

Modifications to the protocol on Cervical Cancer (2005 SLR for the Second Expert Report).

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

June 2016

The outcome of interest of the systematic literature review is cervical cancer (*in situ* (CIS) or invasive), encompassing incidence and mortality. Cervical cancer refers to ICD10 C53. Studies with pre-invasive neoplastic lesions as outcome- dysplasia, cervical intraepithelial neoplasia (CIN I to CIN III) or squamous intraepithelial lesions (SIL) of different grades- are out of the scope of the review and will not be included.

Persistent infections with certain genotypes of Human Papilloma Virus (HPV), has been recognised as a primary causative factor for cervical neoplasms. In approximately two-thirds of the cases these lesions spontaneously regress. HPV infection alone is not a sufficient cause. Dietary factors may be determinants of the persistence of HPV infections, or may affect the progression from infection to intraepithelial and invasive neoplasms.

Summary of judgements of the 2007 Second Expert Report on skin cancer

There is limited evidence suggesting that carrots protect against cervical cancer.

In final summary, there is no strong evidence, corresponding to judgements of “convincing” and “probable”, to conclude that any aspect of food, nutrition, and physical activity modifies the risk of cervical cancer.

1. Research question

The research topic is:

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

The main objective is:

To summarize the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, vitamin, minerals, physical activity, overweight and obesity with the risk of cervical cancer in women.

2. Review team

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Rita Vieira	Research Assistant	Supervisor of data extraction and report preparation.

		Reviewer
Leila Abar	Research Assistant	Reviewer
Christophe Stevens	Database manager	Systematic search, article selection, data extraction

3. Timeline

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

Task	Deadline
Start Medline search of relevant articles published from June 30 2005	30 June 2016
Select papers for data extraction	30 August 2016
End data extraction	15 October 2016
Write review	October-November 2016
Finish writing report	20 December 2016
Send report for review to CUP secretariat	20 December 2016

4. Search strategy

Search strategy for cervical cancer

- a) PubMed [*Only PubMed was used in the searches of other reviews in the CUP. There is no evidence that studies based on cohorts or RCT have been missed because of no search in other electronic reference databases, using the CUP search strategy*]

Searching for all studies relating to cervical cancer (used by the 2005 SLR team):

1. "Cervix Dysplasia"[MeSH] OR "Cervix Neoplasms"[MeSH] OR "Cervical Intraepithelial Neoplasia"[MeSH]
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2. (Cervix OR cervical) AND (cancer* OR tumour* OR tumour* OR neoplasm* OR carcinoma)
3. Cervix adenocarcinoma OR cervical adenocarcinoma OR cervical epidermoid carcinoma OR cervical squamous carcinoma OR cervical squamous cell carcinoma OR cervical large cell carcinoma OR cervical small cell carcinoma OR cervical keratinizing carcinoma OR cervical nonkeratinizing carcinoma OR cervical microinvasive carcinoma OR cervical severe dysplasia OR cervix epidermoid carcinoma OR cervix squamous carcinoma OR cervix squamous cell carcinoma OR cervix large cell carcinoma OR cervix small cell carcinoma OR cervix keratinizing carcinoma OR cervix nonkeratinizing carcinoma OR cervix microinvasive carcinoma OR cervix severe dysplasia
4. Cervical Intraepithelial neoplasm*[tiab]

1 OR 2 OR 3 OR 4

b) Hand searching for cited references

b1) The review team will also hand search the references of reviews and meta-analyses identified during the search.

b2) The database manager will identify the papers that are in the database for more than one cancer site (“multi-cancer paper”). The database manager will check if data on cervical cancer has been extracted from these papers. The database manager will give that references of the “multi-cancer” papers for which no data on cervical cancer was extracted to the reviewers who will verify in the corresponding pdf that the paper has no data on cervical cancer.

5. Study selection criteria for the update

5.1 Inclusion criteria

The articles to be included in the review:

- Have to present results on an exposure/intervention relevant to the CUP
- Must have as outcome of interest incidence or mortality for cervical cancer
- Have to present results from an epidemiologic study in men and women 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
 - Historical cohort study
- Have any publication date

6. Article selection

All references obtained with the search in PubMed will be imported in a Reference Manager Database using the filter Medline.

Additionally, customized fields will be implemented in the RefMan database (see Section 6.1).

The article selection will follow three steps:

1. The database manager did the search and exported it to RefMan. The database manager will indicate in User Def 1 (exclusion) if the article should be excluded based on an algorithm under test.
2. The reviewers will assess first the titles and abstracts of the studies not excluded by the algorithm.
3. If a paper reports outcomes for more than one cancer site, the reviewer will extract the data for the other cancer sites in the database, using the WCRF code of the cancers in question

6.1 Reference Manager Files

Five customized fields will be created in the reference manager database. They will be used to indicate if the study was selected upon reading of title, abstract, or entire article, the study design of included articles, the status

of data extraction of the included article, the WCRF code assigned and for excluded articles, the reason for exclusion (**Table 1**)

Table 1. User-defined fields to be created in Reference Manager during article selection and data extraction.

Field	Use	Terms used	Notes
User Def 1	Indicate if article is relevant to the CUP review	Excludedabti; Included; excluded;	Excludedabti means excluded basing on abstract and title of the article. Without “abti” means full text is reviewed.
User Def 2	If excluded, reasons	No associations of interest; No original data/duplicates; Commentary; Foreign article in [<i>language</i>] Not adequate study design Pooled studies/meta-analyses	No associations of interest include situations such as “out of the research topic”, “no measure of relationship”, “no specific outcome”
User Def 3	Study design	Randomized controlled trial (RCT) Prospective cohort study Retrospective cohort study Nested case-control study Case cohort study Population-based case-control study Hospital-based case-control study Case-control study- other type of controls or control type unclear	The CUP only extract data from RCT, cohort/cohort based studies. Case-control studies are identified but the data is not extracted to the database.

User Def 4	WCRF code of the article	This is done during the data extraction	WCRF codes are assigned automatically in the application when performing extraction.
User Def 5	Other notes, name of study	Indicate if includes more than one anatomical localization	

7. Data extraction

The IC team will update the CUP central database.

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

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

For each result, the reviewer will extract the covariates included in the analytical model and the matching variables. Measures of association, number of cases and number of comparison individuals or person years for each category of exposure will be extracted for each model used in the analyses. Stratified and subgroup analyses, and results of interaction analyses will also be extracted.

7.1 Study identifier

The unique identifier for an article will be constructed using a 3-letter code to represent the cancer site: CER, followed by a 5-digit number that will be allocated in sequence automatically by the interface during data extraction.

8. Data summary

The study results will be summarised in tables and figures. The Expert Panel will judge on the likelihood of association.

8.1 Meta-analysis

(See original protocol for details)

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

The meta-analysis will include studies identified during the 2005 SLR and studies identified during the CUP SLR.

The statistical methods will be the same used in the SLR for the Second Expert Report (see protocol). Linear dose-response meta-analysis will be conducted to express the results of each study in the same increment unit for a given exposure. The measure of association for the highest vs. the lowest comparison for each study will be displayed graphically in forests plots, but a summary estimate will not be calculated, to avoid pooling exposure levels that are different across studies.

