World Cancer Research Fund International

Systematic Literature Review

The Associations between Food, Nutrition and Physical Activity and the Risk of Cervical Cancer

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List of Abbreviations used in the CUP SLR

CUP	Continuous Update Project
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
SLR	Systematic Literature Review
RR	Relative Risk
LCI	Lower Limit Confidence Interval
UCI	Upper Limit Confidence Interval
HR	Hazard Ratio
CI	Confidence Interval

Other abbreviations used in Tables

FFQ	Food Frequency Questionnaire
hr	hour
HvL	highest vs lowest
Yrs	Years
W	Women

List of Abbreviations of cohort study names used in the CUP SLR

CNBSS	Canadian National Breast Screening Study
CPS II	Cancer Prevention Study
CPRD	Clinical Practice Research Data link
DOS	Obese Danish Cohort
EPIC	European Prospective Investigation into Cancer and Nutrition
JACC	Japan Collaborative Cohort Study
KPMCP	Kaiser Permanente Medical Care Program
KRIS	Kaunas Rotterdam Intervention Study and Multifactorial Ischemic Heart Disease Prevention Study
KNHIC	Korea National Health Insurance Corporation Study
Korea 2004-2013	Korea Cohort 2004-2013
KRIS-MIHDPS	Kaunas Rotterdam Intervention Study (KRIS) and Multifactorial Ischemic Heart Disease Prevention Study (MIHDPS)
MCS I	Miyagi Prefecture Cohort I
MWS	Million Women Study
NHANES	National Health and Nutrition Examination Survey
NIH-AARP	NIH-AARP Diet and Health Study
NSPT	Norwegian screening programme for tuberculosis
VHM&PP	The Vorarlberg Health Monitoring and Prevention Program
WHI	Women Health Initiative Study

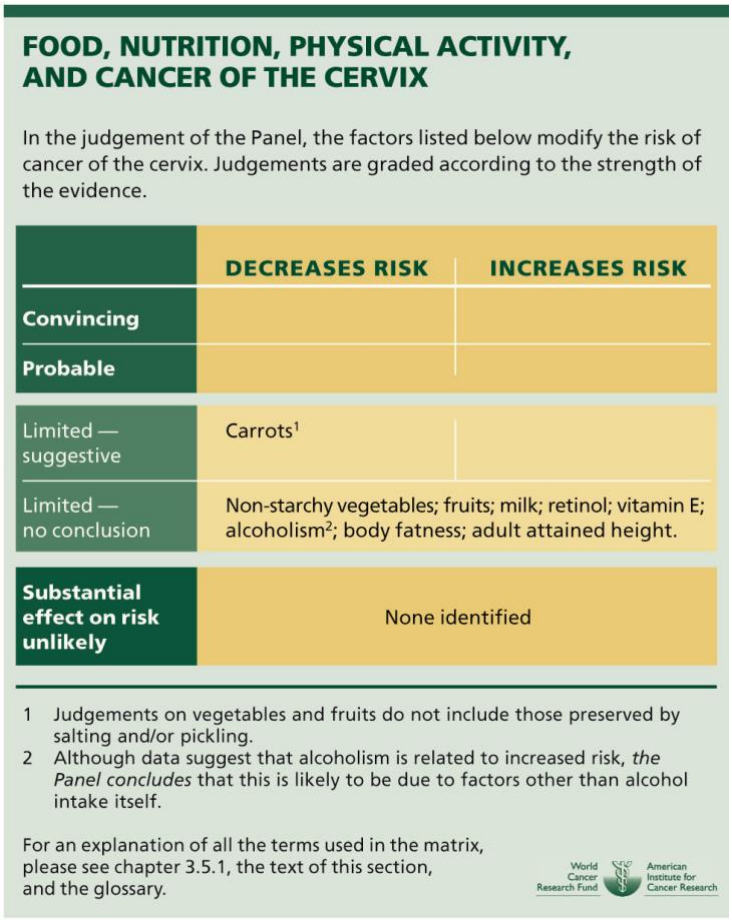
BACKGROUND

The main objective of the present systematic literature review is to update the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of cervical cancer.

This SLR does not present conclusions or judgements on the strength of the evidence. The CUP Panel will discuss and judge the evidence presented in this review.

The methods of the SLR are described in details in the protocol for the CUP review on cervical cancer.

Cervix cancer. Judgement of the WCRF/AICR Second Expert Report 2007



FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE CERVIX

In the judgement of the Panel, the factors listed below modify the risk of cancer of the cervix. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		
Limited — suggestive	Carrots[1]	
Limited — no conclusion	Non-starchy vegetables; fruits; milk; retinol; vitamin E; alcoholism[2]; body fatness; adult attained height.	
Substantial effect on risk unlikely	None identified	

1 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
2 Although data suggest that alcoholism is related to increased risk, *the Panel concludes* that this is likely to be due to factors other than alcohol intake itself.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

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Notes on methods

- The article search and WCRF database update for the Second Expert Report ended in December 31st 2005. The CUP team at IC updated the search from January 1st 2006 up to May 31st 2016 (See Flowchart).
- 2005 SLR refers to the first update of the 2005 SLR and CUP refers to the current update (2016 SLR).
- Dose-response meta-analysis were updated when at least two new publications with enough data for dose-response meta-analysis were identified during the update and if there were in total five relevant published cohort studies or five randomised controlled trials. The meta-analyses include all relevant published studies.
- The term "dose-response meta-analysis" refers to meta-analysis conducted using log-linear dose-response models. Non-linear meta-analysis refers to meta-analysis using log-non-linear models.
- Exposures for which the evidence was judged as convincing, probable or limited-suggestive in the Second Expert Report are reviewed in the CUP even if the number of publications was below the previous figures; in most cases, the new data on these

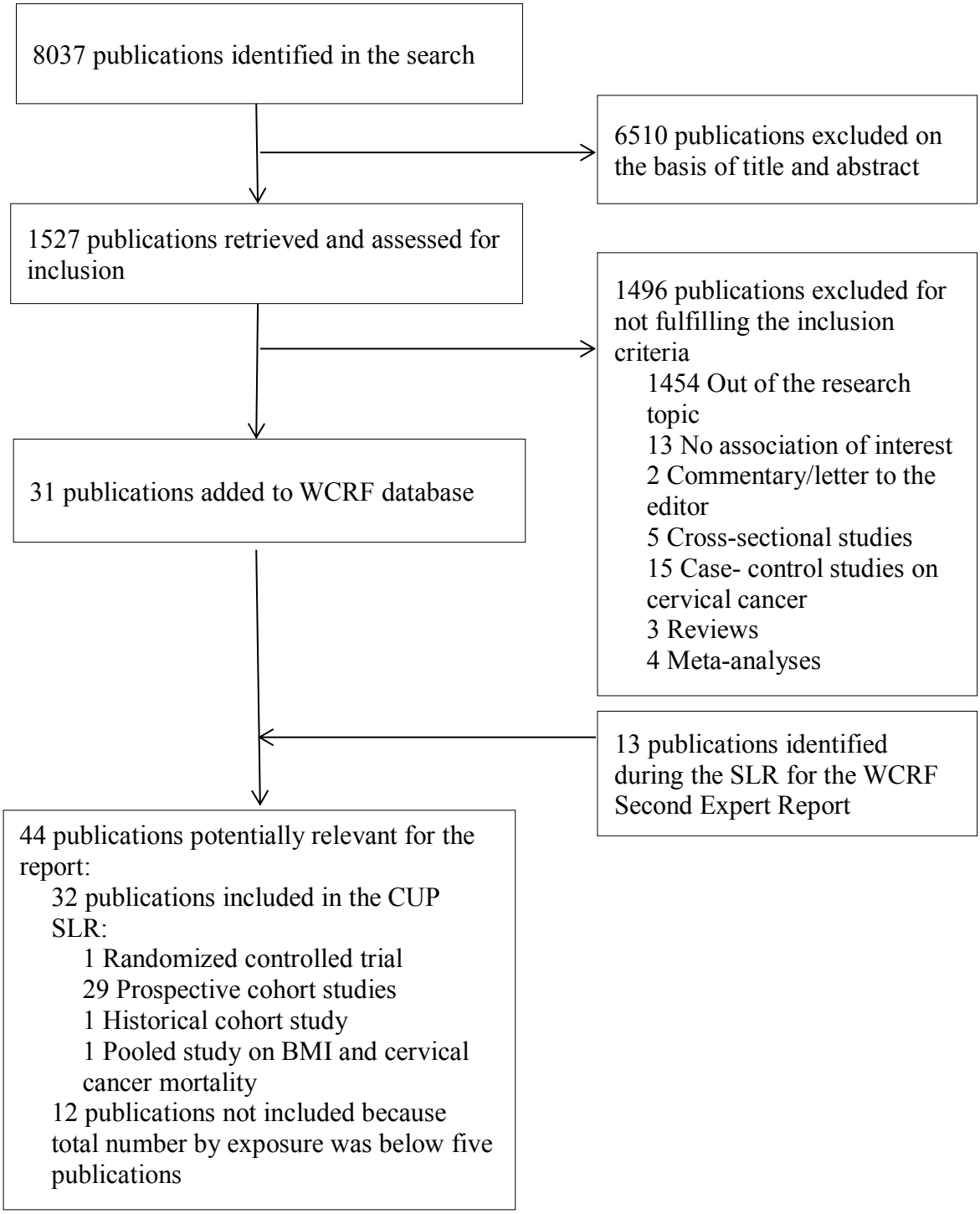
exposures are tabulated and no meta-analyses are conducted. The evidence on carrots intake was judged as "limited suggestive" in the 2007 WCRF second expert report and this exposure and related nutrients were reviewed here.

