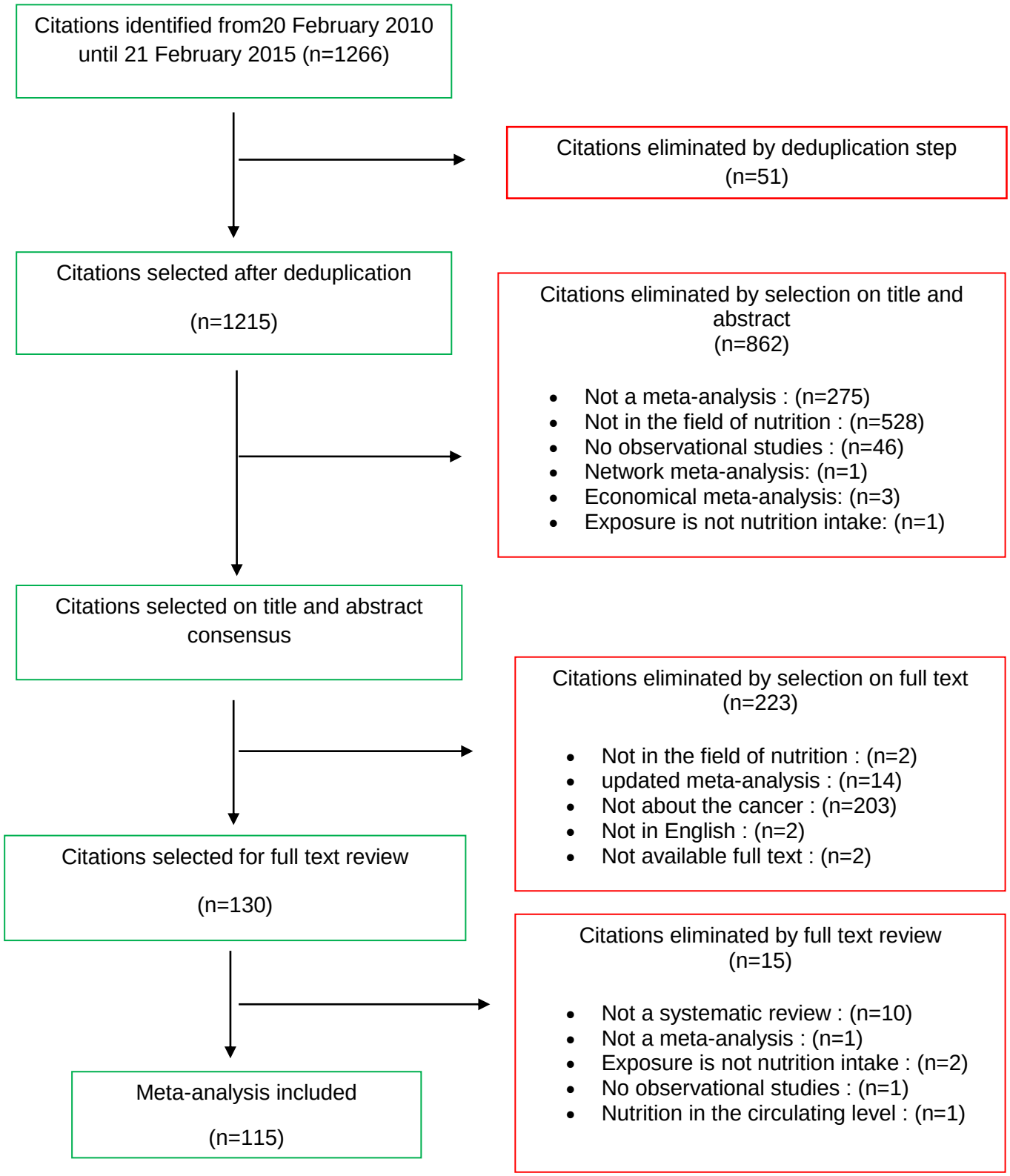

Table 1. General characteristics of 115 systematic reviews with meta-analyses that include observational studies