For comparability, the increment units for the linear dose-response analyses will be those used in the meta-analyses in the previous SLRs.

Publication and related bias (e.g. small study bias) will be explored through visual examination of funnel plots using precision ($1/SE(\beta)$) in the vertical axis and Egger's test *egger*. Funnel plots will be shown when there are at least five studies included in the analysis. Heterogeneity between studies will be quantified with the I^2 statistic - and assessed visually from forest plots and with statistical tests (P value <0.05 will be considered statistically significant). The interpretation will rely mainly in the I^2 values as the test has low power and the number of studies for some exposures will probably be limited.

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

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

All analyses will be conducted in Stata/SE 12.1.

APPENDIX A:

**ORIGINAL
SYSTEMATIC LITERATURE REVIEW PROTOCOL**

*Title: The associations between food, nutrition and physical activity
and the risk of cervical cancer and underlying mechanisms.*

**In support of the Revision of the World Cancer Research Fund International's Report on
Diet, Nutrition, Physical Activity and Cancer**

National Cancer Institute, Milan

April 30, 2004

1.0 Research Question

The research question concerns:

The associations between food, nutrition and physical activity and the risk of cervical cancer and underlying mechanisms.

According to the specification manual, only studies answering to etiological questions will be included, that is studies testing whether diet, nutrient intake, nutritional status, levels of physical activity or body size influence the development of cervical cancer.

Besides classical dietary assessment tools (e.g. Food Frequency Questionnaires), dietary factor exposures can also be assessed by mean of biological markers of dietary intake (such as serum alpha-tocopherol, serum carotenoids, serum selenium).

The outcome of interest is cervical cancer (*in situ*, microinvasive or invasive), encompassing incidence and mortality. Cervical cancer refers to ICD10 C53.

Studies considering the relationship between diet and cervical intraepithelial neoplasia (CIN I to CIN III) will also be reported.

The research question (entirely defined with exposures and outcome) will be forwarded to the information specialist to develop the search strategy.

The search strategy will not include genetic and hormone related terms; however, when literature on nutrient-endocrine and nutrient-gene interactions will arise, it will be also retrieved and reviewed (but we will not include these studies in meta-analyses).

Table 1: SLR Team

1.1.1.1.1 <u>Team</u>	Current position	Skills relevant to SLR	Role within team	% of time
Franco Berrino	Director of the Department of Preventive and Predictive Medicine; Director of the Epidemiology Unit	Cancer Epidemiology Pathology	Epidemiology and methodology	10%
Vittorio Krogh	Senior Research in medical statistics	Medical statistics and nutritional epidemiology	Statistical and methodological support, reviewer	10%
Sabina Sieri	Senior Research in nutritional Epidemiology	Nutritional epidemiology, nutritional methodology	Nutritional epidemiology, reviewer	10%
Valeria Pala	Senior Research in nutritional Epidemiology	Nutritional epidemiology, nutritional methodology	Nutritional epidemiology, reviewer	25%
Patrizia Pasanisi	Research assistant	Master in Epidemiology	Project manager, reviewer	50%
Elisabetta Fusconi	Research fellow in nutritional Epidemiology	Pharmacologist	Reviewer	50%
Eugenio Mugno	Senior Research in medical statistics	Statistician	Statistical and methodological support	100%
Holger Schünemann	Associate Professor of Dep. of Social and Preventive Medicine at Buffalo University, NY, & of Dep. of Clinical Epidemiology and Biostatistics, at McMaster University, Hamilton, Ontario, Canada	Medical statistics and systematic review	consultant on statistical methodology and metaanalyses	10%
Idalia Gualdana	Strategy search coordinator	Bibliographic database searching and management skills	Information specialist	50%
M.Grazia Guerrini	Secretary	Administrative project managing	Project Secretary	50%
Cancer mechanisms expert				
Reina Garcia-Closas	Senior research of Cancer Epidemiology & Registration Unit, Institut Catala' d'Oncologia,	Epidemiologist	Consultant on mechanistic issues	5%

	Barcelona, Spain			
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2.1 Brief biographies of team members:

Dr Berrino is a cancer epidemiologist, employed at the National Cancer Institute in Milan since 1976, Director of the Epidemiology Unit since 1988 and Director of the department of Preventive and Predictive Medicine since 2002. Prior to that he was IARC research assistant from 1970 to 1972 and from 1973 to 1975 assistant pathologist at “Ospedale Civile” in Legnano, Italy. He has also been Director of the Lombardy Cancer Registry from 1976 to 2000.

He has had a major research interest in the epidemiology of cancer (in particular breast cancer) especially investigating the association between endocrine and nutritional factors and risk of cancers.

At present, he is involved in the following studies:

- ORDET Study (Hormones and Diet in the Aetiology of Tumours): Cohort study with biological bank of 10000 women to study hormones, diet and breast cancer.
- EURO CARE: European cancer registries based study of cancer patients' survival and care (Project Leader)
- EPIC Study (European Prospective Investigation into Cancer and Nutrition), Italian section: On going prospective study with biological bank of 50.000 subjects in Varese, Torino, Firenze and Ragusa. (National Co-ordinator)
- DIANA (Diet and Androgens) Project: Randomized trial on the effect of dietary changes on serum levels of endogenous hormones
- COS project: European Case-Only Study on gene-environment interaction in breast cancer in young women (Project Leader)

Dr Krogh is a cancer epidemiologist, with a background in epidemiology and biostatistics, employed as research scientist (tenured) at the National Cancer Institute in Milan since 1991. Prior to that he was research Instructor,

Department of Social and Preventive Medicine, University at Buffalo, State University of New York, Buffalo, NY USA from 1985 to 1991. Since 2001 he is Research Associate Professor at the same department.

At present he is involved in the following research studies:

- EPIC Project, (European Prospective Investigation on Cancer and Diet), European multicentre study on the role of diet in the aetiology of cancer as co-ordinator of the Varese centre.
- ORDET Study. Prospective Study on the role of hormones and diet in the aetiology of Breast cancer as co-investigator.
- Alpine Troup Project, Prospective study on Diet and chronic diseases in a cohort of Alpine Troup as PI.
- IMMIDIET Project, Multicentre study on the interaction gene-environment on the determinants of chronic diseases as PI of the Milan centre.
- DIETSCAN Project, Multicentre study with the main aim on the identification of common methods for the definition of dietary patterns at greater risk for cancer developing as PI of the Milan centre.
- ORDET Study of the Pooling Project of Prospective Studies of Diet and Cancer. Collaborative Project involving the main European and North American Cohort Studies established to examining the association between dietary factor and cancer as PI.

Dr Sieri is a nutritionist, with a background in biology and nutrition. She was a research scientist at the Human and Hereditary Pathology Department of the University of Pavia, Italy from 1993 to 1995. She works at the Epidemiology Unit of the National Cancer Institute in Milan as a research scientist (tenured) since 1996.