- For comparability, the increment units for the dose-response analyses were those used in the meta-analyses in the CUP- SLR conducted for other cancers. However, if most of the identified studies reported in a different unit (servings or times/day instead of g/day) these were used as increment unit, as indicated in the Protocol.
- The statistical methods to derive missing data are described in the protocol.
- The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.
- The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity. Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.
- Only summary relative risks estimated with random effect models are shown.
- Highest vs lowest forest plots show the relative risk estimates for the highest vs the reference category in each study. The overall summary estimate was not calculated except for exposures such as physical activity or multivitamin supplement use where dose-response analysis could not be conducted or when the pooling project results could be included in a highest compared to lowest analysis, but not in a dose-response analysis.
- The dose-response forest plots show the relative risk per unit of increase for each study (most often derived by the CUP review team from categorical data). The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and in the summary table for each exposure.
- Dose-response plots showing the RR estimates for each exposure level in the studies are also presented for each reviewed exposure. The relative risks estimates were plotted in the mid-point of each category level (x-axis) and connected through lines.
- Exploratory non-linear dose-response meta-analyses were conducted only when there were five or more studies with three or more categories of exposure – a requirement of the method. Non-linear meta-analyses are not included in the sections for the other exposures. For exposures where the test for non-linearity is non-significant, the non-linear figures are not displayed.
- The interpretation of the non-linear dose-response analyses should be mainly based on the shape of the curve and less on the p-value as the number of observations tended to be low, in particular in the extreme levels of exposure.

Continuous Update Project: Results of the search

Flow chart of the search for cervical cancer – Continuous Update Project

Search period January 1st 2006 - May 31st 2016.



Randomized Controlled Trials

Only one randomized controlled trial, Women's Health Initiative-Dietary Modification Trial (WHI DM trial) (Prentice, 2007) that comprised a low-fat diet was identified after the 2005 SLR.

An update of the WHI DM trial (Prentice, 2007) did not support a significant effect of low-fat dietary intervention on cervix cancer prevention.

The WHI-DM trial (recruitment 1993-1998, end of intervention 2005) was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy and increasing consumption of vegetables and fruit to at least 5 servings daily and grains to at least 6 servings daily. Comparison group participants were not asked to make dietary changes. Postmenopausal women (age 50-79 years) with ≥33% of total energy from fat were randomly assigned to the intervention group (40%, n=19 541) or the comparison group (60%, n=29 294).

Results for an average 8.1 years of follow-up showed a non-significant reduction in cervix cancer risk with the low-fat dietary intervention (HR for intervention vs comparison=0.46, 95% CI=0.15-1.42) (4 cervix cancer cases in the intervention group and 13 in the comparison group).

Cohort studies. Results by exposure

Data from cohort studies published in 13 papers identified in the search for the Second Expert Report and 18 papers identified in the CUP search are included in the tables and figures in this review. The data is not shown if less than five papers with relevant data had been published with the exception of exposures whose evidence of association with cervical cancer was judged strong in the Second Expert Report (see Table 1).

Table 1 Number of relevant publications identified during the 2005 SLR and the 2016 SLR and total number of publications by exposure.
The exposure code is the number in the database. Only exposures identified during the CUP are shown. Note: a number higher than five does not necessarily mean that there are sufficient studies with the data required to conduct meta-analysis.

Exposure Code	Exposure Name	Number of Publications		Total number of publications
		Cohort 2005 SLR	Cohort 2016 SLR	
1.1.1	Mediterranean diet	0	1	1
1.3.2	Seventh day Adventists	1	0	1
1.4	Healthy pattern	0	3	3
1.5	Other dietary patterns	0	1	1
1.7	Other dietary pattern issues	0	1	1
2.1.1.2.3	Rice	0	1	1
2.1.2	Root vegetables	0	1	1
2.1.2.1	Potatoes	0	1	1
2.2	Total fruits	0	1	1
2.2.1	Total vegetables	1	2	3
2.2.1.1	Garlic and onion	0	1	1
2.2.1.1.1	Carrots	0	1	1
2.2.1.2.2	Chinese cabbage	0	1	1
2.2.1.2.3	Cabbage	0	1	1
2.2.1.4.2	Spinach	0	1	1
2.2.1.4.4	Seaweed	0	1	1

2.2.1.5.13	Tomatoes	0	1	1
2.2.2	Fruit	0	1	1
2.2.2.1	Citrus fruits	0	2	2
2.2.2.2	Other fruits	0	1	1
2.3.1.1	Miso soup	0	1	1
2.3.2	Beans	0	1	1
2.5.1.2	Processed meat	0	2	2
2.5.1.3	Red meat	0	1	1
2.5.1.3.1	Beef	0	1	1
2.5.1.3.3	Pork	0	1	1
2.5.1.4	Poultry	0	2	2
2.5.1.5	Liver	0	1	1
2.5.2	Fish	0	2	2
2.5.2.3	Dried and salted fish	0	1	1
2.5.4	Eggs	0	1	1
2.6	Fat preference	0	1	1
2.6.1.1	Butter	0	1	1
2.6.1.4	Cod liver oil	0	1	1
2.6.3	Margarine	0	1	1
2.7	Dairy products	1	0	1
2.7.1	Milk	1	1	2
2.7.2	Cheese	0	1	1
2.7.3	Yoghurt	0	1	1
2.9.13	Sweets	0	1	1
3.5	Fruit juices	0	1	1
3.6.1	Coffee	0	1	1
3.6.2	Tea	0	1	1
3.6.2.2	Green tea	0	1	1

3.7.1	Alcoholic drinks	2	3	5
3.7.1	Alcoholism	4	1	5
4.2	Preserved foods	0	1	1
4.2.5.1	Salt	0	1	1
4.4.2.5	Fried foods	0	1	1
5.1.4	Sugars (as nutrients)	0	1	1
5.2	Cholesterol, blood	0	1	1
5.2	Fat	0	1	1
5.2	Serum triglycerides	1	1	2
5.2.5	Trans fatty acids	0	1	1
5.5.1	Vitamin A, blood	1	0	1
5.5.1	Vitamin A	2	0	2
5.5.1.1	Retinol, dietary	1	1	2
5.5.1.1	Retinol, blood	4	0	4
5.5.1.2	Beta-carotene, supplement	4	0	4
5.5.1.2	Beta-carotene, dietary	0	1	1
5.5.1.2	Beta-carotene, blood	2	0	2
5.5.1.2	Carotene	1	0	1
5.5.1.2	Alpha-carotene, blood	1	0	1
5.5.1.2	Cryptoxanthin, blood	1	0	1
5.5.10	Vitamin D, dietary	0	1	1
5.5.10	Vitamin D, blood	0	1	1
5.5.11	Vitamin E, blood	2	0	2
5.5.11	Alpha-tocopherol, blood	2	0	2
5.5.11	Gamma-tocopherol, blood	1	0	1
5.5.11	Vitamin E from foods	0	1	1
5.5.11	Vitamin E from supplements	0	1	1
5.5.13	Multivitamin supplement	0	1	1

5.5.2	Lutein, blood	1	0	1
5.5.2	Lycopene, blood	1	0	1
5.5.2	Total carotenoids, blood	1	0	1
5.5.3	Folates and associated compounds	1	0	1
5.5.3	Folic acid	0	1	1
5.5.3	Folate, blood	2	0	2
5.5.3	Homocysteine, blood	2	0	2
5.5.5	Thiamin (vitamin B1) supplement	0	1	1
5.5.8	Cobalamin (vitamin B12), blood	3	0	3
5.5.9	Vitamin C, dietary	0	1	1
5.5.9	Vitamin C, blood	1	0	1
5.5.9	Vitamin C, supplement	0	1	1
5.6.4	Selenium, blood	1	0	1
5.6.6	Phosphorus	0	1	1
5.6.7	Zinc	1	0	1
6.1.1.1	Occupational physical activity	1	0	1
6.1.1.2	Recreational physical activity	1	1	2
6.1.4	Duration of physical activity	0	1	1
6.1.4.2	Duration of walking	0	1	1
7.1	Energy intake	0	1	1
8.1	Markers of body composition	1	0	1
8.1.1	BMI	2	8	10
8.1.2	Obesity	3	1	4
8.1.3	Weight	0	1	1
8.3.1	Height	2	5	7
8.3.2	Leg length	1	0	1
8.3.2	Sitting height	1	0	1
8.4.1	Birth weight	0	1	1

2.2.1.1.1 Carrot or pumpkin

In the 2nd expert report, the evidence of the association of carrots intake and invasive cervical cancer was judged as limited suggestive. The judgement was based in the results of four hospital-based case-control studies. No cohort study was identified in the 2005 SLR. One study (JACC) was identified in the CUP, which reported on uterine cervix cancer mortality and intake of carrot or pumpkin combined. No meta-analysis was conducted.