Item and subcategory	No (%) of reports
General Information	
Journal type (n=115)	
Specialized journal	98 (85)
General journal	17 (15)
Medical area (Cancer type) (n=115)	
Gastrointestinal cancer	51 (44.3)
Breast cancer	24 (20.8)
Prostate cancer	11 (9.6)
Cancer in general	8 (7)
Ovarian cancer	5 (4.4)
Renal cancer	4 (3.5)
Lung cancer	3 (2.7)
Liver cancer	2 (1.7)
Bladder cancer	2 (1.7)
Skin cancer	1 (0.8)
Endocrine system cancers	1 (0.8)
Other	3(2.7)
Type of intervention	
Food in general (n=124)	**102(82.3)**
Fish (n=102)	12(11.7)
Vegetables (n=102)	11(10.8)
Read meat (n=102)	9 (8.8)
Fruits (n=102)	7 (6.8)
Poultry (n=102)	6 (5.8)
Soy (milk) products (n=102)	4 (3.9)
Dietary fat (n=102)	3 (2.9)
Coffee (n=102)	2(1.9)
Milk products (n=102)	1(0.9)
Other (n=102)	71(69.6)
Specific nutrition supplement (n=124)	**19 (15.3)**
Vitamins (n=19)	6 (31.5)
Calcium (n=19)	4 (21)
Minerals (n=19)	1 (5.2)
Other (n=19)	13 (68.4)
Other (n=124)	**3 (2.4)**
Funding sources (n=115)	
Public	59(51.3)
Not reported	42(36.6)
No specific funding	10(8.7)
Private	2 (1.7)
Both	2(1.7)

Table 2. Introduction of 115 systematic reviews with meta-analyses that include observational studies

Item and subcategory	No (%) of reports
Have a systematic review protocol (n=115)	**17 (14.8)**
Study registered at PROSPERO (n=115)	**1(0.8)**
The author clearly define the intervention (n=115)	**65 (56)**
The primary outcomes pre-defined (n=115)	**105 (91)**
The authors justify why they included observational studies (n=115)	**14 (12.2)**
Included Studies	
Number of included studies (n=115) equal / more than 10	**94 (81.7)**
The median number of included studies	**16**
Only observational studies (n=115)	**111(96.5)**
Observational studies and RCTs (n=115)	**4 (3.5)**
Type of observational studies included (n=115)	
Cohort	106(92.1)
Case-control	77(66.9)
Nested case-control	16(13.9)
Unclear	1 (0.8)
Other	2(1.7)

Table 3. Systematic review methods of 115 systematic reviews with meta-analyses that include observational studies

Item and subcategory	No (%) of reports
Search Strategy	
The number of the databases (n=115) more than 2	**55 (47.8)**
Electronic databases searched (n=115)	
MEDLINE (via PubMed)	112 (97.3)
EMBASES	73 (63.4)
Central	10 (8.7)
Google Scholar	5 (4.3)
DARE	2 (1.7)
Not reported	1(0.8)
Other	49(42.6)
Grey literature searched (n=115)	**3 (2.6)**
Experts (n=3)	3(100)
The date reported (or time period) in the search strategy (n=115)	**103 (89.5)**
Available search strategy (n=115)	**74 (64.3)**
Study Selection	
Study selection done in duplicate (n=115)	**52 (45.2)**
A language restriction (in the search and selection) (n=115)	
Only English papers	49(42.6)
No restriction (all language)	41(35.6)
Not reported	19(16.6)
Other	6(5.2)
Flow chart (or clear description) included (n=115)	**85(73.9)**
Included studies characteristics table available (n=115)	**109(94.7)**
Data Extraction	
Data extraction done in duplicate (n=115)	**75 (65.2)**
Contact the authors of the included studies for clarification or additional results (n=115)	**9 (7.82)**
Assessing Risk of Bias	
Methodological risk of bias (n=115)	**51(44.3)**
Newcastle-Ottawa Scale (NOS) (n=51)	33 (64.7)
Unclear (n=51)	4 (7.8)
Downs and Black Instrument (n=51)	1 (1.9)
Other Scale (n=51)	15(29.4)
Results of the Quality assessment reported for each included study (n=51)	**35(68.6)**
Methodological risk of bias discussed (n=51)	**21 (41.2)**