At present she is involved in the following studies:

- EPIC Project (European Prospective Investigation on Cancer and Diet), European multicentre study on the role of diet in the aetiology of cancer as co-investigator for the Varese Centre.
- ORDET Study. Prospective Study on the role of hormones and diet in the aetiology of Breast cancer as co-investigator.
- Alpine Troup Project, Prospective study on Diet and chronic disease in a cohort of Alpine Troup as co-investigator.

- IMMIDIET Project, Multicentre study on the interaction gene-environment on the determinants of chronic diseases as co-investigator for the Milan centre.
- ORDET Study of the Pooling Project of Prospective Studies of Diet and Cancer. Collaborative Project involving the main European and North American Cohort Studies established to examining the association between dietary factor and cancer as co-investigator.

Dr Pala is a epidemiologist with a background in nutrition with a major research interest in diet and cancer. She received her post-doctoral degree in general nutrition with a thesis project on dietary assessment methods. She has experience in analysing food and nutrient data originated from different dietary assessment methodologies. She has also a background in food biochemistry, including effects of food production and processing and in evaluation and assessment of biomarker of dietary intake in human tissues.

At present she is involved in the following research studies:

- EPIC Project (European Prospective Investigation on Cancer and Diet), European multicentre study on the role of diet in the aetiology of cancer. Granted by European Community and by Italian Association for Research on Cancer (AIRC) As co-ordinator of the the Italian dietary 24-hour interview team.
- ORDET study prospective study on hormones and diet in relation to prediagnostic breast cancer as co-investigator.
- DIANA (Diet and Androgens) project: Randomized trial on the effect of dietary changes on serum levels of endogenous hormones as co-investigator.

Dr Pasanisi is a Medical Doctor; she has a background in Public Health and a PhD in Epidemiology. She works at the Epidemiology Unit of the National Cancer Institute in Milan since 1998 as postgraduate fellow and since 2001 as research scientist.

At present she is involved in the following research studies:

- DIANA (Diet and Androgens) project: Randomized trial on the effect of dietary changes on serum levels of endogenous hormones as co-investigator

- COS project: European Case-Only Study on gene-environment interaction in breast cancer in young women as co-investigator.
- Project on the metabolic and endocrine influence on the penetrance of genetic cancer granted by the Italian Ministry of Public Health as co investigator.

Dr Fusconi is a medical chemist; she has a background in pharmacology and a particular interest in dietary epidemiology. She works at the Epidemiology Unit of the National Cancer Institute in Milan since June 2001 where she is involved in several prospective studies on diet and chronic disease.

At present she is involved in the following projects:

- EPIC study European Prospective Investigation into Cancer and Nutrition, particularly in evaluation and assessment of biomarkers of dietary intake in human tissue as co-investigator.
- C.O.S. Case-Only Study on gene-environment interaction in breast cancer in young women as co-investigator.

Dr Mugno is a statistician, with a background in mathematics and physics. He was a research scientist at the Epidemiology Unit of the National Cancer Institute in Milan, from 2000 to 2003 where he was involved in the following projects:

- EUROPREVAL: project to estimate the prevalence of cancers in european countries.
- EUROCHIP: project to evaluate the relationship between cancer survival in Europe and macroeconomic and European health system indicators.
- EUROCARE-3: European cancer registries based study of cancer patients' survival and care.
- ORDET: prospective study on hormones and diet in relation to prediagnostic breast cancer as co-investigator

Dr. Schünemann, M.D., Ph.D., is a methodologist and full time faculty member at the University at Buffalo, USA, and part-time faculty member at McMaster University in Hamilton, Ontario, Canada. He is a member of the OKATT research group at McMaster University (Chairs: Drs. Gordon Guyatt, Deborah Cook, Maureen

Meade, PJ Devereaux and Holger Schünemann) and has participated in and led several systematic reviews including reviews of observational studies (e.g., a comparison of for profit versus not for profit healthcare delivery). As co-chair of the OKATT research team he interacts closely with colleagues who have a long term experience in systematic review methodology, Drs. Gordon Guyatt and Deborah Cook, and co-tutors the graduate degree course in “Systematic Reviews” at McMaster University. The staff of the OKATT group includes statisticians, e.g. Lauren Griffith, MS, PhD (Cand.), who have participated in numerous systematic reviews. He has received funding for systematic reviews and led the conduct of a series of systematic literature reviews for the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. He is co-editor of this respected document with expected publication in the summer of 2004.

Mrs Galdana has expertise in information management and in literature database maintenance. She worked at the Library of the National Cancer Institute of Milan from 1971 to 1974 as librarian assistant, and from 1975 to 1991 as Chief of the Library. At present, she is the Co-ordinator of SBBL (Biomedical Library System of Lombardy).

Mrs Guerrini has a 20 years expertise in secretary management. She has been working as scientific secretary in the Epidemiology Unit of the National Cancer Institute since 1991.

2 3.0 Timeline

The review processes will follow the deadline described in table 2. Table 3 provides monthly activities for the whole cervical cancer SLR.

Table 2: Deadline schedule

2.1.1.1 Processes	Deadline
Preliminary output from the search strategy (all databases search) (EndNote file1)	20 of April
Design of the data extraction sheets	30 of March (We shall use the Leeds' Access software)
List of all relevant paper included in the review (EndNote file3)	31 of May
Results of the preliminary analyses	30 of July

2.1.2

2.1.3 Table 3: Activities

Month	Activities
February	Discussion on preparing operative protocol for cervical cancer, design of all the sections of the protocol (mainly define the proper search strategy and the selection criteria)
March	Test of chosen search strategy, protocol for cervical cancer.
April	Discussion on the reviewed protocol, revision of the protocol. Production of the preliminary output for the search, decision in duplicate about the inclusion or exclusion of the identified references, production of the EndNote file1 (Cervix1_INT), start of the retrieval of papers, design of the data extraction sheets and start of the production of the EndNote file 2 containing reasons for references exclusion based on full paper (in duplicate).
May	Start of data extraction, completed EndNote file2, list of all the relevant paper included in the review (EndNote file3).
June	Data extraction.

July	Data extraction and preliminary analyses.
September 2004	Final analysis, review and review summary.
October-March 2006	Update.

All these activities are discussed and finalised in weekly meeting (Dr. Schünemann will be participating via conference calls) with the entire team..

These meetings are also useful to check the processing of work and to discuss problems.

4.0 Background

4.1 Cervical cancer

Although incidence and mortality from cervical cancer decreased dramatically in the second half of the last century in more developed countries, cervical cancer is still the first cause of cancer death among women in many countries of the third world, and worldwide almost 500,000 new cases are diagnosed per year. In the nineties the age standardised incidence rate for cervical cancer ranged from less than 10 new cases per 100,000 woman-years in US and most European countries to over 50 in some African populations. The vast majority of cervical cancer are epidermoid (squamous cell) carcinomas arising from the squamous epithelium of the outer part of the cervix, frequently at the squamocolumnar junction, and between 10 to 25% are adenocarcinomas arising from the columnar epithelium and the glands of the cervical canal. Squamous cell carcinomas are preceded by preinvasive neoplastic lesions called dysplasia, carcinoma in situ (CIS) cervical intraepithelial neoplasms (CIN) or squamous intraepithelial lesions (SIL) of different grades, according to different classification systems. Low grade SIL (LSIL) includes condylomatous atypia and grade I of the CIN classification system and High grade SIL (HSIL) includes CIN II and CINIII/CIS. These asymptomatic lesions can be detected by cytological screening.

