WCRF/AICR Systematic Literature Review Continuous Update Project Report

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

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List of abbreviations used in the CUP report

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

List of Abbreviations of cohort names

CTS	California Teachers Study
AHS	Adventist Health Study
BCDDP	Breast Cancer Detection Demonstration Project
CCPPS	Copenhagen Centre for Prospective Population Studies
CPS II	Cancer Prevention Study II
EPIC	European Prospective Investigation into Cancer and Nutrition
IWHS (or IOWA)	Iowa Women's Health Study Cohort
JCCS	Japan Collaborative Cohort study
JPHC	Japan Public Health Centre-based Prospective Study
KCPS	NIH-AARP Diet and Health Study
MCCS	Melbourne Collaborative Cohort Study
MCS	Miyagi Cohort Study
MDCC	Malmo Diet and Cancer Cohort
MWS	Million Women's Study
NHS	Nurses' Health Study
NIH-AARP	NIH-AARP Diet and Health Study
NLCS (or NCS)	The Netherlands Cohort Study
NSHDS	Northern Sweden Health And Disease Cohort Study
NTVS	Norwegian Tuberculosis Screening Study
NYUWHS	New York University Women's Health Study
OVS	Oxford Vegetarian Study
SMC	Swedish Mammography Cohort Study
STC	Swedish Twin Cohort
VIP	Västerbotten Intervention Project
WHI	Women's Health Initiative
WLHS	Women's Lifestyle and Health Study

Background

Matrices presented in the WCRF/AICR 2007 Expert Report

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

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Adult attained height[1]**
Limited — suggestive	Non-starchy vegetables[2] Lactation	
Limited — no conclusion	Dietary fibre; fruits; pulses (legumes); meat; poultry; fish; eggs; milk and dairy products; total fat; cholesterol; coffee; tea; alcohol; carbohydrate; lactose; protein; vitamin A; folate; vitamin C; vitamin E; recreational activity; body fatness; abdominal fatness; weight change; energy intake	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).

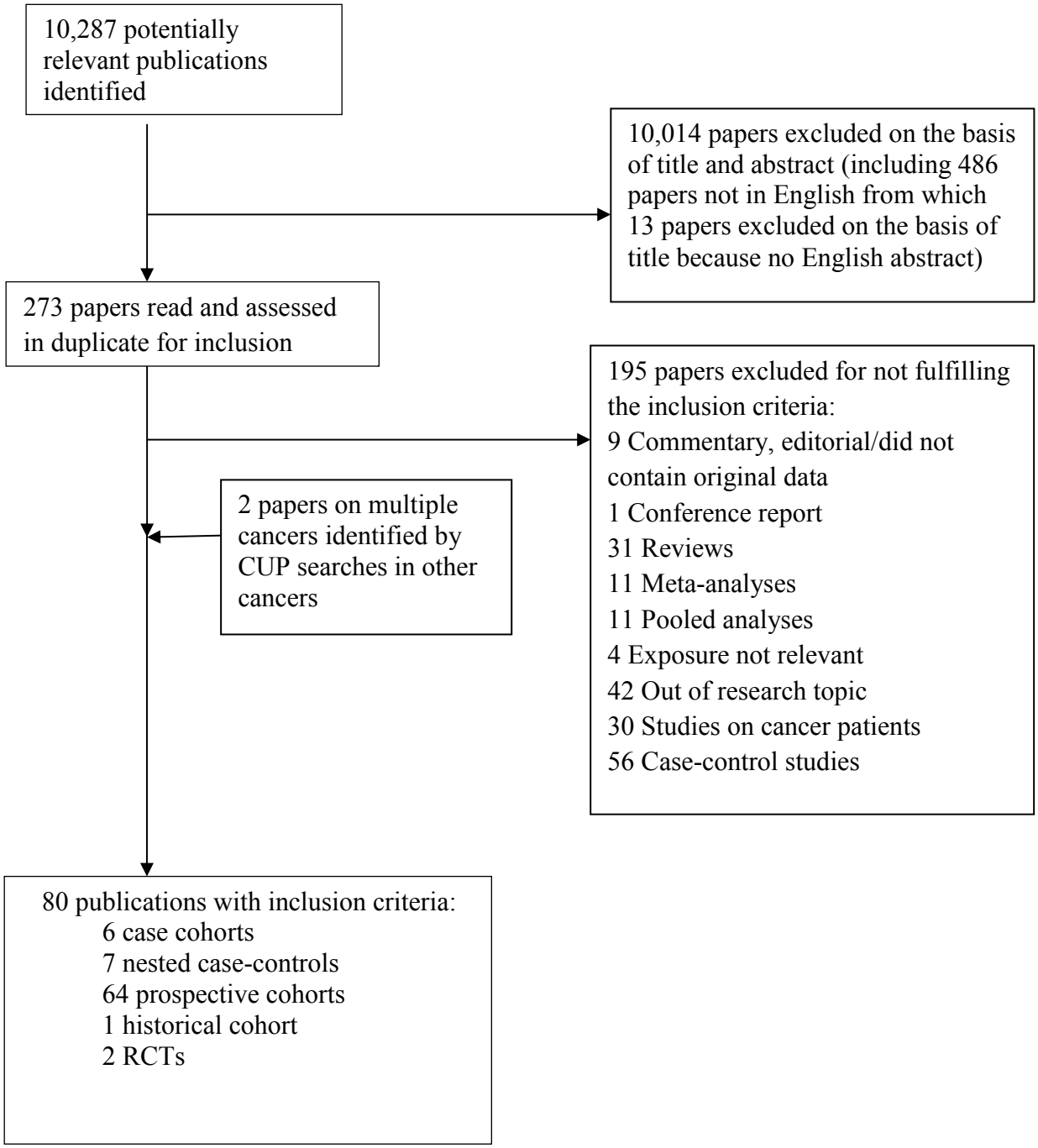
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

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.

Continuous Update Project. Results of the search

The search period is from the 1st of January 2006 until the 31st of December 2012.