Table 4. Meta-analysis methods of 115 systematic reviews with meta-analyses that include observational studies

Item and subcategory	No (%) of reports
Analysis of Meta-analysis	
Meta-analysis on the crude or adjusted (n=115)	
Adjusted	**86 (74.8)**
Unclear	**16 (13.9)**
The authors combined crude and adjusted estimates	**8 (6.9)**
Not reported	**4(3.5)**
Crude & adjusted separately	**1 (0.9)**
Confounding factors (age, sex, severity of condition) (n=115)	**101 (87.8)**
Combination of results from observational studies and RCTs (n=4)	**2 (50)**
Combination of results from different design types of observational studies (n=77)	**66(85.7)**
Heterogeneity assessed (n=115)	**113(98.2)**
Subgroup and sensitivity analysis done (n=115)	**109(94.7)**
If subgroup and sensitivity analysis done, based on (n=109)	
Study design	51 (46.7)
Type of intervention	34(31.1)
Type of outcomes	32(29.3)
Risk of bias (ROB)	23(21.1)
Unclear	5(4.6)
Other	83(76.1)
Leave-one-out method used (n=109)	**59(54.1)**
Reporting Bias Assessment	
Likelihood of reporting bias assessed (n=115)	**106 (92.1)**
Egger regression test (n=106)	**91(85.8)**
Funnel plot (n=106)	**76(71.7)**
Begg's rank correlation test (n=106)	**63(59.4)**
Unclear (n=106)	**2(1.8)**
Other (n=106)	**1(0.9)**
Likelihood of publication bias discussed (n=106)	**48(45.2)**

Appendix 1. PubMed Search Equation

1	diet [tiab]
2	diet [mh]
3	dietary [tiab]
4	nutrition [tiab]
5	food [tiab]
6	foods [tiab]
7	nourishment [tiab]
8	meal [tiab]
9	“food, formulated” [mh]
10	“daily intake” [tiab]
11	“nutritional requirements” [mh]
12	“dietary supplements” [mh]
13	“eating behavior” [tiab]
14	“feeding behavior”[tiab]
15	“diet therapy” [mh]
16	#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
17	“Systematic review” [tiab]
18	“Systematic reviews” [tiab]
19	meta-analysis [tiab]
20	meta-analyses [tiab]
21	meta-analysis [pt]
22	#17 OR #18 OR #19 OR#20 OR #21
23	observational [tiab]
24	non-randomized[tiab]
25	non-randomised[tiab]
26	cohort [tiab]
27	“cohort studies”[mh]
28	case-control [tiab]
29	“case-control studies” [mh]
30	cross-sectional [tiab]
31	“cross-sectional studies” [mh]
32	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33	#16 AND #22 AND #32

Search limits: Published between 20 February 2010 and 21 February 2015

Citations retrieved: 1266

Date of the search: 5 March 2015

Appendix 2. Data extraction form

Date of form completed:	
Name of person extracting data:	

General Information		
Meta-analysis ID:		
Year of publication:		
Title:		
Journal type：		
□General journal	□Specialized journal	
Medical area (Cancer type):		
□Cancer in general □Breast cancer □bladder cancer □Thyroid cancer □Brain cancer □Other	□Lung cancer □Ovarian cancer □Renal cancer □Skin cancer □Bone cancer	□Gastrointestinal cancer □Prostate cancer □Leukemia □Endocrine system cancers □Liver Cancer
Type of intervention:		

Appendix 2. (Continued)

Food in general:			
□Red Meat	□ Poultry	□Fish	□Dietary fat
□Fruits	□Vegetables	□Milk Products	□Soy (milk) Products
□Coffee	□Tea	□Other	
Specific nutrition supplement:			
□Vitamins	□Calcium	□Minerals	□Other
Other:			
Funding sources:			
□Public	□Private	□Both	□No specific funding □Not Reported
Did the study have a systematic review protocol?			
□Yes	□Not Reported		
Was the study registered at PROSPERO?			
□Yes	□Not Reported		
Did the author clearly define the intervention?			
□Yes	□No		

Appendix 2. (Continued)

Were the primary outcomes pre-defined?
□Yes □No □Unclear □Not Reported
Did the authors justify why they included observational studies?
□Yes □No □Unclear