Persistent infections with certain genotypes of Human Papilloma Virus (HPV), such as 16,18,31,33,35,45,51,52 or 56 has been recognised as a primary causative factor for cervical neoplasms (1;2). Most women with HPV infection, however, do not develop cervical cancer. The HPV infection is very common in young and sexually active women but is usually transient, and also the pre-invasive lesions associated with the infection do not necessarily proceed to invasive ones. In approximately two-thirds of the cases these lesions spontaneously regress. HPV infection alone, therefore is not a sufficient cause.

Before the discovery of HPV as the major cause for cervical cancer various risk factors were already identified: lower socio-economic status, early age at first intercourse, multiple parity, history of multiple sexual partners, promiscuous male sexual partners, oral contraceptive use, smoking, and micronutrient poor diet. (3) Some of these factors are explained (and their association totally confounded) by the infectious etiology, others, including

dietary factors, are likely to be determinants of the persistence of HPV infections, or may affect the progression from infection to intraepithelial and invasive neoplasms, and still others may act through independent pathways as a part of a multi(co)factorial process.

Before the publication of the 1997 WCRF review, Potischman *et al.* (4) reviewed the effect of diet and nutrition as cofactors of cervical HPV carcinogenesis; the conclusion was either that there was fairly consistent evidence, that the risk of cervical cancer and its precursors may be related to low intake of vitamin C and carotenoids, and lesser evidence for low intake of vitamin E and folate, or that there was no convincing evidence that any dietary factor increases the risk of cervical cancer, but that diets high in vegetable and fruits, carotenoids, vitamin C and vitamin E are possibly protective, while folate and retinol possibly have no relationship.

4.2 Conclusions of the 1997 WCRF Review on Nutrition Food and Cervical cancer (5)

- Evidence on physical activity and the risk of cervical cancer, while suggestive of a protective association, is limited.

A study on college athletes showed a lower prevalence rate (RR 0.40, 0.18-0.85) of cervical cancer compared to non-athletes. (6;7)

Also the follow-up of NHANES-1 cohort study (8) showed an inverse association between cervical cancer and occupational physical activity.

- Regarding the relationship between cervical cancer and the intake of complex carbohydrates, no judgement is possible since the evidence is limited and inconsistent.

Three case-control studies, two on cervical cancer (9;10) and one on CIN III, (11) showed no association with complex carbohydrate intake. In a previous study on CIN III and complex carbohydrates intake Ziegler (12) reported a positive association. (OR 2.2, p<0.01)

- Regarding the relationship between cervical cancer and the intake of Non-starch polysaccharides/ dietary fibres, no judgement is possible since the evidence is limited and inconsistent.
- Regarding the relationship between cervical cancer and Fat and cholesterol intake no judgement is possible since the evidence is limited and inconsistent.
- Regarding the relationship between cervical cancer and protein intake no judgement is possible since the evidence is too limited.
- There was limited evidence that high intakes of alcohol increase the risk of cervical cancer.

Out of two case-control studies on alcohol consumption and risk of cervical cancer, one did not found any association.(13) The second showed a positive association only with beer intake. (14)

- High dietary intake of carotenoids possibly decrease the risk of cervical cancer

Several case-control studies examined the relationship between invasive cervical cancer or its precursors and intakes of carotenoids. Four studies (10;11;13;15) showed a protective effect of high dietary intake of total carotenoids on cervical invasive cancer. No reduction in risk was found in three studies that examined the relationship between precursor lesions and carotenoids. (15) (11;16) However, DeVet (17) found an increased risk with high intake of β -carotene. A negative association between β -carotene and other carotenoids and invasive cervical cancer was reported in a hospital-based case-control study. (9)

Five studies, conducted to test the relationship between serum levels of β -carotene and risk of invasive and pre-invasive cervical cancer, showed an inverse association.(18-22) In addition, the three Palan's studies (19-21) reported a protective association between levels of plasma β -carotene and neoplasia severity.

Four studies investigated CIN /CIS. (14) (23) (24) (25) Brock found that women in the top quartile of total dietary carotene had half of the risk of CIS. This protection disappeared with adjustment for confounders.

However, further investigation on β -carotene intake showed that women in the top quartile were at a 80%

reduced risk compared to those in the lowest quartile with a significant trend. (14) The same study reported a negative association for Lycopene. (14)

Van Eenwijk investigated several carotenoids; no association was found with lutein intake. (23)

No association was reported with levels of total plasma carotenoids in women with CIN I,II,III in the Butterworth study. (24)

However, results from the Maryland cohort study showed that high levels of several of the individual carotenoids (except lutein) were associated with a reduced risk of CIS and invasive cancer. (25)

- High dietary intake of Vitamin C possibly decrease the risk of cervical cancer

Three case-control studies reported a negative association between high intake of Vitamin C and cervical cancer.(9;10;16) Two other case-control studies reported a statistically non-significant protective association between intake of Vitamin C and cervical cancer.(12;14) In the Ziegler study a protective effect from Vitamin C only appeared in heavy smokers.

Protective association between Vitamin C intake and cervical dysplasia or intraepithelial neoplasia was found in case-control studies, in the USA and the Netherlands. (17;23)

Two ecological studies and a serological case-control study showed no correlation between Vitamin C and cervical cancer mortality.(24;26;27)

- High dietary intake of folate possibly has no relationship with the risk of cervical cancer

Butterworth *et al.*,(28) tested in a randomised controlled trial whether the folate supplementation influences the progression of cervical dysplasia. During the three months trial the severity of dysplasia decreased among the women who were using the folate *vs* who were using placebo. However, several methodological problems made the interpretation of these results very difficult. Butterworth *et al.*,(29) tested in another intervention trial whether the folic acid supplementation influences the progression of CIN I and CIN II, but no significant differences were observed between supplemented and no

supplemented subjects after 6 months of study. Childers *et al.*, (30) in another trial did not find any beneficial association between folate supplementation and CIN I or CIN II disease.

Six case-control studies, three of dysplasia or carcinoma in situ(11;14;31) and three of invasive cancer(9;10;12) examined the relationship between dietary folate and cervical neoplasia. None of these studies reported any statistically significant reduction of risk.

Three case-control studies(24;31) examined the relationship between serum or erythrocyte levels of folate and CIN I-III or invasive cancer(22). Only the Van Eenwyk *et al.* study(31) was consistent with a lower level of folate in serum and erythrocyte.

- High dietary intake of retinol possibly has no relationship with the risk of cervical cancer

The Cohort study by Hirayama(32) reported a strong inverse relationship between per capita vitamin A intake and cervical cancer mortality in Japan.

Among case control studies that examined the relationship between dietary intake of preformed Vitamin A and risk of cervical cancer, any association was not found.(9-18;33)

Four case control studies(13;32;34;35) showed a protective association with the risk of cervical cancer for consumption of foods containing Vitamin A, particularly those with β -carotene content.

The ecological study by Correa(26) found no significant correlations between various dietary items consumption and cervical cancer risk.