In this study by Iso, 2007, carrot or pumpkin intake was not associated with uterine cervical cancer mortality. The HR comparing ≥3-4 times/week of carrots intake to <1 time/week intake was 1.10 (95% CI; 0.31-3.93). The number of cases was low (29 deaths) and the analysis was only adjusted for age and study area.

Table 2 Carrot or pumpkin intake and cervical cancer risk. Main characteristics of studies identified in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Iso, 2007 CER93754 Japan	JACC, Prospective Cohort, Age range: 40-79 years	29/ 55 480 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, uterine cervix cancer	≥3-4 times/week vs <1 time/week	1.10 (0.31-3.93)	Age, area of study

3.7.1 Alcoholic drinks

Two cohort studies were identified in the 2005 SLR, one on HPV persistence (Richardson, 2005) and a nested case-control study on incidence of in situ and invasive cervix cancer (Sriampron, 2004). Three studies (Ozasa, 2007; Allen, 2009; Kaltsky, 2015) were identified in the CUP, two studies on cervical cancer incidence and one study on cervical cancer mortality. There were not enough data to do dose-response meta-analysis.

None of the studies reported a significant association of alcoholic drinks intake and incidence or mortality from cervical cancer.

The study on HPV persistence in 621 female university students in Montreal followed for 24 months at 6-month intervals showed a non-significant positive association of alcohol consumption and rate of clearance for both high-risk and low-risk HPV infections when adjusted for other potential predictors of clearance, including tobacco use (Richardson, 2005).

Table 3 Alcohol intake and cervical cancer risk. Main characteristics of studies identified in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Klatsky, 2015 CER93773 USA	KPMCP, Prospective Cohort, Mean age: 41 years, W	727/ 70, 906 17.8 years	Cancer registry		Incidence, cervical cancer	≥3 drinks/day vs never-drinkers	1.00 (0.70-1.60)	Age, sex, BMI, educational level, ethnicity, marital status, smoking status
Allen, 2009 CER93746 UK	MWS, Prospective Cohort, Mean age: 55 years, W	468/ 1 280 296 7.2 years	National health service central registers		Incidence, cervical cancer	≥15 vs ≤2 drinks/week	1.02 (0.69-1.50) Ptrend:1.0	Age, residence area, socioeconomic status, BMI, HRT use, physical activity, smoking, oral contraceptives
		325/ 1 280 296 7.2 years				per 10 g/day	1.00 (0.84-1.19)	

Ozasa, 2007 CER93749 Japan	JACC, Prospective Cohort, W	36/ 740 415 person-years/ follow-up years not reported			Mortality, cervix uteri cancer	Ex-drinkers vs rare/ none	1.69 (0.22-12.70)	Age, study area
						Almost every day vs rare/none	0.61 (0.08-4.61)	
						3-4 drinks/week vs rare/none	0.70 (0.23-2.10)	
Richardson, 2005 CER08790 Canada	Montreal, 1996, Prospective Cohort, Age at baseline: 17 years or more W, University students	222/ 621 2 years	Screening registry	Questionnaire	Clearance of high oncogenic risk HPV	>3 vs 0 drinks/week	2.00 (1.00-4.90)	Age, age at first intercourse, barrier contraceptives, cervicovaginal infections, duration of oral contraceptive use, ethnicity, lifestyle factors, smoking, vegetable Intake
		105/ 621 2 years			Clearance of low oncogenic risk HPV		1.90 (0.70-5.30)	
Sriamporn, 2004 CER08007 Thailand	Khon Kaen province, 1990, Nested Case Control, Age: 35 or more years, W	54/ 224 controls 3.1 years	Study cohort	Questionnaire	Incidence, In situ and invasive cervical cancer	Alcohol consumption vs none	1.40 (0.70-3.00)	(Matched on age and date of recruitment)

3.7.1 Alcoholism

In the four cohort studies (Weiderpass, 2001; Sigvardsson, 1996; Tonnesen, 1994; Adami, 1992) on alcoholics identified in the 2005 SLR, alcoholic women had an increased risk of cervical cancer compared to the women in the general population. In all the studies, the standard incidence ratio (SIR) using the general population as comparison were reported. The analyses can be affected by residual confounding.

A follow-up of a Danish study (Thygesen, 2009) was identified in the CUP. In this update of the Copenhagen Alcohol Cohort the SIR of cervical cancer mortality was 1.80 (95%CI=1.20-2.60).

No dose-response meta-analysis was conducted.

Table 4 Alcoholism and cervical cancer risk. Main characteristics of studies identified in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	SIR (95% CI)	Adjustment factors
Thygesen, 2009 CER93747 Denmark	Copenhagen Alcohol Cohort 1954-1999, Prospective Cohort	29/ 3552 women 14 years	Danish cancer registry	Assessed by social worker, outpatient clinic	Incidence, cervical cancer, women	Alcoholic women vs general population	1.80 (1.20-2.60)	
Weiderpass, 2001 CER07433 Sweden	Sweden, alcoholic women, hospital discharges 1965-1994, Mean age: 42.7 years	502/ 36 856 9.4 years	Cancer registry	Hospital discharge records	Incidence, In situ cervical cancer	Alcoholic women vs general population	1.70 (1.60-1.90)	
		129/ 36 856 9.4 years			Incidence, Invasive cervical cancer	Alcoholic women vs general population	2.90 (2.40-3.50)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	SIR (95% CI)	Adjustment factors
Sigvardsson, 1996 CER06374, Sweden	Alcoholic Women, matched follow-up of alcoholic to non-alcoholics women	187/ 15508/ 19 years	Swedish Cancer Registry	Through review of temperance boards records	Incidence, cervix uteri	Alcoholics vs unexposed group	3.9 (2.8-5.4)	Each alcoholic matched to one non-alcoholic women by age and geographic region
Tonnesen, 1994* CER06970 Denmark	Copenhagen, outpatients cohort, 1954-1987, Alcoholic women	22 cases/ 3 093 women Mean follow-up: 9.4 years	Cancer registry	Assessed by social worker, outpatient clinic	Incidence, cervical cancer	Alcoholics vs Danish women (Observed vs expected)	2.00 (1.20-3.00)	
Adami, 1992 CER00068 Sweden	Sweden, alcoholic women, 1965, Historical Cohort, Mean age: 49.4 years,	6 cases/ 1013 women Mean follow-up: 7 years	Cancer registry	Hospital discharge records	Incidence, cervical cancer All women	Alcoholics vs Uppsala health care region population	4.20 (1.50-9.10)	Confounding by smoking, sexual habits, dietary pattern and perhaps a lower compliance with cytological screening programs are likely explanations of this excess
					Age < 50 years at start follow-up		6.50 (2.10-15.20)	

*Updated in Thygesen, 2009

5.5.1.1 Dietary retinol

One cohort study was identified in the 2005 SLR. One new study (EPIC) was identified in the CUP. None of the studies reported an association.

In the EPIC study (Gonzalez, 2011) dietary retinol intake was not associated with carcinoma in situ and invasive squamous cervical cancer risk. The HR was 0.98 (95%CI; 0.93-1.02) per 200 mcg/day intake of dietary retinol.

No meta-analysis was conducted.