Figure 1 Flow chart of search for ovarian cancer - Jan 2006-December 2012



1) Randomised controlled trials (RCT)

Only one randomized controlled trial on ovarian cancer (as secondary outcome) was identified: the Women's Health Initiative (WHI) Dietary Modification Controlled Trial. Two reports were identified. One reported the results of the trial on low fat diet (Prentice et al., 2007) and the other reported the results of the trial on calcium and vitamin D supplementation (Brunner et al., 2011)

1.5 Low fat dietary pattern

Post-menopausal women were randomly assigned to the "low-fat dietary pattern" (intervention group, 19 541 women) or to continue their usual diet (29 294 women). The low fat dietary pattern consisted in reduced fat intake (≤ 20% energy from fat) and increased intake of vegetables and fruits (≥5 servings/day) and grains (≥6 servings/day). Compliance with the assigned dietary regimen was assessed with self-reported intake using diet records, 24-h recalls, and a food frequency questionnaire. In year 6 the intervention group reported a mean intake of 28.8% of calories from fat, while the control group reported 37.0%, for a difference of 8.2% rather than the 14% that was anticipated. However, there were no differences between the changes in HDL or fasting triglycerides between the low-fat intervention and control groups suggesting that the 8.2% reported difference in fat intake is a serious overstatement of compliance. After 8.1 years of follow-up on average, there was a lower incidence of ovarian cancer amongst women with the low-fat "dietary pattern than in the comparison group (P=0.03). The incidence of ovarian cancer per 1000 person-years was 0.36 in the treatment group (57 cases) and 0.43 in the comparison group (103 cases). There was little evidence for an intervention effect on ovarian cancer during the first intervention years, and the significant risk reduction emerged in the later years. Women in the intervention arm lost about 2 kg compared to the control group during the early years of follow-up . Any effect of dietary fat reduction cannot be distinguished from weight reduction. The authors acknowledged that this could have readily been due to chance given the many comparisons that were made.

5.6.3 Calcium and vitamin D

Postmenopausal women (N = 36,282) participating in the WHI trial were randomized to daily use of 1,000 mg of calcium carbonate combined with 400 IU of vitamin D3 or placebo. After a mean follow-up of seven years, ovarian cancer incidence (or any cancer) differed significantly between the treatment and the control group. About one quarter of the participants stopped taking pills by the end of the study and serum 25(OH)D values were not measured (Brunner et al, 2011).

2) Cohort studies

Table 1 Number of publications included in the WCRF-AICR database by exposure and publication date

Only exposures included in articles identified in the CUP (1st January 2006-December 31st 2012) are listed.

Code	Exposure heading	Publication date		Total
		SLR-> Dec 2005	CUP Jan2006-Dec 2012	
1.3	Vegetarian pattern		1	1
1.4	Individual level dietary pattern		2	2
1.6.1	Breastfeeding - Mother	1	2	3
2.1.1.1	Whole grains and cereal products	-	1	1
2.1.2.1	Potatoes	-	1	1
2.2	Fruit and (non-starchy) vegetables	3	-	3
2.2.1	Non starchy vegetables	5	1	6
2.2.1.2	Cruciferous vegetables	3	1	4
2.2.1.2	Broccoli	1	1	2
2.2.1.2	Cabbage	2	1	3
2.2.1.2	Cauliflower	1	1	2
2.2.1.1.1	Carrots	1	2	3
2.2.1.5	Other non-starchy vegetables	-	1	1
2.2.2	Fruits	5	2	7
2.2.2.1.1	Oranges	1	1	2
2.2.2.2	Apples	-	1	1
2.2.2.2	Berries	-	1	1
2.3	Pulses (legumes)	2	1	3
2.3.1	Soybean products	-	2	2
2.5.1.2	Processed meat	-	4	4
2.5.1.3	Red meat	2	3	5
2.5.1.3.1	Beef	-	3	3
2.5.1.4	Poultry	1	4	5
2.5.2	Fish	1	4	5
2.5.4	Eggs	4	4	8
2.6.1.1	Butter	1	2	3
2.6.4	Sugars (as foods)	-	2	2
2.7	Dairy	2	4	6
2.7.1	Milk	3	5	8
2.7.1.1	Whole milk	2	2	4
2.7.2	Cheese	4	5	9
2.7.3	Yoghurt	3	2	5

Table 1 (cont.)

Code	Exposure heading	Publication date		Total
3	Caffeinated drinks	-	2	2
3.5	Fruit juices	-	2	2
3.6.1	Coffee	3	7	10
3.6.1	Caffeinated Coffee	-	3	3
3.6.1	Decaffeinated Coffee	-	3	3
3.6.2	Tea	2	6	8
4.1.2.7.1	Cadmium	-	2	2
4.2	N-nitrosamines	1	1	2
4.4.2	Acrylamide	-	3	3
5.1.1	Total carbohydrate	1	2	3
5.1.1	Glycemic index	-	2	-
5.1.1	Glycemic load	-	2	-
5.1.2	Dietary fibre	1	3	4
5.1.2.1	Insoluble fibre	-	2	-
5.1.2.1	Lignin	-	1	-
5.1.2.1	Cellulose	-	1	-
5.1.2.2	Soluble fibre	-	1	-
5.1.2.2	Cereal fibre	-	1	-
5.1.2.2	Vegetable fibre	-	1	-
5.1.2.2	Fruit fibre	-	1	-
5.1.4	Lactose	3	3	6
5.1.4	Sucrose	-	1	-
5.1.4	Mono/disaccharides	-	1	-
5.2.1	Total fat	2	3	5
5.2.1	Animal fat	2	2	4
5.2.1	Vegetable fat	2	2	4
5.2.1	Fat from dairy	-	3	-
5.2.2	Saturated fatty acids	2	3	5
5.2.3	Monounsaturated fatty acids	2	2	4
5.2.4	Polyunsaturated fatty acids	2	2	4
5.2.5	Trans fatty acids	1	2	3
5.4.1	Total alcohol (as ethanol)	4	8	12
5.4.1.1	Alcohol (as ethanol) from beer	1	2	3
5.4.1.2	Alcohol (as ethanol) from wine	2	2	4
5.5.1	Vitamin A, diet and supplements	1	2	3
5.5.1	Dietary vitamin A	2	2	4
5.5.1	Vitamin A supplement	-	1	-
5.5.1.1	Retinol, diet	2	1	3
5.5.1.2	Alpha-carotene	1	2	3
5.5.1.2	Total beta-carotene	1	2	3
5.5.1.2	Dietary beta-carotene	2	3	5