The phase III randomised trial by Meyskens *et al.* (36) to test if topically applied retinoic acid reversed CIN II or CIN III showed regression of CIN II in women receiving the therapy vs those who receiving placebo. No regression was observed in women with CIN III.

- High dietary intake of vitamin E possibly decrease the risk of cervical cancer

The cohort study of Batieha (25) showed no association between high plasma levels of vitamin E intake and the risk of cervical cancer. A Finland prospective study showed a statistically non significant inverse association between the risk of cervical cancer and Vitamin E intake. (37)

Among case-control studies, two USA studies found respectively, a statistically non significant (16) and a significant inverse association (10) for highest intake of Vitamin E. Among three serological case-control studies, two studies(20;38) showed a lower risk for cervical cancer with higher levels of total Vitamin E; the Potischmann *et al.* (22) study, however, did not find the same lower risk.

Cuzick *et al.*(38) also observed that the Vitamin E levels decreased from controls to CIN I to CIN III.

A case-control study, that investigated the use of multivitamin supplements and cancer risk, showed an unadjusted RR of 0.94 for cervical cancer among long term users *vs* non users of Vitamin E. (12)

- Diets high in certain vegetables and fruits possibly decrease the risk of cervical cancer and its precursor lesions.

Among the five studies on the relationship between invasive cervical cancer and consumption of fruit and vegetables, four reported a reduced risk. In particular Marschall *et al.*(13) reported a reduced risk with higher intake of broccoli, carrots, and tomatoes. La Vecchia *et al.*(15) reported a reduced risk with higher intake of green vegetables and carrots. Verreault *et al.*(10) showed a protective effect with a frequent consumption of dark green and yellow vegetables. Herrero *et al.*(9) found a reduced risk with increasing consumption of fruit juices or vegetables. The Ziegler *et al.*(12) study found no association with vegetables and fruits consumption.

Of the four studies on dysplastic lesions La Vecchia *et al.*(15) reported no association. Brock *et al.*(14) found a protective association with fruit juices and salad. Ziegler *et al.*(12) reported a protective association with higher intakes of dark-yellow-orange vegetables and fruits, and De Vet *et al.*(17) reported a reduced risk with increased consumption of tomatoes, fruits and orange juices, but an increased risk with cabbages, spinach and carrots.

The ecological study of Armstrong and Doll (39) showed a positive correlation between frequency of fruit consumption and cervical cancer mortality.

- No conclusion was made with reference to intake of meat and the risk of cervical cancer since the evidence was limited
- No conclusion was made with reference to intake of milk and dairy products and the risk of cervical cancer since the evidence was limited and inconsistent.

4.3 Recent Research

Diet and nutrition as cofactors of cervical HPV carcinogenesis have been recently reviewed by R. Garcia-Closas *et al.* (submitted). (40) Garcia-Closas *et al.* (40) included in their review 23 observational studies that controlled for HPV and 6 randomised trials. The authors concluded that there was a fairly consistent inverse association between fruits and vegetables and HPV persistence. As for nutrients, evidence for this inverse association was considered strongly consistent for lycopene (but not for other carotenoids nor for retinol) and vitamin E, and moderately consistent for vitamin B12 and vitamin C. An increased risk associated with plasma homocysteine, which is inversely associated with folate, vitamin B12 and vitamin B6, was also considered strongly consistent. However, no consistent protective effect of folic acid was observed. A recent study suggested that folic acid may be protective only for to women with the variant 677C→T allele of methylenetetrahydrofolate reductase. (41)

The relationship of cervical cancer with body weight and physical activity was recently reviewed by the IARC working group on ‘Weight control and physical activity’(42). The working group concluded that the evidence for an association is inadequate.

The same IARC working group recently reviewed the relationship between fruit and vegetable consumption and the risk of cancers.(43) Regarding cervical cancer (either invasive or precancerous lesions), the review concluded that the findings are inconsistent and there is little evidence for a strong effect of vegetable and fruit intake on risk.

Chemoprevention trials with natural vitamins or synthetic analogs on histologic or colposcopic regression of cervical preinvasive lesions have also been recently reviewed. (44) Phase II and/or III trials were carried out with topical all-trans-retinoic acid, and oral 4 hydroxyphenilretinamide, beta-carotene, vitamin C and folate. None reported statistically significant differences in regression of cervical lesions.

5.0 Search strategy

The aim of the literature search strategy is to retrieve studies that report the associations between food, nutrition, anthropometry and physical activity and the risk of cervical cancer, thus responding to the research question.

To produce the EndNote file¹ for cervical cancer, we have used the search strategy provided by WCRF for Medline with the addition of the following MeSH terms:

“Food Habits” [MeSH]
“Micronutrients” [MeSH]

the following Text-words:

Lactose
Galactose
Cheese
Sausage
Ham

and a few specific Text-words for vegetables:

Potato*
Cabbage*
Brassica
Cruciferous
Radish
Carrot*
Lettuce*
Spinach
Onion*
Tomato*
Soybean

Referring to the Physical activity list of exposures we shall add the Text-word “Sport*”.

As for the outcome we have used the following strategy:

5. "Cervix Dysplasia"[MeSH] OR "Cervix Neoplasms"[MeSH] OR "Cervical Intraepithelial Neoplasia"[MeSH] “

6. (Cervix OR cervical) AND (cancer* OR tumour* OR tumor* OR neoplasm*)
7. Cervix adenocarcinoma OR cervical adenocarcinoma OR cervical epidermoid carcinoma OR cervical squamous carcinoma OR cervical squamous cell carcinoma OR cervical large cell carcinoma OR cervical small cell carcinoma OR cervical keratinizing carcinoma OR cervical nonkeratinizing carcinoma OR cervical microinvasive carcinoma OR cervical severe dysplasia OR cervix epidermoid carcinoma OR cervix squamous carcinoma OR cervix squamous cell carcinoma OR cervix large cell carcinoma OR cervix small cell carcinoma OR cervix keratinizing carcinoma OR cervix nonkeratinizing carcinoma OR cervix microinvasive carcinoma OR cervix severe dysplasia
8. Cervical Intraepithelial neoplasm*[tiab] OR Cervix dysplasia [tiab]
9. Endocervix OR endocervical canal OR cervical canal OR cervix canal uterine OR squamocolumnar junction) AND (cancer* OR tumour* OR tumor* OR neoplasm*)
10. LOW GRADE SQUAMOUS LESION* or SIL or LOW GRADE SQUAMOUS intra-epithelial lesion* OR squamous intraepithelial lesion* OR LSIL OR L-SIL OR HSIL OR H-SIL OR high grade squamous intraepithelial lesion*

1 OR 2 OR 3 OR 4 OR 5 OR 6

The complete search strategy developed for MedLine is reported in the **Appendix 1** of this protocol. We have not used the Mesh descriptor “Human” because many references potentially relevant for the review (containing terms for the outcome recently introduced in Medical literature such as SIL or LSIL or HSIL) were still in process.

As for the other Databases we have searched all those in the recommended list of WCRF.

We did no use any epidemiologic filter to produce the search for Medline and for the other databases.