Table 5 Dietary retinol intake and cervical cancer risk. Main characteristics of studies identified in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Gonzalez, 2011 CER93779, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, 9 years	1 070/ 299 651/ 9 years	Cancer registry	Self-administered FFQ	Incidence, in situ and invasive squamous cervical cancer	per 200 mcg/day	0.98 (0.93–1.02)	BMI, educational level, physical activity, number of pregnancies, marital status, smoking, alcohol, energy intake, oral contraceptive use, number of birth
		1 070/				949.40 vs 426.29 mcg/day	1.01 (0.99–1.02)	
		253/			Incidence, invasive squamous cervical cancer	per 200 mcg/day	0.81 (0.62–1.06)	
						949.40 vs 426.29 mcg/day	0.97 (0.67–1.41)	
		817/			Incidence, cervical carcinoma in situ	per 200 mcg/day	0.97 (0.92–1.03)	
						949.40 vs 426.29 mcg/day	1.01 (0.81–1.27)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Nagata, 1999 CER04716 Japan	Miyagi-Japan, 1987, Prospective Cohort, Age: 18-74 years, Cervical dysplasia patients	8/ 123 6.3 years	Hospital records	Semi-quantitative FFQ	Incidence, cervical cancer	1-50 vs 51-100 centiles	0.56 (0.13-2.43)	Age, smoking habits, stage of dysplasia

5.5.1.2 Dietary beta-carotene

No cohort study was identified in the 2005 SLR. One new study (EPIC) was identified in the CUP. No meta-analysis was conducted.

In the EPIC study (Gonzalez, 2011), dietary beta-carotene intake was not associated with carcinoma in situ and invasive squamous cervical cancer risk. The HR was 1.00 (95%CI; 0.94-1.06) per 1500 mcg/day intake of dietary beta-carotene.

Table 6 Dietary beta-carotene intake and cervical cancer risk. Main characteristics of studies identified in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Gonzalez, 2011 CER93779 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, 9 years	1 070/ 299 651 9 years	Cancer registry	Self-administered FFQ	Incidence, in situ carcinoma and invasive squamous cervical cancer	Per 1500 mcg/day	1.00 (0.94-1.06)	BMI, educational level, physical activity, number of pregnancies, marital status, smoking, alcohol, energy intake, oral contraceptive use, number of birth
		1 070/				3960.06 vs 1907.18 mcg/day	0.92 (0.77-1.11)	
		253/			Incidence, invasive squamous cervical cancer (ISC)	Per 1500 mcg/day	0.91 (0.78–1.05)	
						3960.06 vs 1907.18 mcg/day	0.86 (0.59–1.27)	
		817/			Incidence, cervical carcinoma in situ (CIS)	Per 1500 mcg/day	1.02 (0.95–1.10)	
						3960.06 vs 1907.18 mcg/day	0.94 (0.76–1.15)	

8.1.1 BMI

Two cohort studies (Calle, 2003; Tornberg, 1994) were identified in the 2005 SLR. Eight new studies (9 publications) were identified in the CUP, of which 6 studies were on cervical cancer incidence, one study reported on cervical cancer mortality and one study reported data both on cervical cancer incidence and mortality in two different publications (Fujino, 2007; Reeves, 2007).

In 6 studies, the lowest category of BMI (usually including underweight individuals) was not used as the referent category (Bhaskaran, 2014; Song, 2014; Bjorge, 2008; Jee, 2008; Fujino. 2007; Reeves, 2007). The relative risks in these studies were recalculated using the lowest category as referent for their inclusion in dose-response meta-analysis by using the Hamling method.

Nine studies (5 144 cases) were included in the dose-response meta-analyses. No significant linear dose-response association was observed with cervical cancer risk or mortality.

The only two studies which showed a significant association were the CPRD study on cancer incidence (Bhaskaran, 2014) and the CPS II (Calle, 2003) on cancer mortality.

In meta-analysis by geographic location the association with cervical cancer risk remained non-significant.

In influence analysis, the summary RRs ranged from 1.00 (95% CI=0.96-1.05) when Bhaskaran, 2014 was omitted to 1.03 (95% CI=0.98-1.08) when Rapp, 2005 was omitted.

There was high heterogeneity. Visual inspection of forest plot and funnel plot suggests that this is driven by the results of the CPRD study (Bhaskaran, 2014) in the analysis on cancer incidence and the Japanese study on mortality (Fujino, 2007).

There was no evidence of significant publication bias (p=0.71).

There was evidence of non-linear association (p=<0.001) (7 studies on cancer risk included). The curve shows a significant increased risk of cervical cancer with BMI's more than 31 kg/m^2. Only two studies contributed to information with data above this value of BMI: the CPRD study in UK women (Bhaskaran, 2014), in which an increased risk of cervical cancer with increasing BMI was observed in the entire study population and in never smokers and a Finish study (Song, 2014).

All studies except one adjusted for smoking. No study adjusted for screening practice.

In a pooled analysis of Asian-Pacific cohort studies the RR for 5 kg/m2 increment of cervical cancer mortality in age, smoking and study adjusted models was 1.45 (1.00-2.11) (60 cases).

Table 7 BMI and cervical cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and 2016 SLR.

Cervical cancer		
	2005 SLR	**CUP**
Increment unit used		5 kg/m^2
All studies		
Studies (n)		9
Cases (total number)		5 144
RR (95%CI)		1.02 (0.97-1.07)
Heterogeneity (I^2, p-value)		69.2%, 0.001
Stratified analysis by outcome		
Incidence		
Studies (n)		7
Cases (total number)		4 837
RR (95%CI)		1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)		63.9%, 0.01
P value Egger test		
Mortality		
Studies (n)		3
Cases (total number)		307
RR (95%CI)		1.04 (0.88-1.24)
Heterogeneity (I^2, p-value)		69.5%, 0.04
Stratified analysis by geographical location (excluding studies on mortality)		
Asia		
Studies (n)		2
Cases (total number)		2 676
RR (95%CI)		0.99 (0.95-1.03)
Heterogeneity (I^2, p-value)		0%, 0.47
Europe		
Studies (n)		5
Cases (total number)		2 195
RR (95%CI)		1.01 (0.95-1.06)
Heterogeneity (I^2, p-value)		70%, 0.009

Table 8 BMI and cervical cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2016 SLR.

Author, Year	Number of cohort studies	Total number cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
-								
Pooled analyses								
Parr, 2010 (Asia-Pacific Cohort Studies Collaboration)	39	60	Asia and Australia/New Zealand	Mortality	Per 5 kg/m^2 increase	(Adjusted by age and smoking) 1.45 (1.00-2.11)	0.02	
					Compared to 18.5-24.9 kg/m^2 12.0-18.4 25.0-29.9 30.0-60.0	 2.11 (0.93, 4.77) 1.29 (0.68, 2.46) 4.21 (1.89, 9.39)		

Table 9 BMI and cervical cancer risk. Main characteristics of studies included in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Bhaskaran, 2014 CER93766 UK	CPRD, Prospective Cohort, Age: 16 years or older, W	1 389/ 5 243 978 25 years	Medical record	Weight and height measured	Incidence, cervix cancer	per 5 kg/m^2	1.10 (1.03-1.17)	Age, sex, alcohol, calendar year, diabetes, smoking, socio-economic status	Mid-point categories Distributions of person-years Hamling method was used to recalculate the RR's
				Weight and height measured	Incidence, cervix cancer	≥35 vs 18.5-24.9 kg/m^2	1.49 (1.15-1.95)		
				Weight and height measured	Incidence, cervix cancer, never smokers	per 5 kg/m^2	1.14 (1.03-1.26)		
Song, 2014 CER93767 Finland	FINRISK, Prospective Cohort, Age: 24-74 years, W	141/ 54 725 20.6 years	Cancer and mortality registries	Height and weight were measured	Incidence, cervix uteri cancer	Compared to 23.0-24.9 kg/m^2 21.0-22.9 >35 kg/m^2	 0.95 (0.55-1.63) 1.45 (0.62-3.38)	Age, area, educational level, leisure time physical activity, smoking	Mid-point categories Distributions of person-years Hamling method was used to recalculate the RR's
Jee, 2008 CER93751 Korea	KNHIC, Prospective Cohort, Age: 30-95 years, W	2 627/ 1 213 829 10.8 years	Cancer registry and hospital records	Height and weight measured	Incidence, cervix cancer	≥30 vs 23-24.9 kg/m^2	1.16 (0.77-1.74) Ptrend:0.4937	Age, smoking	Mid-point categories Distributions of person-years Hamling method was used to recalculate the RR's