Code	Exposure heading	Publication date		Total
5.5.1.2	Beta-carotene supplements	-	1	1
5.5.1.2	Dietary beta-cryptoxanthin	1	2	3
5.5.2	Lutein	-	1	-
5.5.2	Lutein and zeaxanthin	1	1	2
5.5.2	Dietary lycopene	1	2	3
5.5.3.1	Total folate	1	2	3
5.5.3.2	Dietary folate	3	3	6
5.5.3.4	Methionine	-	3	-
5.5.4	Riboflavin	-	1	1
5.5.5	Thiamin (vitamin B1)	-	1	1
5.5.6	Niacin	-	1	1
5.5.7	Pyridoxine (vit B6)	-	1	1
5.5.9	Dietary vitamin C	2	3	5
5.5.9	Total vitamin C	1	3	4
5.5.10	Serum vitamin D	-	5	5
5.5.11	Dietary vitamin E	2	2	4
5.5.11	Total vitamin E	1	3	4
5.5.13	Antioxidant indices	-	2	2
5.5.13	Multivitamin/mineral supplements	1	1	2
5.6.3	Calcium supplement	1	1	2
5.6.3	Total calcium	1	3	4
5.6.3	Dietary calcium	2	2	4
5.6.4	Selenium, supplements	-	1	1
5.6.6	Phosphorus	-	1	1
5.7.2	Isothiocyanates	-	1	1
5.7.5	Phytoestrogens	-	3	3
5.7.5	Total isoflavones	-	2	2
5.7.6	Caffeine	-	1	1
5.8	Flavonoids	-	2	2
6.1	Physical activity			
7.1	Energy Intake	1	2	3
8.1.1	BMI	14	18	32
8.1.2	Other weight adjusted for height measures	3	1	4
8.1.3	Weight	2	3	5
8.1.5	Other body fatness indicators	-	2	2
8.1.6	Weight change	2	2	4
8.2.1	Waist circumference	1	6	7
8.2.2	Hips circumference	1	4	5
8.2.3	Waist to hip ratio	4	5	9
8.2.5	Somatotype in childhood	-	1	1
8.3.1	Height	7	11	18
8.4.1	Birthweight	2	2	4

Results of cohort studies: by exposure

(the heading numbers indicate the exposure code in the database)

1 Patterns of diet

1.3 -1.4 Vegetarian pattern and individual level dietary pattern

Methods

No cohort study was identified during the SLR. Three studies on dietary patterns were identified during the CUP. Different definitions of dietary patterns were used and it was not possible to estimate a summary measure of association.

Results

In one study, no association with a methyl score was observed. A high methyl group score was defined as alcohol intake <5 g/day and intake of either folate or methionine in the top tertile; a low methyl group score was defined as alcohol intake ≥10 g/day and intake of either folate or methionine in the bottom tertile; and all other levels were considered intermediate (Tworeger, 2006).

In another study, dietary patterns were derived using principal components analysis. The only significant result was a higher risk of ovarian cancer in association with the plant based component score. The surprising finding might be due to uncontrolled or residual confounding by factors such as long-term oestrogen-only HT use and OC non-use. This study reported a positive association between wine intake and ovarian cancer risk that was attributed to imperfect control for known or unknown confounders, rather than a direct effect of wine. The patterns explained only 18.9% of the total diet variance (Chang, 2008).

A comparison of vegetarians and fish eaters with meat eaters suggested a reduced risk in vegetarian and fish eaters compared with meat eaters. The number of cases of ovarian cancer was low (Key, 2009).

Table 2 Studies on dietary patterns identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Contrast
Tworoger, 2006	USA	NHS	481 epithelial ovarian cancers	22	0.95	0.70	1.30	Low vs high (ref) methyl group score
Chang, 2008	USA	CTS	311 epithelial ovarian cancer	~ 9				Highest vs lowest score
					1.65	1.06	2.54	Plant based
					1.31	0.82	2.10	High protein/high fat
					1.69	0.97	2.95	High carbohydrate
					1.10	0.75	1.59	Ethnic
					1.00	0.66	1.53	Salad and wine
Key, 2009	UK	OVS, EPIC-Oxford	98 meat eater, 8 fish eater, 34 vegetarian	12.2	0.37	0.18	0.77	Fish eater vs meat eater
					0.69	0.45	1.07	Vegetarian vs meat eater

1.6 Breastfeeding

Methods

Three studies were identified, one study during the SLR for the Second Expert Report and two studies during the CUP.
All studies reported results for comparisons between having ever breastfed or not amongst parous women.
Only a forest plot showing the comparison for Yes vs No having breastfed is shown.

Main results

Breastfeeding was not related to the risk of ovarian cancer in postmenopausal parous women in the Iowa Women's Health Study Cohort (HR $_{\text{Yes vs No}}$=1.03; 95% CI:0.66-1.61; 79 cases) (Mink et al, 1996). It was not significantly associated with the risk of ovarian cancer in women with at least one full term pregnancy the European Prospective Investigation into Cancer (HR $_{\text{ever vs never}}$ = 0.86; 95% CI: 0.70 – 1.07; 658 cases) (Tsidilis et al, 2011) and in parous women participating in the Japan Public Health Centre-based Prospective Study cohort (HR $_{\text{Yes vs No}}$= 1.0; 95% CI: 0.5-1.9; 80 cases).

The 2005 SER concluded that there was limited-suggestive evidence that lactation decrease risk of ovarian cancer, based on a meta-analysis of case-control studies

Table 3 Studies on breastfeeding identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Contrast
Tsidilis, 2011	Europe	EPIC	658	9	0.86	0.70	1.07	Ever vs never breastfed, parous women
Weiderpass, 2012	Japan	JPHC	80	16	1.0	0.5	1.9	Yes vs no, parous women