Our EndNote file1 for cervical cancer contain 7860 references with 345 references (marked “IN”) potentially relevant for the review by reading title and/or abstract..

After having completed the search of the recommended database we shall check also CINAHL, IMSEAR, IMEMR, AIM, AMI, Amed and ExtraMed.

All searches have been produced from the inception date of the database. All the language limiters have been removed from each database search in order to identify studies in all languages.

6.0 Study selection criteria

The criteria used for including and excluding literature in the systematic review rise logically from the research question defined above.

All the relevant articles helping to answer the review question, will be identified, retrieved, and reviewed.

The results of our all databases search (7860 references) has been sent to WCRF international in a specific EndNote file 1 (**Cervix1_INT**) according to the deadline reported in Table 2 of the “Timeline” section of this protocol.

In this file all the references have been entered in the field “label” with their specific codes. This field contains a unique identification code (3-letter code “CER” for cervical cancer specific site prefixing a 5-digit number, CER00001 onwards) for each reference. The same file contains a custom field named “inclusion” that, marked “In” or “Out”, describes papers potentially relevant or not (only by title or abstract) as specified in the SLR manual. The 6 reviewers into 3 couples have undertaken in duplicate the initial scan of the 7860 references to remove all the obviously irrelevant ones (only based on title and/or abstract) and to decide which references were to be included. Each reviewer has checked through the assigned references alone and then has compared his results with the second reviewer in order to reach a final consensus.

All the full papers referenced marked “In” in the file1 (345) , will be identified and retrieved.

At this stage also, any decisions about their inclusion or exclusion in the review will be performed in duplicate using the same criteria. When, after reading the paper there is evidence that the paper doesn't refer to the research question, and agreement among the two reviewers for excluding, the paper will be excluded and no data extraction will be performed on it. Specifically, the papers to be included in the review:

- 1. Have to present results from a study type (contained in the study design algorithm of the Appendix J of the Specification Manual)**
- 2. Must have as outcome of interest cervical cancer (or its precancerous lesions) incidence or mortality**

3. Have to present results on relevant exposures (food, nutrient, anthropometry or physical activity) in to cervical cancer risk.

Any disparity in including/excluding paper should be resolved initially within the SLR team, then with the Review Coordinator and only at the end with the Advisory group. A document containing reasons for excluding papers will be submitted to the WCRF International as an EndNote file (EndNote file2). In this file all the references excluded will be entered in the field “label” with their specific codes. The same file will contain a custom field named “reason” that will specify the reasons for exclusion for each paper (e.g. review, no reference to the research topic, migrants study etc.). A list of the “reasons” for exclusion is enclosed in the Appendix 2 of this protocol. The references section of the reviews will be checked to identify papers that may have been missed in the search.

The list of papers to be included in the review will be recorded in an EndNote file (EndNote file3). In this file all the references will be entered in the field “label” with their specific codes. The same file will contain a custom field named “study design” marked with a letter that will specify the study type for each paper according to the Appendix J of the Specification manual.

At the end of the SLR, copies of all the references included will be sent to WCRF International with the EndNote database.

6.1 Definition of selection criteria

Selection criteria have been defined in terms of population characteristic, type of exposure, types of study and outcome.

6.1.1 Population

All the studies on human population will be reviewed with respect to the review question.

Also mechanistic studies on animal model (considering only “in vivo” studies) will be included if relevant for human cervical cancer process as explained in the section 13.8 of the SLR specification manual. In fact, experimental data may help in evaluating epidemiological associations and in inferring causation. Our cervical cancer mechanisms expert, Dr. Garcia-Closas, will be responsible for a comprehensive narrative of the mechanisms relevant to the research question and will participate in the SLR “Mechanisms Working Group”.

6.1.2 Exposure

General foods, diet, nutrition status, physical activity and anthropometric measures will be investigated in relation to risk of cervical cancer according to the etiologic criteria of the review question.

As described in the Research question section of this protocol, besides classical dietary assessment tools (e.g Food Frequency Questionnaires), dietary factor exposures could also be assessed by mean of direct biological markers of dietary intake (such as serum alpha-tocopherol, serum carotenoids, and serum selenium).

Life course exposure (childhood, adolescent and adulthood diet or anthropometry) measurement will be included in the review.

6.1.3 Types of study

Studies will be only excluded if they are unrelated to the topic and are therefore external to the research question. According to the study design definitions of the Appendix J of the Specification Manual, eligible study designs to be included in the review are:

Study design A Case-study / case series

Study design B	Cross-sectional study
Study design C	Randomised controlled trial
Study design D	Group randomised control trial
Study design E	Uncontrolled trial
Study design F	Ecologic study
Study design G	Case-control study
Study design H	Non-randomised control trial
Study design J	Prospective cohort study
Study design K	Nested case-control study
Study design L	Historical cohort study
Study design M	Case-cohort study
Study design N	Time series with multiple measurement
Study design P	Case only study with retrospective exposure measurement
Study design Q	Case only study with prospective exposure measurement

A study may produce a number of publications that satisfy the inclusion criteria; a table describing the number of papers derived from that study and the specific study identifiers will be add in appendix to the SLR report (following the instruction of the 13.11.1 section of the manual).

According to WCRF instructions, case series studies will be recorded but no data extraction will be carried out unless these are the only available.

For the inclusion of mechanistic studies we will follow the specific instructions reported in the specification manual (Section 13.8). Only “*in vivo*” studies in human volunteers, transgenic animal models germane to human cancer and rodent cancer models (**Class 1 of evidence**) will be included. First, a search for recent (within last 12 months) mechanistic reviews will be carried out; their exposure should be well defined and relevant (to human

exposure) and their end-point (e.g. cervical cancer) should be defined. If no suitable review is available, original papers will be retrieved.

Studies that investigate the gene-nutrition interaction in causing cervical cancer will be included.

6.1.4 Outcome

The outcome of interest is cervical cancer encompassing incidence and mortality.

Whenever a study provides sufficient information, data will be summarised by histological subtype (squamous cell carcinoma, epidermoid carcinoma (large cell or small cell, keratinizing or nonkeratinizing) or adenocarcinoma) and by invasive *vs in situ* carcinomas.

Studies on cervical intraepithelial dysplasia (CIN I to CIN III) or squamous intraepithelial lesions (SIL) will also be reviewed.

All the papers reporting outcome for more than one cancer site, will be sent to the Review Coordinator.

6.2 Hand searching

According to the SLR specification manual (section 13.9), we will do hand searching when a journal not included in the electronic database will consistently appear in the citation list of papers identified by the search.

In fact, hand searching will be useful to identify missed articles or journals not routinely included in electronic databases.

6.3 Data Range

All the studies for inclusion in the review will be identified by searching the databases for literature as expressed in the Search Strategy section and will cover all the databases time period going back to their date of inception.

A multi-database search will ensure the collection of a comprehensive list of references.

6.4 Quality

Studies will not be excluded on the basis of reviewers perceived quality. The Panel will be in charge of judgement of studies quality analysing the results of the review. The SLR team will display to the Panel all type of evidence and highlight the study characteristics that may influence the results. As explained in the following section n.7 of this protocol, several quality markers of a study will be included in the Access input software. Referring to the assessment method, for example, information about validity and repeatability, if a different assessment method is used in cases and control, information about the modality of administration or the source of information etc. will be reported.