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Fujino, 2007 CER93748 Japan	JACC, Prospective Cohort, W	34/ 1 314 653 person-years 12 years		Self-reported in survey	Mortality, cervix cancer	≥30 vs 18.5-24 kg/m^2	1.54 (0.20-11.50)	Age, study area	
Reeves, 2007 CER93757 UK	MWS, Prospective Cohort, Age: 50-64 years, W	330/ 1 222 630 5.4 years	National health records	Self-reported	Incidence, cervix cancer	per 10 units	1.04 (0.79-1.38)	Age, alcohol intake, geographic region, hormone replacement therapy, physical activity, reproductive history, smoking status, socio-economic status, time since menopause	Mid-point categories Distributions of person-years Hamling method was used to recalculate the RR's RR rescaled to the increment used
		330/ 1 222 630 5.4 years			Incidence, cervix cancer	≥30 vs 22.5-24.9 kg/m^2	1.02 (0.80-1.31)		
		189/ 1 222 630 5.4 years			Incidence, cervix cancer, excluding first 2 years of follow-up	per 10 units	0.95 (0.65-1.38)		
		118/ 1 222 630 5.4 years			Incidence, cervix cancer, never smokers	per 10 units	0.93 (0.58-1.51)		
		109/ 1 222 630 5.4 years			Mortality, cervix cancer	per 10 units	1.53 (0.95-2.47)		
		109/ 1 222 630 5.4 years			Mortality, cervix cancer	≥30 vs 22.5-24.9 kg/m^2	1.15 (0.79-1.70)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Kuriyama, 2005 CER93761 Japan	MCS I, Prospective Cohort, Age: 40 years or older, W	15/ 15 054 9 years	Cancer registry	Self-reported weight and height	Incidence, cervix cancer	≥27.5 vs 18.5-24.9 kg/m^2	1.89 (0.49-7.35) Ptrend:0.47	Age, age at first child birth, age at menarche, alcohol consumption, intakes of bean-paste soup, fish, fruits, meat, green yellow vegetables, health insurance, menopause status, parity, smoking status	Mid-point categories Distributions of person-years
Rapp, 2005 CER93760 Austria	VHM-PP, Prospective Cohort, Age: 19-94 years, W	64/ 78 484 10.18 years	Cancer registry and death certificates	Collected by medical staff at physical examination	Incidence, cervix cancer	≥30 vs 18.5-24.9 kg/m^2	0.69 (0.29-1.66) Ptrend:0.37	Age, occupation, smoking status	Mid-point categories
Calle, 2003 CER00987 USA	CPS II, Prospective Cohort, Mean age: 57 years, W	164/ 495 477 16 years	Volunteers		Mortality, cervix cancer	≥35 vs 18.5-24.9 kg/m^2	3.20 (1.77-5.78) Ptrend:0.001	Age, alcohol consumption, drug use, educational level, ethnicity, HRT use, marital status, physical	Mid-point categories Distributions of person-years

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								activity, smoking habits, vegetable intake other nutrients, foods or supplements	
Tornberg, 1994 CER06975 Sweden	Central Sweden, 1963, Prospective Cohort, Age: 25-75 years, W, Screening Program	271/ 47 003 23 years	Area residency lists	Directly measured	Incidence, cervix cancer	≥28 vs ≤21.99 kg/m^2	0.87 Ptrend:0.48	Age, length of follow-up	Missing confidence intervals calculated
		147/ 47 003 23 years			Incidence, cervix cancer, age >= 55 yrs	≥28 vs ≤21.99 kg/m^2	0.77 Ptrend:0.25		
		124/ 47 003 23 years			Incidence, cervix cancer, age < 55 yrs	≥28 vs ≤21.99 kg/m^2	1.09 Ptrend:1		

Table 10 BMI and cervical cancer risk. Main characteristics of studies excluded in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bjørge, 2008 CER93759 Norway	NSPT, Age: 14-19 years, W	113/ 111 701 34.9 years	Death register	height and weight measured	Mortality, cervix uteri cancer	Q 4 vs Q 2	1.90 (1.10-3.20) Ptrend:0.007	Age, birth year	No specified categories
Song, 2008 CER93758 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, W, Postmenopausal	550/ 170 481 8.75 years	Cancer registry, death report and Korea national health Insurance corporation	Weights and heights were measured	Incidence, cervix uteri cancer	≥30 vs 21-22.9 kg/m^2	1.25 (0.79-1.96)	Age, alcohol intake, height, pay level at study entry, physical exercise, smoking status	Duplicate of Jee, 2008 CER93751
		488/ 170 481 8.75 years			Incidence, cervix uteri cancer	per 1 kg/m^2	1.02 (0.99-1.05)		

Figure 1 RR estimates of cervical cancer by levels of BMI

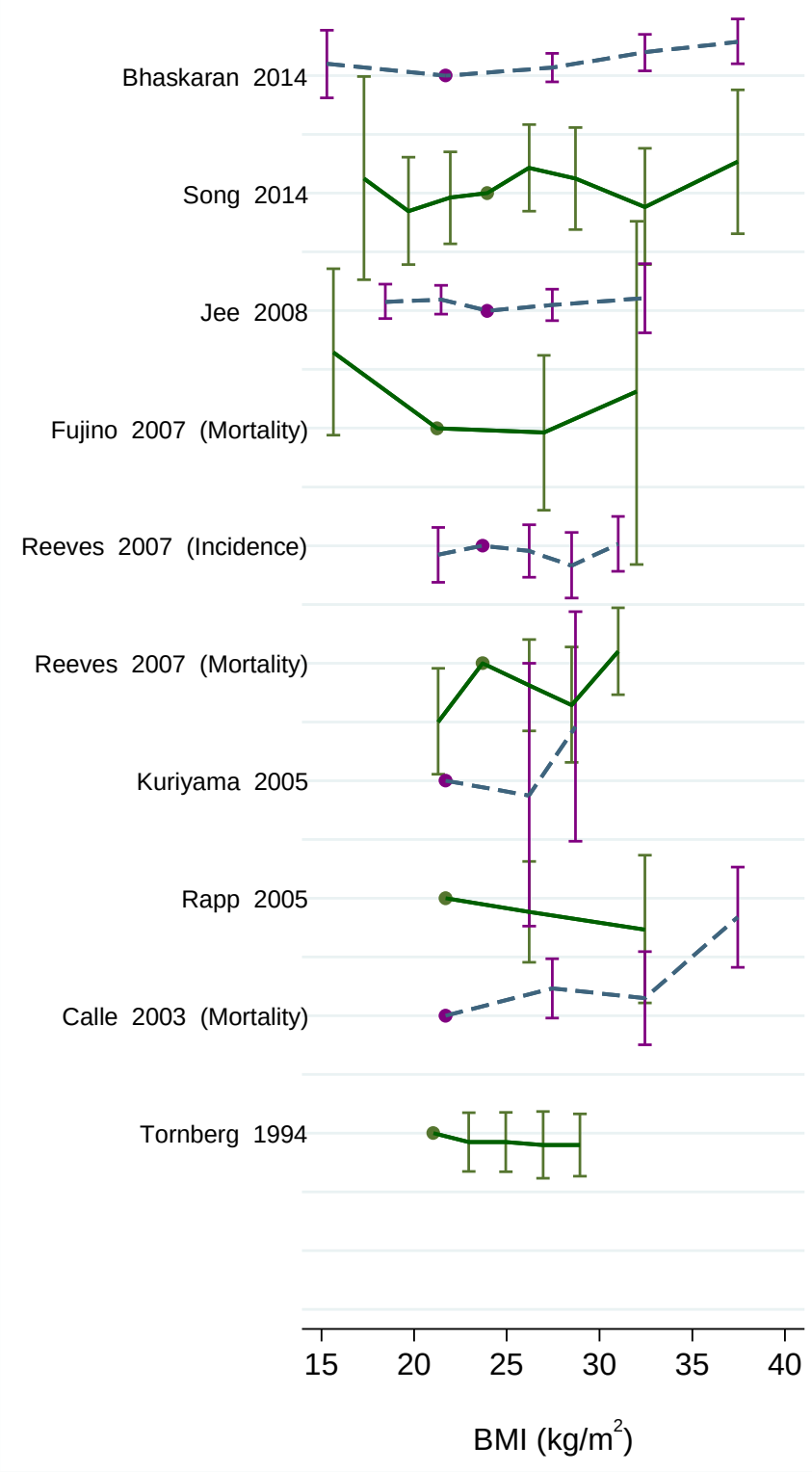


Figure 2 RR (95% CI) of cervical cancer for the highest compared with the lowest level of BMI