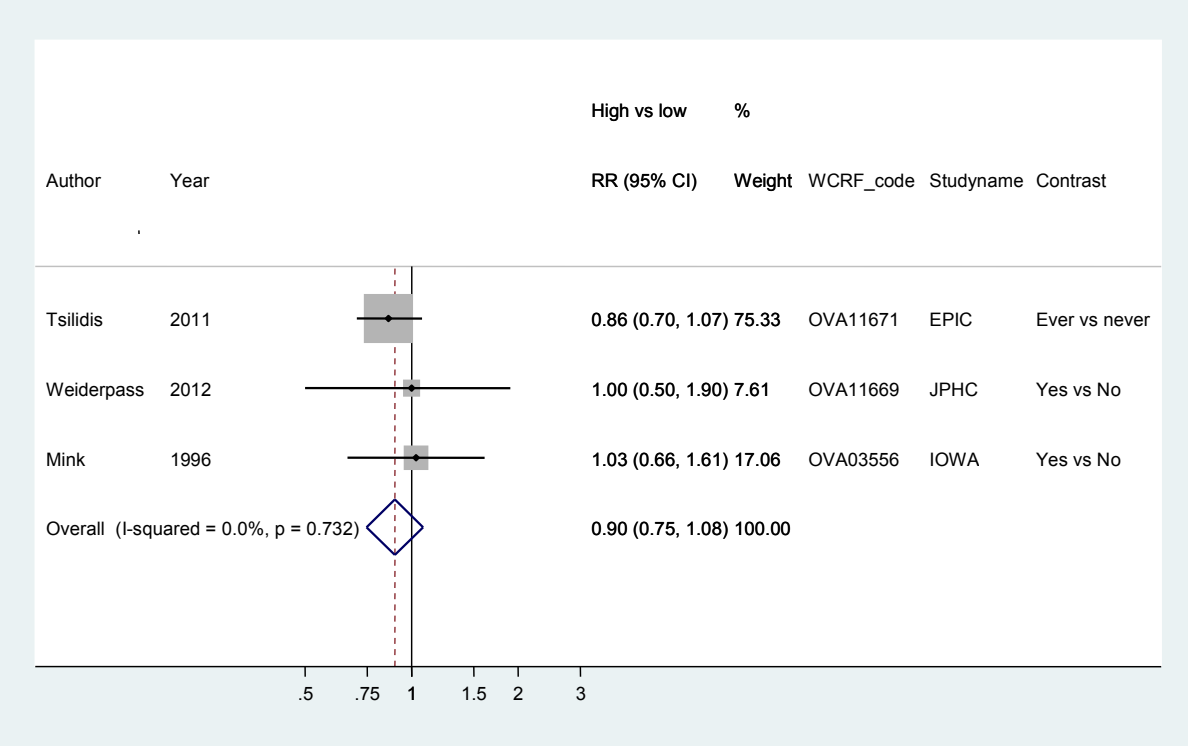
Table 4 Overall evidence on breastfeeding and ovarian cancer

	Summary of evidence
SLR	One study was identified. No association was observed.
Continuous Update Project	Two cohort studies identified. None of them reported significant associations.

Table 5 Summary of results of the highest versus lowest meta-analysis on breastfeeding and ovarian cancer

Ovarian cancer	
	Continuous Update Project
Studies (n)	3
Cases (n)	817
Overall RR (95%CI)	0.90 (0.75-1.08)
Contrast	Yes vs. No
Heterogeneity (I^2, p-value)	I^2: 0%, P=0.732

Figure 2 Highest versus lowest forest plot of breastfeeding and ovarian cancer



2 Foods

2.2 Total fruit and non-starchy vegetables

Methods

A total of 3 cohort studies on fruit and vegetable intake and ovarian cancer risk were identified during the SLR for the Second Expert Report. There were no new studies identified in the CUP. The dose-response analyses were conducted again with RR expressed per 100 grams per day increase. The unit of increase used in the SLR was 5 serving/day.

Main results

The summary RR per 100 grams per day was 1.01 (95% CI: 0.98-1.05, I^2=0%, $p_{heterogeneity}$=0.91).

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.91.

Published pooled analysis

A pooled analysis of 12 cohort studies including 560,441 participants and 2,130 cases found a pooled RR of 0.99 (95% CI: 0.86-1.14) for the highest versus lowest quartile of total fruit and vegetable intake (Koushik et al, 2005). When fruit and vegetable intakes were modelled as continuous variables, the pooled multivariate RR was 0.99 (95% CI: 0.97-1.01) for an increment in intake of 100 g/d, which is approximately 1 serving per day.

The EPIC study (Schulz et al, 2005) is the only study identified in the SLR that was not included in the published pooled analysis. If the published results of EPIC are combined with those of the pooling project the RR per 100 gram/day increase is 0.99 (95% CI: 0.97-1.01).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was no judgement of the association between total fruit and vegetable intake and ovarian cancer.

Table 6 Overall evidence on total fruit and vegetables and ovarian cancer

SLR	Summary of evidence
2005 SLR	Three cohort studies had reported on fruit and non-starchy vegetables and ovarian cancer. All of these reported no significant association.
Continuous Update Project	No additional cohort studies have been identified. A pooled analysis of 12 cohort studies reported a RR of 0.99 (95% CI: 0.97-1.01) for an increment in intake of 100 g/d.

Table 7 Summary of results of the dose-response meta-analysis of fruit and non-starchy vegetable intake and ovarian cancer

Ovarian cancer		
	SLR	Continuous Update Project
Studies (n)	3	3
Cases (n)	1134	1134
RR (95% CI)	1.06 (0.84-1.35)	1.01 (0.98-1.05)
Increment	Per 5 serv/d	Per 100 g/d
Heterogeneity (I^2, p-value)	0%, p=not available	0%, p=0.91
EPIC study and Pooling Project		13 studies
Cases (n)		2711
RR (95% CI)		0.99 (0.97-1.01)
Increment		Per 100 g/d

Table 8 Inclusion/exclusion table for meta-analysis of fruit and non-starchy vegetables and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11850	Mommers	2005	Case-cohort study	The Netherlands Cohort study	Incidence	Yes	Yes	Yes		
OVA09823	Schulz	2005	Prospective cohort study	EPIC study	Incidence	Yes	Yes	No		Only continuous results presented
OVA01437	Fairfield	2001	Prospective cohort study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Recalculated from servings to grams per day	

Figure 3 Highest versus lowest forest plot of fruit and non-starchy vegetables and ovarian cancer