Search Strategy
The number of the databases:
Which electronic databases were searched?
□MEDLINE (via PubMed) □ EMBASE □Central □ DARE □Google Scholar □Unclear □Not Reported □ Other
Did the authors search for grey literature?
□Yes □No □Unclear □Not Reported
If yes, what type(s) of grey literature did the authors search?
□Registries □Conference abstracts □ Experts □ Contact with the authors of unpublished studies □Other
Did the authors report the date of the search done in their search strategy?
□Yes □Not Reported

Appendix 2. (Continued)

Was the search strategy available?
□Yes □No □Unclear

Study Selection
Was study selection done in duplicate?
□Yes □No □Unclear □Not Reported
Did the authors select only observational studies or both observational studies and RCTs?
□ Only observational studies □ Observational studies and RCTs □Unclear
What types of observational studies were included?
□Cohort □Case-control □Cross-sectional □ Ecological □ Nested case-control □ Unclear □Other
Did the study include a study selection flow chart with excluded reasons?
□Yes □No
Did the study include a table of characteristics of the included studies?
□Yes □No
Was there a language restriction (in the search and selection)?
□No, no restriction (all languages) □Yes, only English papers □Not Reported □Other

Appendix 2. (Continued)

Data Extraction
Was data extraction done in duplicate?
□Yes □No □Extracted by one, checked by another □Unclear □Not Reported
Did the authors contact the authors of the included studies for clarification or additional results?
□Yes □No □Unclear □Not Reported

Assessing Risk of Bias
Did the authors assess the methodological risk of bias of the included studies?
□Yes □No □Unclear □Not Reported
If yes, how was the quality/risk of bias of the included studies assessed?
□Cochrane Collaboration Risk of Bias Tool □ Newcastle-Ottawa Scale (NOS) □RTI item bank □Downs and Black instrument □Unclear □Other scale
Were the results of the risk assessment reported for each study?
□Yes □No □Unclear

Reporting Bias Assessment
Was the likelihood of reporting bias assessed?
□Yes □No □Unclear □Not reported

Appendix 2. (Continued)

If yes, how did the authors assess reporting bias?		
□ Funnel plot	□ Egger regression test	□Hedges-Olken
□Begg's rank correlation test	□Unclear	□ Other

Analysis of Meta-analysis			
Did the study perform the meta-analysis on the crude or adjusted estimates?			
□ Crude	□ Adjusted	□Both crude & adjusted separately	
□The authors combined crude and adjusted estimates			
□ Unclear	□Not reported	□Other	
If the study reported the confounding factors which were adjusted for in the selected adjusted estimates? (age, sex, severity of condition)			
□Yes	□No	□Unclear	□Not reported
Did the study combine the results of observational studies and RCTs?			
□Yes	□No	□Unclear	□Not reported
Did the study combine the results of observational studies of different design types?			
□Yes	□No	□Unclear	□Not reported
Did the study assess heterogeneity?			
□Yes	□No	□Unclear	□Not reported
Did the authors do subgroup and sensitivity analysis?			
□Yes	□No	□Unclear	□Not reported

Appendix 2. (Continued)

If yes, based on what?
□Study design □Risk of bias □Type of intervention □Type of outcomes □Unclear □Other
Did the authors take account the results from risk of bias assessment into the interpretation of results?
□Yes □No □Unclear
Did the authors discuss the likelihood of publication bias?
□Yes □No □Unclear

Included and Excluded Studies
Number of included studies:
Number of observational studies:
Number of RCTs:

Commentary

Appendix 3. List of included meta-analyses

ID	References
3	Heine-Broring RC, Winkels RM, Renkema JMS, Kragt L, van Orten-Luiten A-CB, Tigchelaar EF, et al. Dietary supplement use and colorectal cancer risk: A systematic review and meta-analyses of prospective cohort studies. Int J Cancer. 2014.
4	Luo J, Yang Y, Liu J, Lu K, Tang Z, Liu P, et al. Systematic review with meta-analysis: meat consumption and the risk of hepatocellular carcinoma. Aliment Pharmacol Ther. 2014;39(9):913-22.
5	Huang T, Yang B, Zheng J, Li G, Wahlqvist ML, Li D. Cardiovascular disease mortality and cancer incidence in vegetarians: a meta-analysis and systematic review. Ann Nutr Metab. 2012;60(4):233-40.
7	Song P, Lu M, Yin Q, Wu L, Zhang D, Fu B, et al. Red meat consumption and stomach cancer risk: a meta-analysis. J Cancer Res Clin Oncol. 2014;140(6):979-92.
8	Choi Y, Giovannucci E, Lee JE. Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis. Br J Nutr. 2012;108(11):1934-47.
9	Shen X-J, Zhou J-D, Dong J-Y, Ding W-Q, Wu J-C. Dietary intake of n-3 fatty acids and colorectal cancer risk: a meta-analysis of data from 489 000 individuals. Br J Nutr. 2012;108(9):1550-6.
10	Alexander DD, Morimoto LM, Mink PJ, Lowe KA. Summary and meta-analysis of prospective studies of animal fat intake and breast cancer. Nutr Res Rev. 2010;23(1):169-79.
11	Lin HL, An QZ, Wang QZ, Liu CX. Folate intake and pancreatic cancer risk: an overall and dose-response meta-analysis. Public Health. 2013;127(7):607-13.
12	Qu X-L, Fang Y, Zhang M, Zhang Y-Z. Phytoestrogen intake and risk of ovarian cancer: a meta- analysis of 10 observational studies. Asian Pac J Cancer Prev. 2014;15(21):9085-91.
13	Xie B, He H. No association between egg intake and prostate cancer risk: a meta-analysis. Asian Pac J Cancer Prev. 2012;13(9):4677-81.

Appendix 3. (continued)

14	Chi F, Wu R, Zeng Y-C, Xing R, Liu Y, Xu Z-G. Post-diagnosis soy food intake and breast cancer survival: a meta-analysis of cohort studies. Asian Pac J Cancer Prev. 2013;14(4):2407-12.
15	Liu X-O, Huang Y-B, Gao Y, Chen C, Yan Y, Dai H-J, et al. Association between dietary factors and breast cancer risk among Chinese females: systematic review and meta-analysis. Asian Pac J Cancer Prev. 2014;15(3):1291-8.
16	Xing M-Y, Xu S-Z, Shen P. Effect of low-fat diet on breast cancer survival: a meta-analysis. Asian Pac J Cancer Prev. 2014;15(3):1141-4.
17	Wen Y-Y, Yang S-J, Zhang J-X, Chen X-Y. Methylenetetrahydrofolate reductase genetic polymorphisms and esophageal squamous cell carcinoma susceptibility: a meta-analysis of case-control studies. Asian Pac J Cancer Prev. 2013;14(1):21-5.
18	Turner LB. A meta-analysis of fat intake, reproduction, and breast cancer risk: an evolutionary perspective. Am J Hum Biol. 2011;23(5):601-8.
19	Ben Q, Sun Y, Chai R, Qian A, Xu B, Yuan Y. Dietary fiber intake reduces risk for colorectal adenoma: a meta-analysis. Gastroenterology. 2014;146(3):689-99.e6.
20	Yang Y, Zhang D, Feng N, Chen G, Liu J, Chen G, et al. Increased intake of vegetables, but not fruit, reduces risk for hepatocellular carcinoma: a meta-analysis. Gastroenterology. 2014;147(5):1031-42.
21	Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, et al. Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. Gastroenterology. 2011;141:106-18.
22	Zhou Y, Zhuang W, Hu W, Liu G-J, Wu T-X, Wu X-T. Consumption of large amounts of Allium vegetables reduces risk for gastric cancer in a meta-analysis. Gastroenterology. 2011;141(1):80-9.
23	Zhang Z, Xu G, Ma M, Yang J, Liu X. Dietary fiber intake reduces risk for gastric cancer: a meta-analysis. Gastroenterology. 2013;145(1):113-20.e3.
24	D'Elia L, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P. Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. Clin Nutr. 2012;31(4):489-98.