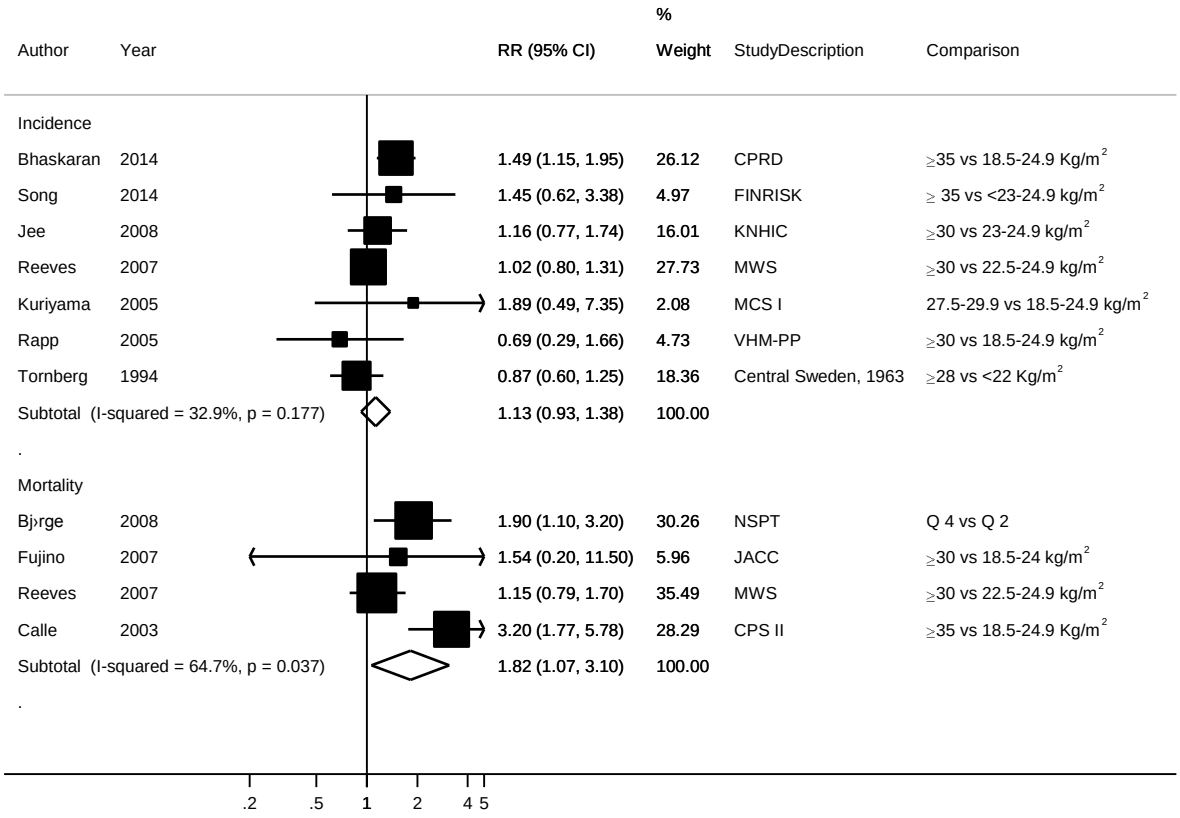


Figure 3 RR (95% CI) of cervical cancer for 5 kg/m^2 increase of BMI

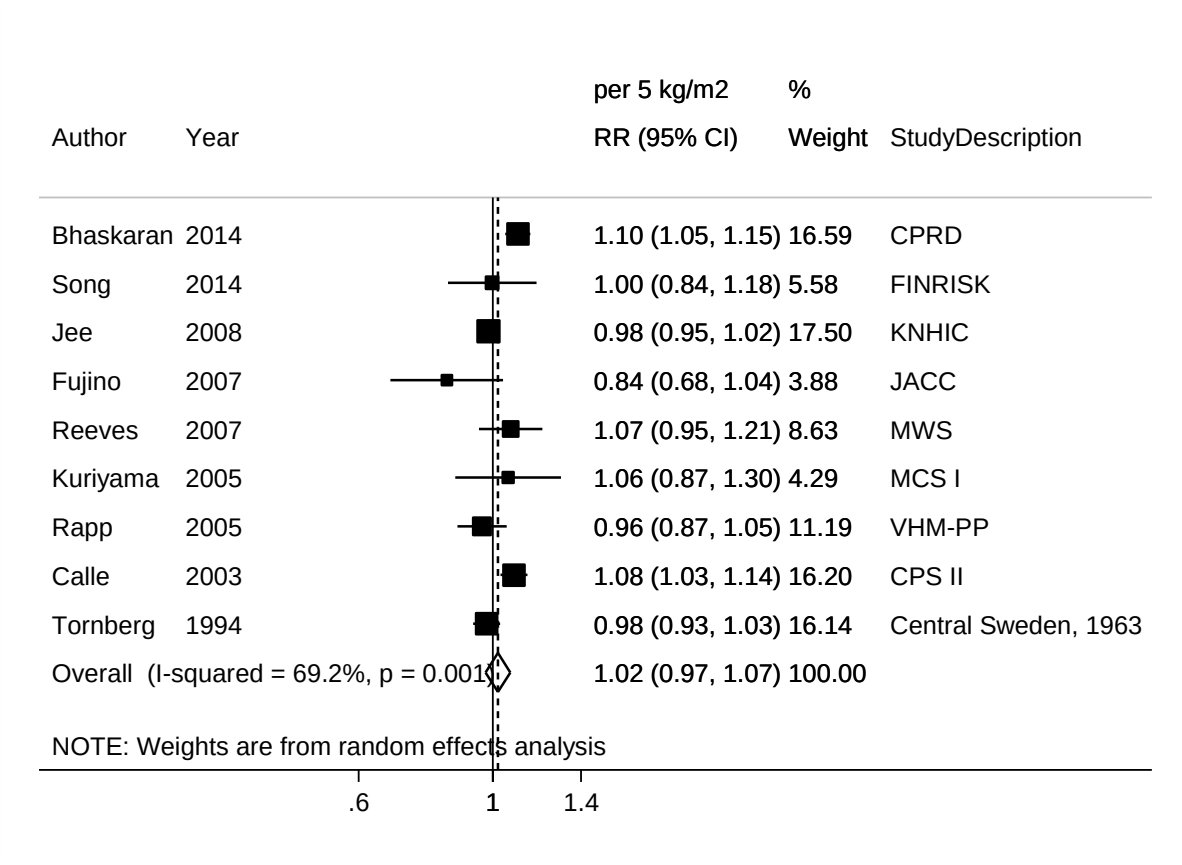


Figure 4 Funnel plot of studies included in the dose response meta-analysis of BMI and cervical cancer risk

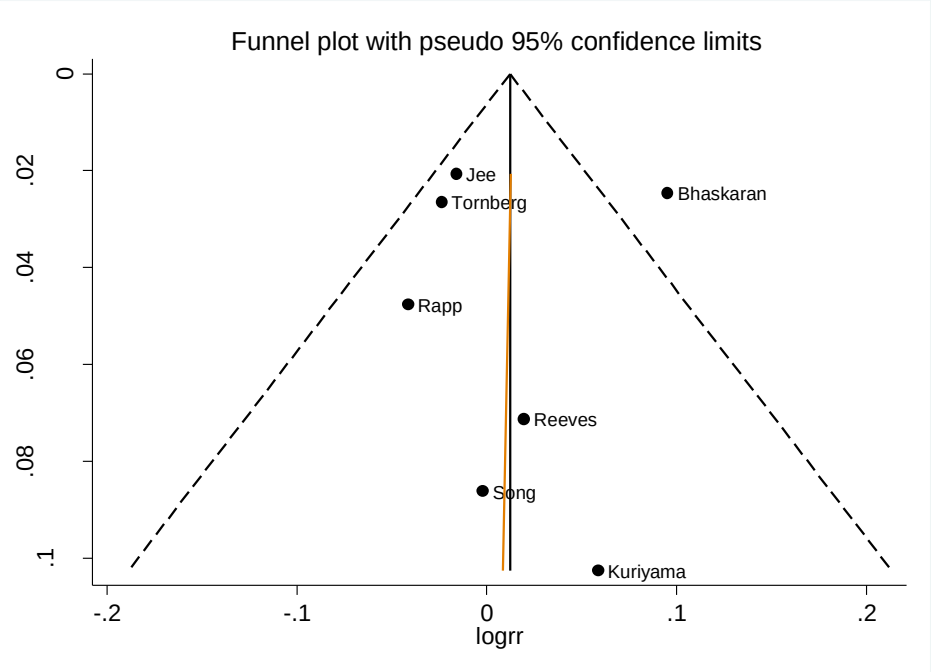


Figure 5 RR (95% CI) of cervical cancer for 5 kg/m^2 increase of BMI by cancer outcome