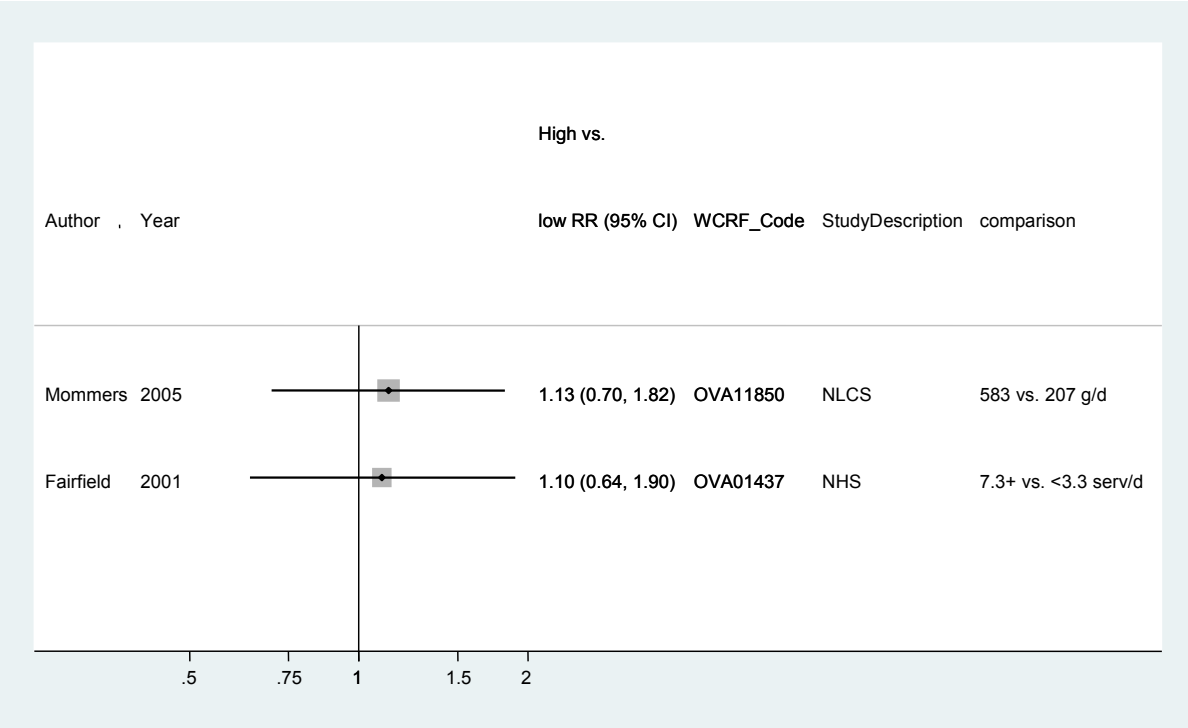


Figure 4 Dose-response meta-analysis of fruit and non-starchy vegetables and ovarian cancer, per 100 g/d

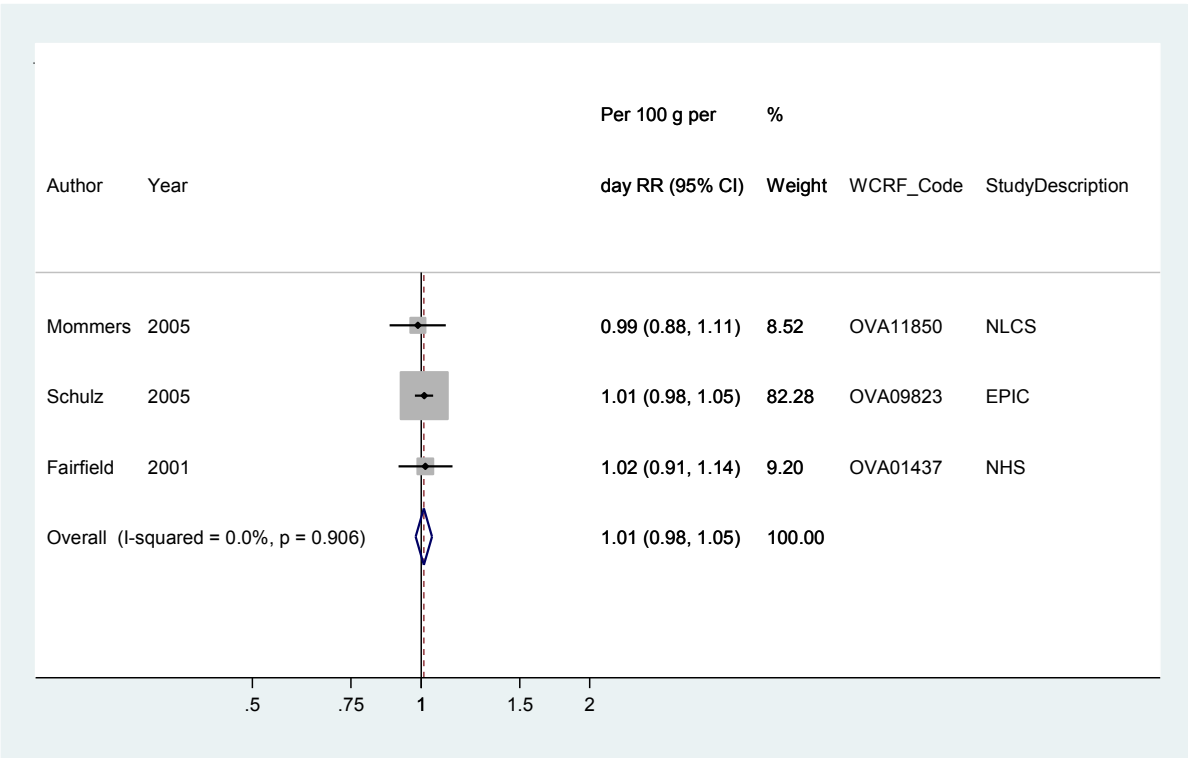


Figure 5 Dose-response graph of fruit and non-starchy vegetables and ovarian cancer

2.2.1 Non-starchy vegetables

Methods

A total of 6 cohort studies have been published on non-starchy vegetable intake and ovarian cancer risk up to 2012, and there was only one new study identified in the CUP. Dose-response analyses were conducted per 100 grams per day.

Main results

The summary RR per 100 grams per day was 0.88 (95% CI: 0.88-1.00, I^2=28.8%, $p_{heterogeneity}$=0.22). Egger's test for publication bias was not significant, p=0.22.

Heterogeneity

There was low heterogeneity, I^2=28.8%, $p_{heterogeneity}$=0.22.

Published pooled analysis

A pooled analysis of 12 cohort studies including 560441 participants and 2130 cases found a pooled RR of 0.90 (95% CI: 0.78-1.04) for the highest versus the lowest quartile of vegetable intake (Koushik, 2005) and for an increment in intake of 100 g/d, the pooled multivariate RR (95% CI) was 0.98 (0.94-1.01)

The EPIC study (Schulz et al, 2005) and the NIH-AARP Diet and Health Study are the only studies identified in the SLR that were not included in the published pooled analysis. If the published results of EPIC and the NIH-AARP study are combined with those of the pooling project the RR per 100 gram/day increase is 0.98 (95% CI: 0.95-1.01).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited suggestive evidence that non-starchy vegetables reduces ovarian cancer risk.