Appendix 3. (continued)

25	Liu X, Lv K. Cruciferous vegetables intake is inversely associated with risk of breast cancer: a meta-analysis. Breast. 2013;22(3):309-13.
26	Chan ALF, Leung HWC, Wang S-F. Multivitamin supplement use and risk of breast cancer: a meta-analysis. Ann Pharmacother. 2011;45(4):476-84.
27	Huang T-b, Ding P-p, Chen J-f, Yan Y, Zhang L, Liu H, et al. Dietary fiber intake and risk of renal cell carcinoma: evidence from a meta-analysis. Med Oncol. 2014;31(8):125.
29	Zhu H-C, Yang X, Xu L-P, Zhao L-J, Tao G-Z, Zhang C, et al. Meat consumption is associated with esophageal cancer risk in a meat- and cancer-histological-type dependent manner. Dig Dis Sci. 2014;59(3):664-73.
30	Li C, Chen P, Hu P, Li M, Li X, Guo H, et al. Folate intake and MTHFR polymorphism C677T is not associated with ovarian cancer risk: evidence from the meta-analysis. Mol Biol Rep. 2013;40(12):6547-60.
31	Dong J-Y, Qin L-Q. Dietary glycemic index, glycemic load, and risk of breast cancer: meta-analysis of prospective cohort studies. Breast Cancer Res Treat. 2011;126(2):287-94.
32	Hu F, Wang Yi B, Zhang W, Liang J, Lin C, Li D, et al. Carotenoids and breast cancer risk: a meta-analysis and meta-regression. Breast Cancer Res Treat. 2012;131(1):239-53.
33	Hong Z, Tian C, Zhang X. Dietary calcium intake, vitamin D levels, and breast cancer risk: a dose-response analysis of observational studies. Breast Cancer Res Treat. 2012;136(1):309-12.
34	Tio M, Andrici J, Eslick GD. Folate intake and the risk of breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;145(2):513-24.
36	Dong J-Y, Zhang L, He K, Qin L-Q. Dairy consumption and risk of breast cancer: a meta-analysis of prospective cohort studies. Breast Cancer Res Treat. 2011;127(1):23-31.
37	Gilbert R, Martin RM, Beynon R, Harris R, Savovic J, Zuccolo L, et al. Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. Cancer Causes Control. 2011;22(3):319-40.

Appendix 3. (continued)

38	Huang W, Han Y, Xu J, Zhu W, Li Z. Red and processed meat intake and risk of esophageal adenocarcinoma: a meta-analysis of observational studies. Cancer Causes Control. 2013;24(1):193-201.
39	Aune D, Chan DSM, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Carbohydrates, glycemic index, glycemic load, and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2012;23(4):521-35.
40	Liu L, Wang S, Liu J. Fiber consumption and all-cause, cardiovascular, and cancer mortalities: a systematic review and meta-analysis of cohort studies. Mol Nutr Food Res. 2015;59(1):139-46.
41	Ge S, Feng X, Shen L, Wei Z, Zhu Q, Sun J. Association between Habitual Dietary Salt Intake and Risk of Gastric Cancer: A Systematic Review of Observational Studies. Gastroenterol Res Pract. 2012;2012:808120.
42	Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ. 2014;349:g4490.
43	Zheng J-S, Hu X-J, Zhao Y-M, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ. 2013;346:f3706.
44	Xu B, Sun J, Sun Y, Huang L, Tang Y, Yuan Y. No evidence of decreased risk of colorectal adenomas with white meat, poultry, and fish intake: a meta-analysis of observational studies. Ann Epidemiol. 2013;23(4):215-22.
45	Kennedy DA, Stern SJ, Moretti M, Matok I, Sarkar M, Nickel C, et al. Folate intake and the risk of colorectal cancer: a systematic review and meta-analysis. Cancer Epidemiol. 2011;35(1):2-10.
46	Paluszkiewicz P, Smolinska K, Debinska I, Turski WA. Main dietary compounds and pancreatic cancer risk. The quantitative analysis of case-control and cohort studies. Cancer Epidemiol. 2012;36:60-7.
48	Harris HR, Orsini N, Wolk A. Vitamin C and survival among women with breast cancer: a meta-analysis. Eur J Cancer. 2014;50(7):1223-31.
49	Wang Q, Chen Y, Wang X, Gong G, Li G, Li C. Consumption of fruit, but not vegetables, may reduce risk of gastric cancer: results from a meta-analysis of cohort studies. Eur J Cancer. 2014;50(8):1498-509.