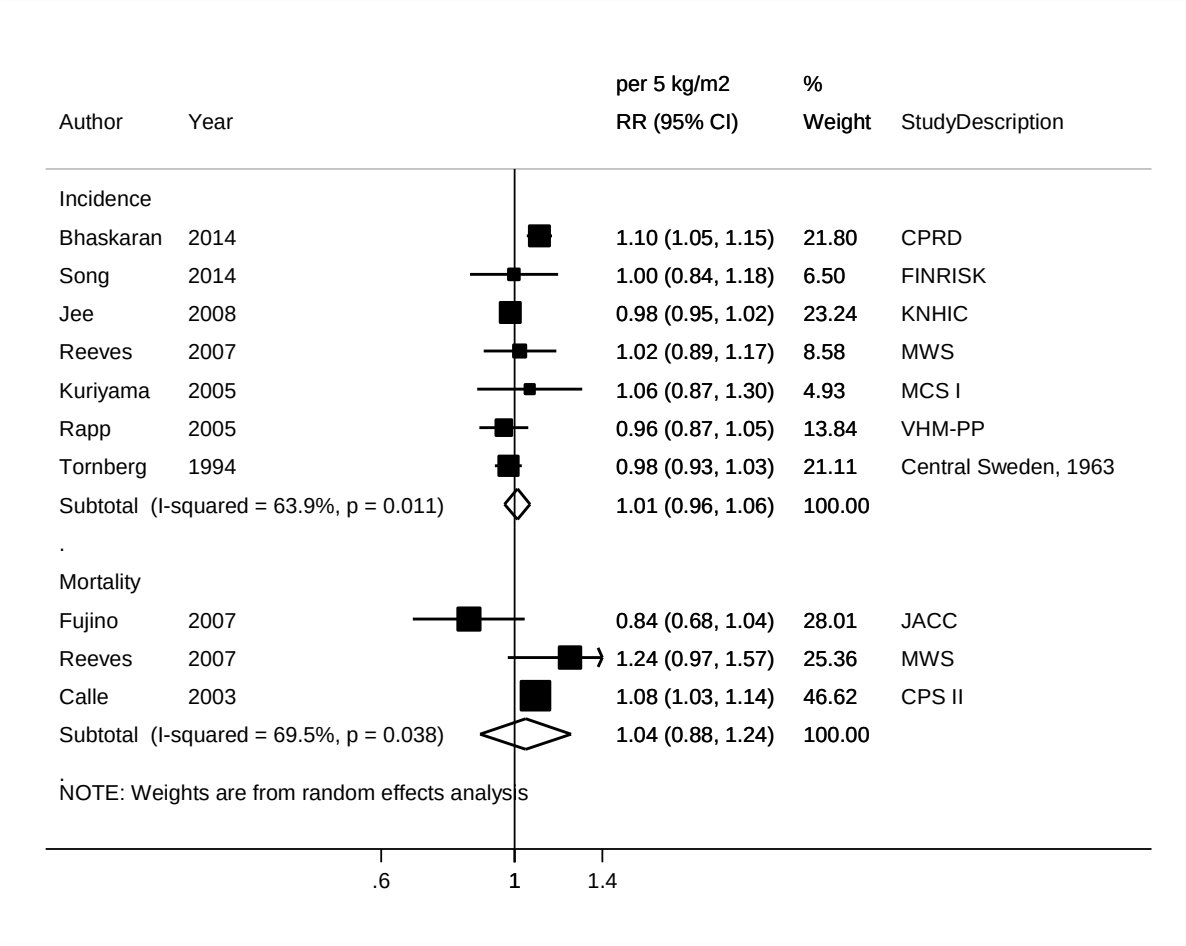


Figure 6 RR (95% CI) of cervical cancer for 5 kg/m^2 increase of BMI by geographic location

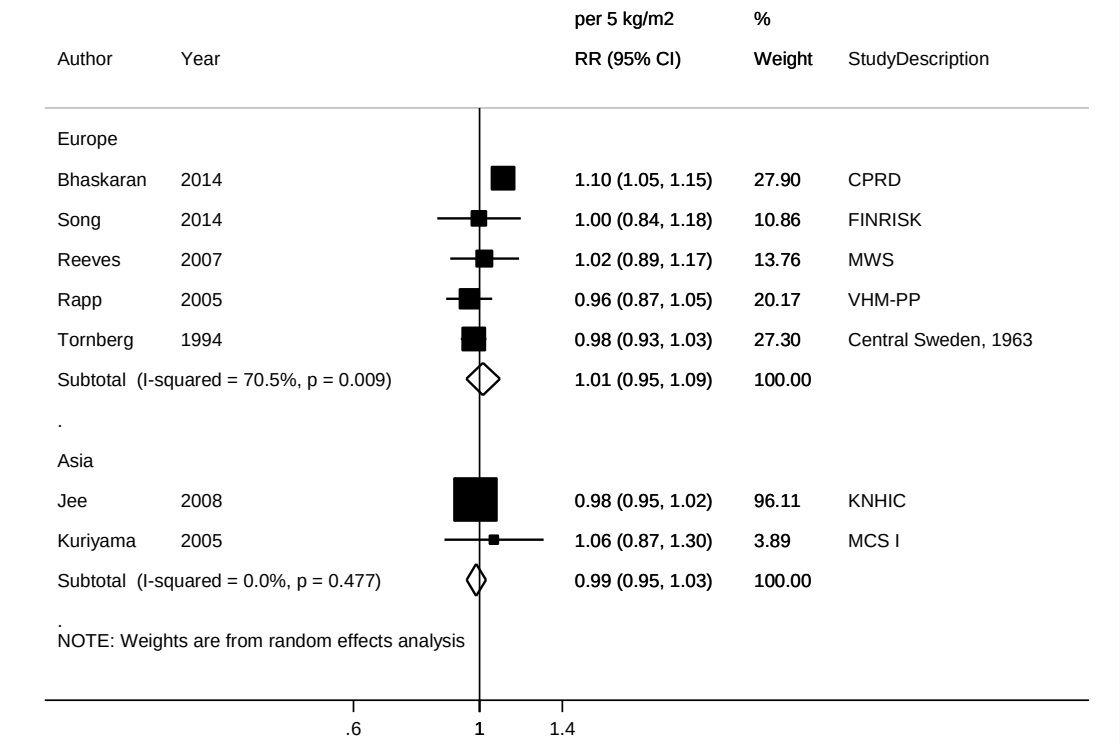
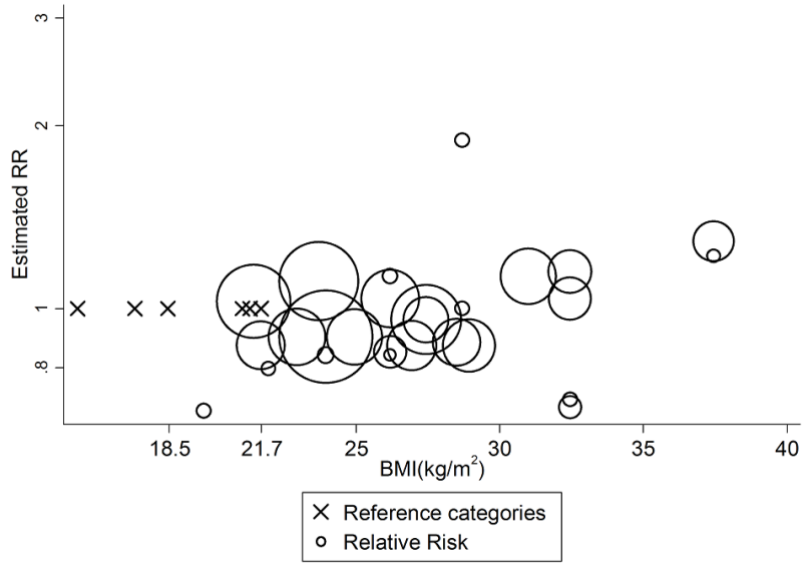


Figure 7 Relative risk of cervical cancer and BMI estimated using non-linear models (excluding studies on mortality)

a) Bubble plot showing RR for each study with X indicating the corresponding referent category. The size of the plotting symbol is inversely proportional to the variance of the estimated RR



P non-linearity <0.001.

Figure 8 (Cont.) Relative risk of cervical cancer and BMI estimated using non-linear models (excluding studies on mortality)

b) Dose-reponse curve

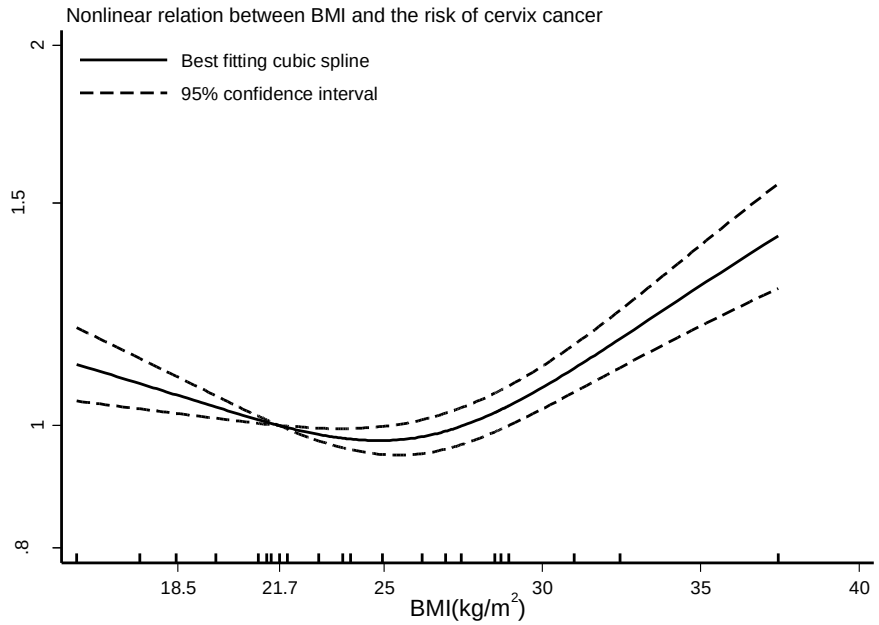


Table 11 BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI and cervical cancer

BMI (kg/m^2)	RR (95%CI)
18.45	1.06 (1.02-1.09)
21.70	1.00
23.70	0.98 (0.96-0.99)
26.20	0.98 (0.95-1.01)
28.95	1.04 (1.00-1.07)
31.00	1.11 (1.06-1.16)

8.3.1 Height

Two cohort studies (Tulinius, 1997; Albanes, 1988) were identified in the 2005 SLR. Five studies were identified during the CUP, of which four studies (NIH-AARP, WHI, CNBSS, KNHIC) reported on cervical cancer incidence and one study reported on cervical cancer mortality (JACC).