6.5 Language

Studies will not be excluded on the basis of languages. Non-English titles or abstract will be included in the search whenever relevant for the review topic. English abstracts of non-English papers will be reviewed. Papers that are written in languages other than those covered by the review team (English, Italian, Spanish, French, Portuguese) and possibly relevant for the review topic will be sent to WCRF Secretariat to ascertain their relevance and, where necessary, arrange a full translation. For non-English abstracts any efforts will be made to translate it locally. If this is not possible, abstracts will be sent to WCRF Secretariat to ascertain their relevance and, to arrange a full translation. The number and the relevance (or not) of non-English abstracts sent to the WCRF Secretariat for translation will be recorded.

2.1.4 6.6 Other publications

Only published and peer reviewed literature will be included in the review.

Grey literature such as dissertations, abstracts, conference proceedings, reports and other non peer-reviewed research will not be included.

The Panel has identified a list of major cohorts studies and randomised control trials to be placed on the WCRF international Website.

According to the WCRF instruction, in-press articles from this predefined list of cohorts/RCTs and relevant for the review topic will be included in the 2006 update.

7.0 Data extraction

Relevant data will be obtained from the full text of each paper included in the review and reported in the EndNote file 3.

The information will be obtained from each paper with three purposes:

- To collect general information about study, study design and methods to review and classify the study as a whole.
- To extract all the exposure-specific data to enable a comprehensive display and description of evidence; information necessary to conduct subsequent eventual meta-analyses will also be kept for each exposure level.
- To allow the necessary assessment of study quality.

To help allocating study design to papers, the study design algorithm and the study design definition (appendix J and K of SLR manual version 10) will be used as guidance. The assignment of the study design to papers will be checked in duplicate in order to ensure a correct data extraction sheet for each reference.

After having received and tested the Access software developed by Leeds, we have decided to use it for data extraction. Several items, that are not expressly requested in the software, will be accommodated in specific open fields. The same design of data extraction sheets used for ovarian cancer, will be followed for cervical cancer review. In our expanded manual for data extraction, sent to WCRF, we have described the rules and the indications to fill in the specific fields of the LEEDS' software. We have also succeeded in using specific Freetext field of the LEEDS' software to accommodate the quality additional items not expressly requested in the Access software . No other software will be used for data extraction.

Data will be extracted for each exposure investigated by papers according to the list of exposures terms included in the Specification Manual.

Even if SLR team does not exclude any studies on the basis on the perceiving quality, a quality assessment of studies is essential to:

- find potential source of bias
- trying to explain heterogeneity in study results
- assisting the Panel in the interpretation of findings
- suggest indication for future research

In assessing the potential biases we will pay special attention to selection bias (follow-up bias in cohort studies), information bias and if confounding is controlled for. The following table reports general confounding in studies on diet and cancer, with special attention to cervical cancer specific site.

3

4 **Table 4: General potential confounders in diet-cancer studies**

Specific for cervix	Human papilloma virus
	Cervical screening
	Immune dysfunction
	Oral contraceptive use
	Age 1 st intercourse
	Parity
	N. of sexual partners
General	Age
	Sex
	Smoking habits (current and history)
	Social class/living conditions/income
	Physical activity
	Body mass index (BMI)
	Total energy intake
	Alcohol consumption
	Ethnicity
	Supplement use
	Family history of specific cancer (1 st degree relatives sufficient)
	Other components of the diet
	Residence
	Hospital/setting
	Interviewer*

*Confounding may result from the allocation of a different number of cases and controls to different interviewers

The adjustment for confounders will be taken into account as quality marker of a study in the heterogeneity assessment phase.

The following table reports potential effect modifiers to be considered in analysing data on diet and cervical cancer.

5
6 Table 5: Potential effect modifiers in diet-cancer studies

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

Data extraction will be completed in duplicate; Dr.Berrino and Dr. Krogh will check the results of the extraction to assess the consistency among the reviewers. Any disparity will be initially discussed within the team then, if necessary, with the Review Co-ordinator and if still unresolved with the Advisory Group.

No data extraction will be carried out for case-series studies unless these will be the only study types available.

Data from studies assessing gene-environment interactions will be extracted.

7.1 Multiple publication

Sometimes the same study is reported in different publication with different outcomes, different updating or different definition of exposures. Data from each individual paper will be extracted; but any overlap will be highlighted in the data extraction sheet to prevent the same study twice in the meta-analysis.

If the suspect will arise that the same data is reported more than once, we will contact firstly the authors for clarification and than, if necessary, the Review Coordinator.

6.1.1.1 8.0 Data analysis

For each specific exposure a decision would be made whether or not to proceed to formal meta-analysis. This decision will be based on the number of the available studies, the availability of sufficient information in an appropriate format, consistency of exposure definition, and heterogeneity of results.

Most likely, meta-analysis will be performed for anthropometry, carotenoids, alcohol, fruit and vegetables, milk, eggs and saturated/polyunsaturated fat.

The statistical software package designed to perform the meta-analysis is STATA 8.

6.1.2 8.1 Heterogeneity analysis

The first step of our meta-analysis will be to assess the presence of heterogeneity in the studies reviewed by both qualitative and quantitative methods. We will formulate *a priori* hypotheses that explain heterogeneity.

To assess heterogeneity, selected study characteristics will be summarised in a table, specific for each study design. In **Appendix 3**, the format for Case-control and Prospective cohort studies table are reported.

These tables include as possible source of heterogeneity:

variables common for all study design (Exposure assessment method, Exposure range, Country/region, Ethnicity, age, type of outcome (hystological type), grading (dysplasia, *in situ*, microinvasive or invasive) adjustment for confounders)

and variables specific for prospective cohort studies (length of follow-up, definition of outcome). In fact, the outcome encompasses incidence and mortality, which may reflect indolent *vs* aggressive disease, heterogeneity between these two outcomes will be carefully examined before proceeding to meta-analysis.

As described in the Data extraction section, a specific quality table, useful to assess heterogeneity, will be produced, whenever possible, for each study designs. Forest plots will be used to assess and display potential heterogeneity; funnel plots will be used to explore the possibility of publication bias. These will be provided as

standard part of data presentation together with the Log rank test of Begg and Mazumdar (45) for publication bias.

The amount of heterogeneity will be measured by the I^2 statistic.

Quantitative test, such as the one devised by Cochran (46) using a standard χ^2 statistic will be performed. The underlying causes of heterogeneity will be explored and when possible a stratified analysis will be performed.

A regression analysis can be also performed to examine if the heterogeneity between studies can be explained by one or more factors (e.g. study characteristics) across all studies. Therefore, a meta-regression will be performed to identify possible sources of heterogeneity.

Should be considered that given the limited number of studies that explore the relationship between cervical cancer and diet, nutrition and physical activity, a formal heterogeneity analysis and the subsequent meta-analysis that take into account more than one of the selected study characteristics will probably be precluded.