Table 9 Studies on non-starchy vegetables identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
George, 2009	USA	NIH-AARP Diet and Health Study	514 cases	~8 years	1.04	0.79	1.37	1.8 vs. 0.4 cup equivalents/1000 kcal/d

Table 10 Overall evidence on non-starchy vegetables and ovarian cancer

SLR	Summary of evidence
2005 SLR	Five studies reported on vegetable intake and ovarian cancer, one of which found a significant inverse association and the remaining four reporting non-significant inverse associations
Continuous Update Project	One cohort study has been published and found no significant association. A pooled analysis of 12 cohort studies reported a pooled RR of 0.98 (95% CI: 0.94-1.01) for an increment in intake of 100 g/d

Table 11 Summary of results of the dose-response meta-analysis of non-starchy vegetable intake and ovarian cancer

Ovarian cancer		
	SLR	Continuous Update Project
Studies (n)	4	6
Cases (n)	1400	2053
RR (95% CI)	0.92 (0.87-0.98)	0.94 (0.88-1.00)
Quantity	Per 1 serv/d	Per 100 g/d
Heterogeneity (I^2, p-value)	0%, p=not available	28.8, p=0.22
EPIC, NIH-AARP study and Pooling Project		15 studies
Cases (n)		3225
RR (95% CI)		0.98 (0.95-1.01)
Increment		100 g/d

Table 12 Inclusion/exclusion table for meta-analysis of non-starchy vegetables and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11685	George	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Distribution of cases and person-years, recalculation from cup equivalents to grams per day	
OVA11850	Mommers	2005	Case-cohort study	The Netherlands Cohort study	Incidence	Yes	Yes	Yes		
OVA09823	Schulz	2005	Prospective cohort study	EPIC study	Incidence	Yes	Yes	No		Only continuous results presented
OVA09697	Larsson	2004	Prospective cohort study	Swedish Mammography Cohort Study	Incidence	Yes	Yes	Yes	Recalculated from servings to grams per day	
OVA01437	Fairfield	2001	Prospective cohort study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Recalculated from servings to grams per day	
OVA02880	Kushi	1999	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Recalculated from servings to grams per day, person-years	

Figure 6 Highest versus lowest forest plot of non-starchy vegetables and ovarian cancer

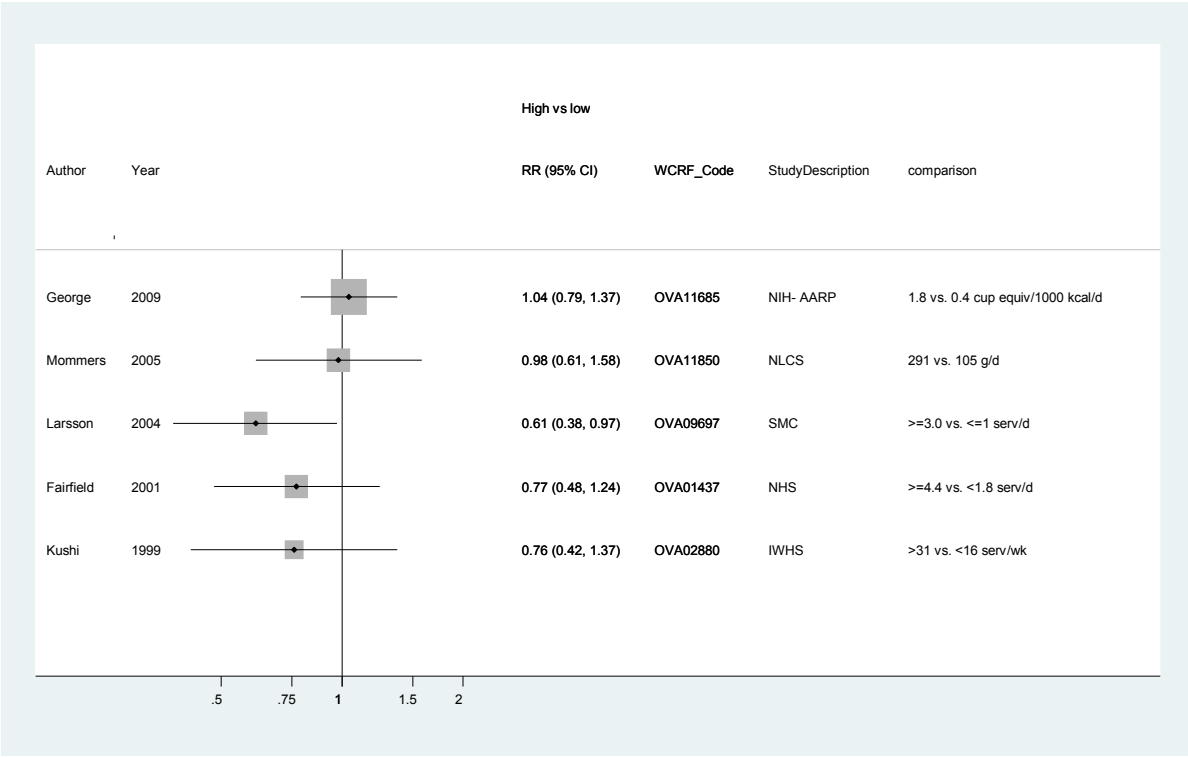


Figure 7 Dose-response meta-analysis of non-starchy vegetables and ovarian cancer, per 100 g/d