Appendix 3. (continued)

50	Chen J, Song Y, Zhang L. Lycopene/tomato consumption and the risk of prostate cancer: a systematic review and meta-analysis of prospective studies. J Nutr Sci Vitaminol (Tokyo). 2013;59(3):213-23.
51	Zhou Z-Y, Wan X-Y, Cao J-W. Dietary methionine intake and risk of incident colorectal cancer: a meta-analysis of 8 prospective studies involving 431,029 participants. PLoS One. 2013;8(12):e83588.
52	Bai H-w, Qian Y-y, Shi B-y, Li G, Fan Y, Wang Z, et al. The association between fish consumption and risk of renal cancer: a meta-analysis of observational studies. PLoS One. 2013;8(11):e81939.
53	Hui C, Qi X, Qianyong Z, Xiaoli P, Jundong Z, Mantian M. Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. PLoS One. 2013;8(1):e54318.
54	Cho YA, Kim J, Woo HD, Kang M. Dietary cadmium intake and the risk of cancer: a meta-analysis. PLoS One. 2013;8(9):e75087.
55	Jiang P-y, Jiang Z-b, Shen K-x, Yue Y. Fish intake and ovarian cancer risk: a meta-analysis of 15 case-control and cohort studies. PLoS One. 2014;9(4):e94601.
56	Li J, Zou L, Chen W, Zhu B, Shen N, Ke J, et al. Dietary mushroom intake may reduce the risk of breast cancer: evidence from a meta-analysis of observational studies. PLoS One. 2014;9(4):e93437.
57	Wien TN, Pike E, Wisloff T, Staff A, Smeland S, Klemp M. Cancer risk with folic acid supplements: a systematic review and meta-analysis. BMJ Open. 2012;2(1):e000653.
58	Carleton AJ, Sievenpiper JL, de Souza R, McKeown-Eyssen G, Jenkins DJA. Case-control and prospective studies of dietary alpha-linolenic acid intake and prostate cancer risk: a meta-analysis. BMJ Open. 2013;3(5).
59	Chua ME, Sio MCD, Sorongon MC, Dy JS. Relationship of dietary intake of omega-3 and omega-6 Fatty acids with risk of prostate cancer development: a meta-analysis of prospective studies and review of literature. Prostate Cancer. 2012;2012:826254.
60	Choi Y, Song S, Song Y, Lee JE. Consumption of red and processed meat and esophageal cancer risk: meta-analysis. World J Gastroenterol. 2013;19(7):1020-9.

Appendix 3. (continued)

61	Yu X-F, Wang Y-Q, Zou J, Dong J. A meta-analysis of the effects of energy intake on risk of digestive cancers. World J Gastroenterol. 2012;18(48):7362-70.
62	Dong J, Zou J, Yu X-F. Coffee drinking and pancreatic cancer risk: a meta-analysis of cohort studies. World J Gastroenterol. 2011;17(9):1204-10.
63	Alexander DD, Mink PJ, Cushing CA, Sceurman B. A review and meta-analysis of prospective studies of red and processed meat intake and prostate cancer. Nutr J. 2010;9:50.
64	Alexander DD, Miller AJ, Cushing CA, Lowe KA. Processed meat and colorectal cancer: a quantitative review of prospective epidemiologic studies. Eur J Cancer Prev. 2010;19(5):328-41.
65	Alexander DD, Weed DL, Cushing CA, Lowe KA. Meta-analysis of prospective studies of red meat consumption and colorectal cancer. Eur J Cancer Prev. 2011;20(4):293-307.
66	Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol. 2012;23(1):37-45.
67	Aune D, Chan DSM, Greenwood DC, Vieira AR, Rosenblatt DAN, Vieira R, et al. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. Ann Oncol. 2012;23(6):1394-402.
68	Aune D, Chan DSM, Vieira AR, Navarro Rosenblatt DA, Vieira R, Greenwood DC, et al. Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol. 2012;23(10):2536-46.
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