6.1.3 8.2 Measure of exposure

Studies that explore the association between diet components and cancers are characterised by a continuous exposure measurement that, however, may be analysed and reported in different ways. This is challenging in formal meta-analysis. For meta-analyses our review team will follow the strategies for different reported measurements (i.e. means of consumption, categories of consumption etc.) addressed by Greenland and Longnecker (47) and Chene and Thompson (48).

Our primary meta-analysis will be based on log odds ratio per unit increase in the exposure variable with its standard error and a dose-response graph will be performed whenever possible to summarise the quantitative results.

However, for some food groups (i.e beverages such as alcohol, tea etc.), when a dose response estimate will not be recommended due to few levels of exposures with open-ended category we will compare the relevant outcomes in the exposed vs unexposed using pooled Or or RR following the Mantel-Haenszel style estimator for

fixed effect models and the DerSimonian and Laird approach for random effects models described by Engels *et al.*(49)

6.1.4 8.3 Fixed effect model and Random effect model

Both models (fixed and random) will be used to compute a summary estimate of effect in our meta-analysis.

If important differences between these estimates occur, we will conduct further sensitivity analysis to explain undetected and residual heterogeneity.

8.4 Sensitivity analysis

Sensitivity analysis will be performed to explore the robustness of any conclusion reached from meta-analysis to the decisions made in the process of statistical analysis.

In particular:

- the sensitivity of results to inclusion or exclusion of individual studies basing on different criteria (type of study, definition of exposure or outcome, one or more large studies that tend to dominate the results)
- fixed or random effect model

6.1.4.1 9.0 References

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Appendix 1: Medline search

#53 Search (#2 OR #3 OR #5 OR #6) AND (#9 OR #11 OR #12 OR #13 OR #16 OR #18 OR #20 OR #22 OR #29 OR #30) Field: All Fields, Limits: 30 Days	09:44:44	30
#34 Search #33 Field: All Fields, Limits: Female, Human	08:52:35	3375
#33 Search #27 OR #32	08:52:04	4636
#32 Search #7 AND #31	08:50:50	755
#31 Search #28 OR #29 OR #30	08:50:31	525213
#30 Search 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 overweight[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]	08:50:13	191625
#29 Search 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]	08:49:55	123253
#28 Search 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]	08:49:42	373766
#27 Search #7 AND #26	08:45:37	4083
#26 Search #23 OR #25	08:45:12	2541775
#25 Search pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]	08:44:31	42182
#23 Search #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	08:31:48	2524833
#22 Search 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]	08:30:46	783406
#21 Search vitamins[MeSH Terms]	08:30:29	156111
#20 Search salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR	08:30:16	520351

- diet*protein*[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]**
- #19 Search **dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR sweetening agents[MeSH Terms]** 08:29:59 [97518](#)
- #18 Search **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]** 08:29:46 [44595](#)
- #17 Search **cookery[MeSH Terms]** 08:29:30 [3586](#)
- #16 Search **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]** 08:29:17 [291299](#)
- #15 Search **food preservation[MeSH Terms]** 08:29:02 [5955](#)
- #14 Search **diet therapy[MeSH Terms] OR nutrition[MeSH Terms] OR Food Habits[MeSH Terms] OR Micronutrients[MeSH Terms]** 08:28:47 [169005](#)
- #13 Search **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]** 08:28:34 [139847](#)
- #12 Search **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]** 08:27:56 [407003](#)
- #11 Search **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]** 08:27:31 [635410](#)

#10 Search food and beverages [MeSH Terms]	08:27:10	251488
#9 Search 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]	08:26:58	354049
#8 Search diet therapy [MeSH Terms] OR nutrition [MeSH Terms]	08:26:43	163396
#7 Search #1 OR #2 OR #3 OR #4 OR #5 OR #6	08:26:12	53605
#6 Search LOW GRADE SQUAMOUS LESION* or sil or LOW GRADE SQUAMOUS intra-epithelial lesion* OR squamous intraepithelial lesion* OR LSIL OR L-SIL OR HSIL OR H-SIL OR high grade squamous intraepithelial lesion* Field: Title/Abstract	08:25:30	3729
#5 Search endocervix OR endocervical canal OR cervical canal OR cervix canal uterine OR squamocolumnar junction) AND (cancer* OR tumour* OR tumor* OR neoplasm*) Field: Title/Abstract	08:25:01	3612
#4 Search Cervical Intraepithelial neoplasm* [tiab] OR Cervix dysplasia [tiab]	08:24:35	110
#3 Search cervix adenocarcinoma OR cervical adenocarcinoma OR cervical epidermoid carcinoma OR cervical squamous carcinoma OR cervical squamous cell carcinoma OR cervical large cell carcinoma OR cervical small cell carcinoma OR cervical keratinizing carcinoma OR cervical nonkeratinizing carcinoma OR cervical microinvasive carcinoma OR cervical severe dysplasia OR cervix epidermoid carcinoma OR cervix squamous carcinoma OR cervix squamous cell carcinoma OR cervix large cell carcinoma OR cervix small cell carcinoma OR cervix keratinizing carcinoma OR cervix nonkeratinizing carcinoma OR cervix microinvasive carcinoma OR cervix severe dysplasia Field: Title/Abstract	08:24:14	6767
#2 Search (Cervix OR cervical) AND (cancer* OR tumour* OR tumour* OR neoplasm*) Field: Title/Abstract	08:22:58	26047
#1 Search "Cervix Dysplasia" [MeSH] OR "Cervix Neoplasms" [MeSH] OR "Cervical Intraepithelial Neoplasia" [MeSH]	08:22:37	35425

Appendix 2: reasons for exclusion papers

Review

Meta-analysis

Migrants study

Out of the research topic

No measure of relationship

No measure of exposure

No exposure of interest

No specific outcome

Suppletive main manuscript

Appendix 3

Table 1: Summarising table for case-control study

<i>Study identifier</i>	<i>Author</i>	<i>Yr</i>	<i>Type of Exposure</i>	<i>Exposure range</i>	<i>Time of exposure assessed</i>	<i>Assessment method</i>	<i>Country/region</i>	<i>Ethnicity</i>	<i>Age</i>	<i>N. of cases</i>	<i>N. of controls</i>	<i>N. of exposure categories</i>	<i>Histological type</i>	<i>Grading</i>	<i>RR/OR</i>	<i>Ref category</i>	<i>CI</i>	<i>P value</i>	<i>p value for trend</i>	<i>Confounders adjusted for</i>	<i>Matching Variables</i>	

Table 2: Summarising table for Prospective cohort studies

<i>Study identifier</i>	<i>Author</i>	<i>Yr</i>	<i>Type of Exposure</i>	<i>Exposure range</i>	<i>Time of exposure assessed</i>	<i>Assessment method</i>	<i>Country/region</i>	<i>Ethnicity</i>	<i>Age</i>	<i>N. of cases</i>	<i>Size of cohort</i>	<i>Length of follow-up</i>	<i>Histological type</i>	<i>Grading</i>	<i>Definition of outcome</i>	<i>N. of exposure categories</i>	<i>RR/OR</i>	<i>Reference category</i>	<i>CI</i>	<i>P value</i>	<i>p value for trend</i>	<i>Confounders adjusted for</i>