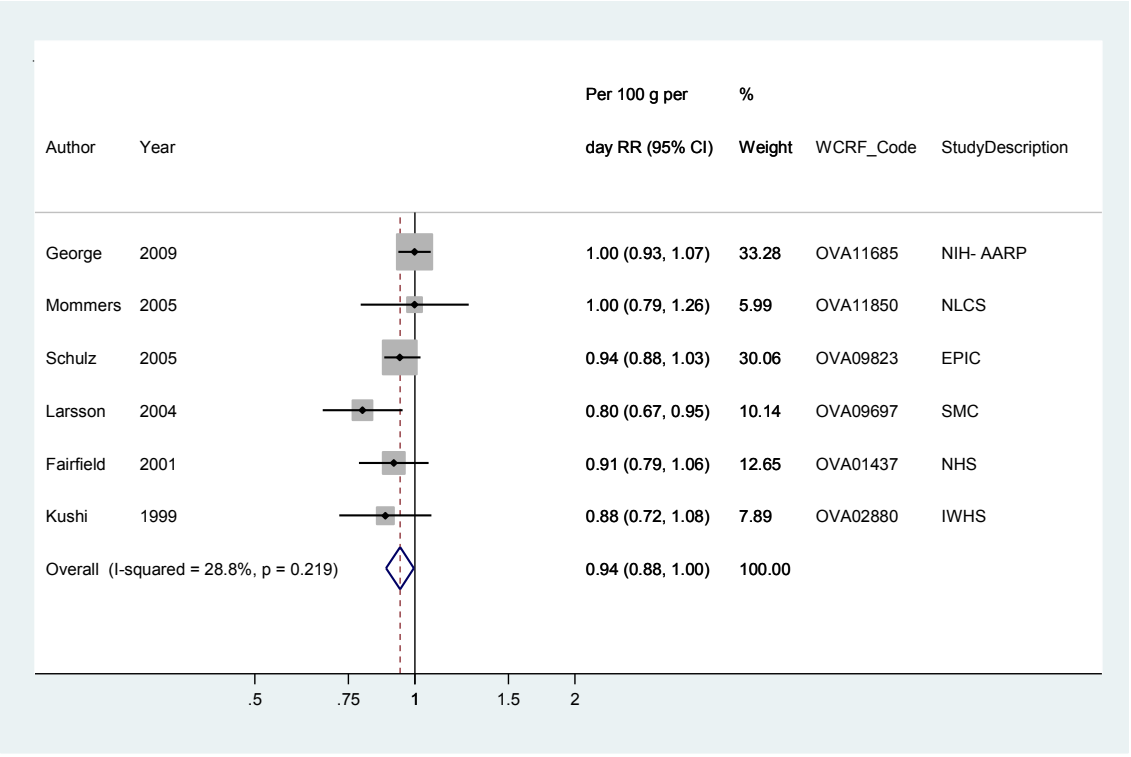


Figure 8 Funnel plot of vegetables and ovarian cancer

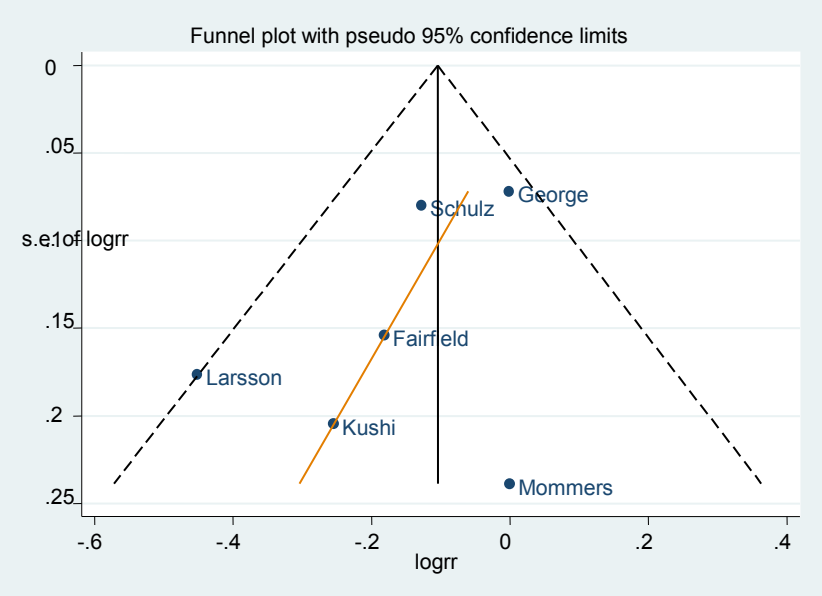
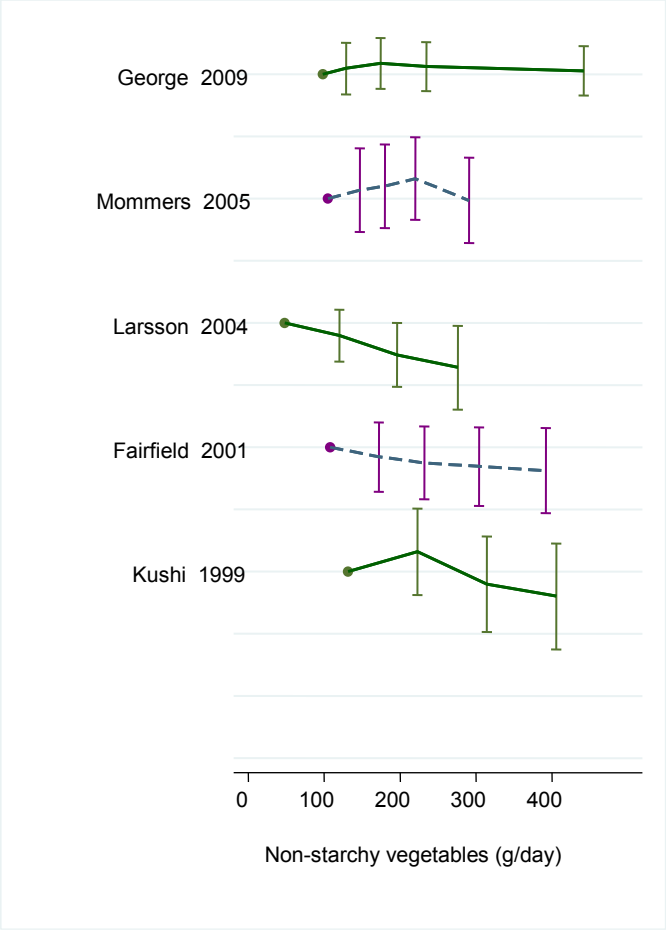


Figure 9 Dose-response graph of non-starchy vegetables and ovarian cancer



2.2.1.3 Cabbage

Methods

Up to December 2012, three cohort studies were identified, one of which was identified during the Continuous Update Project. In Larsson et al, 2004 study intake levels in servings/week were rescaled to g/day using a standard serving size of 80g for vegetables. Dose-response analyses were conducted per 5 gram/day increase.

Main results

The summary RR per 5 grams/day was 1.00 (95% CI: 0.94 - 1.06, $I^2 = 21.3$ %, $P_{heterogeneity} = 0.28$) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.94 – 1.04) when excluding the California Teachers Study, 1995 to 1.05 (95% CI: 0.91-1.21) when excluding the Swedish Mammography Cohort study.

Heterogeneity

There was low heterogeneity across the limited number of published studies ($I^2 = 21.3\%$, $P_{heterogeneity} = 0.28$). Egger's tests suggested no evidence of publication bias (p = 0.34).

Table 13 Studies on cabbage identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Chang, 2007	USA	California Teachers Study 1995	280	8.1	1.12	0.79	1.59	>3.6 vs. 0 g/day

Table 14 Overall evidence on cabbage intake and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR; both studies found no association between cabbage consumption and ovarian cancer.
Continuous Update Project	One study was identified which reported no association. Overall, three studies were included in the meta-analysis.