Four studies (1 217 cases) were included in the dose-response meta-analysis of height and cervical cancer risk. No significant association was observed. There was no evidence of publication bias (p=0.60) but the number of studies was too low for examining publication bias. After stratification by geographic location the results remained non-significant. In influence analysis, the results remained the same after running the analysis excluding one study each time.

No high vs low forest plot or non-linear analysis were conducted because of insufficient number of studies with the required information.

Table 12 Height and cervical cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and 2016 SLR.

Cervical cancer risk		
	2005 SLR	**CUP**
Increment unit used		5 cm
All studies		
Studies (n)		4
Cases (total number)		1 183
RR (95%CI)		1.01 (0.92-1.11)
Heterogeneity (I^2, p-value)		45.8%, 0.13

Table 13 Height and cervical cancer risk. Main characteristics of studies included in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Kabat , 2014 CER93771 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, W	142/ 481 197 10.5 years	Cancer registry and national death Index	Self-reported height	Incidence, cervical cancer	per 10 cm	0.82 (0.62-1.07)	Age, age at first child birth, age at menarche, alcohol, BMI, educational level, HRT use, menopausal status, parity, physical activity, race, smoking	
Kabat , 2013 (a) CER93745 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	91/ 88 256 16.2 years	Record linkages to cancer database and to the national mortality database	Height and weight measured	Incidence, cervical cancer	per 10 cm	1.10 (0.79-1.53)	Age at baseline, BMI, menopausal status, years of education	
Kabat , 2013 (b) CER93763	WHI, Prospective	83/ 144 701	Self-report verified by medical record and pathology	weight, height, waist and hip circumferences	Incidence, cervical cancer	per 10 cm	1.38 (0.96-1.99)	Age, educational level, ethnicity, HRT use, pack-years of	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Cohort, Age: 50-79 years, W	12 years	report	measured				cigarette smoking, randomisation	
Sung, 2009 CER93743 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, W, middle-class adults	866/ 276 072 8.72 years	Linkage with cancer registry, national health Insurance and death report	Measured	Incidence, cervical cancer	≥158.1 vs ≤151 cm	0.94 (0.71-1.25)	Age, age at first child birth, age at menarche, alcohol consumption, area of residence, BMI, cigarette smoking, duration of breastfeeding, oestrogen replacement therapy, menopausal status, monthly salary level, occupation, regular exercise, use of oral birth control pill	
					Incidence, cervical cancer	per 5 cm	1.01 (0.92-1.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Fujino, 2007 CER93748 Japan	JACC, Prospective Cohort, W	34/		Obtained from survey	Mortality, cervical cancer	≥154 vs ≤148.9 cm	0.85 (0.33-2.17)	Age, study area	

Table 14 Height and cervical cancer risk. Main characteristics of studies excluded in the CUP SLR.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Albanes, 1988 CER93765 USA	NHANES I, Prospective Cohort, Age: 25-74 years, W	20/ 7 413 10 years	Death certificate and medical records	Nearest millimetre	Incidence, cervix cancer	169.3 vs 153.1 cm	0.70 (0.40-1.20)	Age	Missing number of cases in each category
Tulinius, 1997 CER07064 Iceland	Icelandic Cardiovascular Risk Factor Study, Prospective Cohort Age:60-87 W	40/ 11 580 27 years	Area residency lists		Incidence, cervical cancer		0.94 (0.89-1.00)	Age	Missing increment unit

Figure 9 RR (95% CI) of cervical cancer for 5 kg/m^2 increase of height

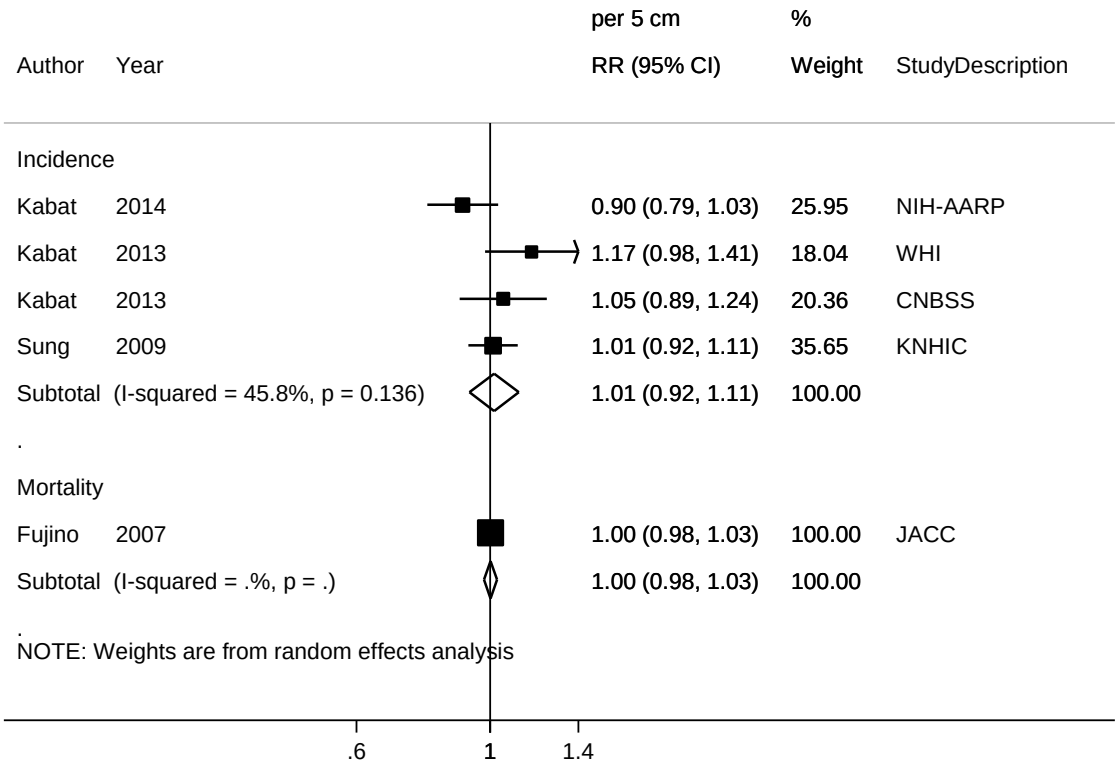
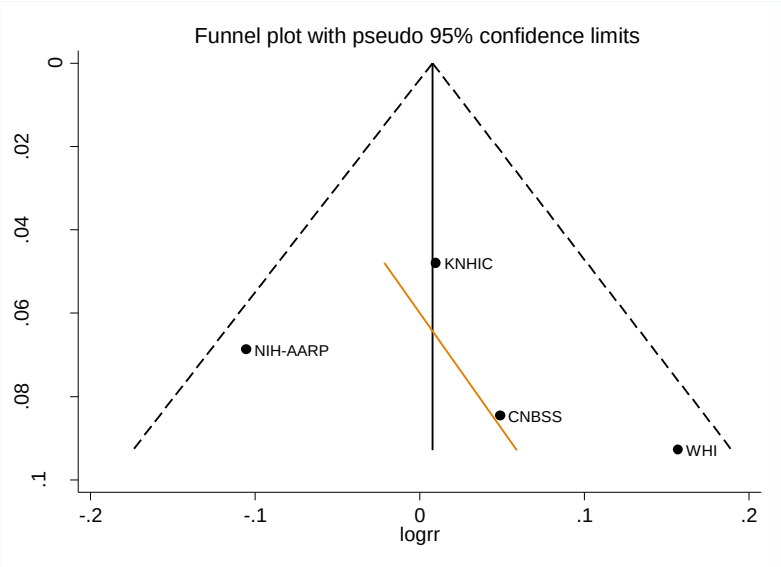


Figure 10 Funnel plot of studies included in the dose response meta-analysis of height and cervical cancer risk



P=0.60

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