Table 15 Summary of results of the dose response meta-analysis of cabbage intake and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1198
Increment unit used	-	Per 5g/day
Overall RR (95%CI)	-	1.00 (0.94 - 1.06)
Heterogeneity (I^2,p-value)	-	21.3 %, p=0.28

*No meta-analysis was conducted in the 2nd report

Table 16 Inclusion/exclusion table for meta-analysis of cabbage intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study, 1995	Incidence	No	Yes	Yes	Person/ years per category	-
OVA09823	Schulz	2005	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition (EPIC) 1993-1998	Incidence	Yes	Yes	No	Rescale of RR for continuous increase	-
OVA09697	Larsson	2004	Prospective Cohort study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Servings/week rescaled to g/day using standard portion size of 80g for vegetables; mid-exposure values	-

Figure 10 Highest versus lowest forest plot of cabbage intake and ovarian cancer

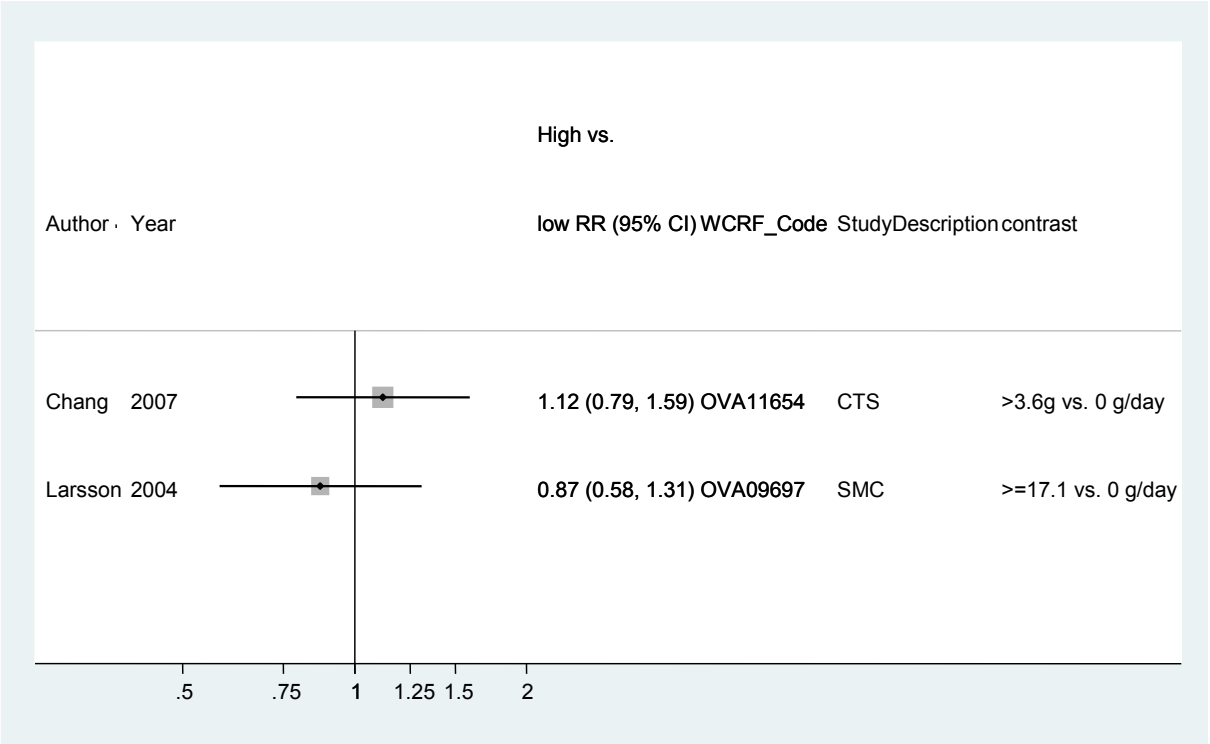


Figure 11 Dose-response meta-analysis of cabbage intake and ovarian cancer - per 5 grams/day

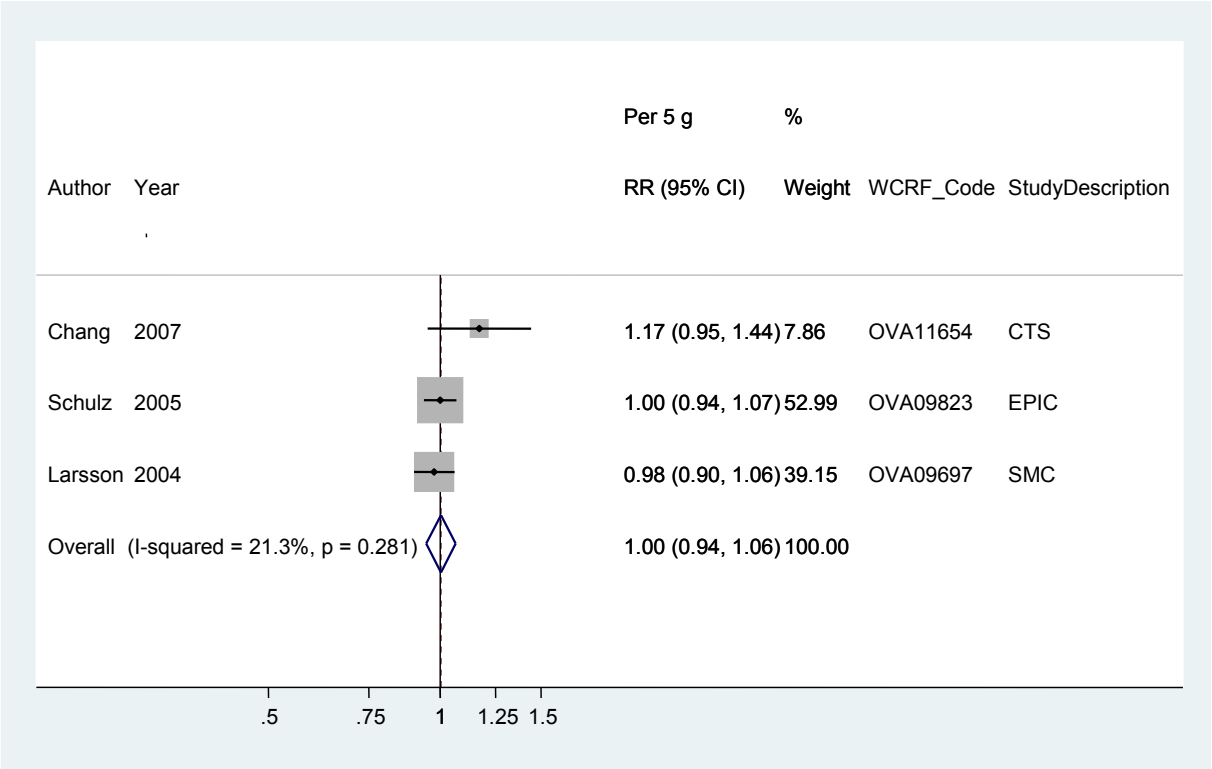


Figure 12 Funnel plot of cabbage intake and ovarian cancer

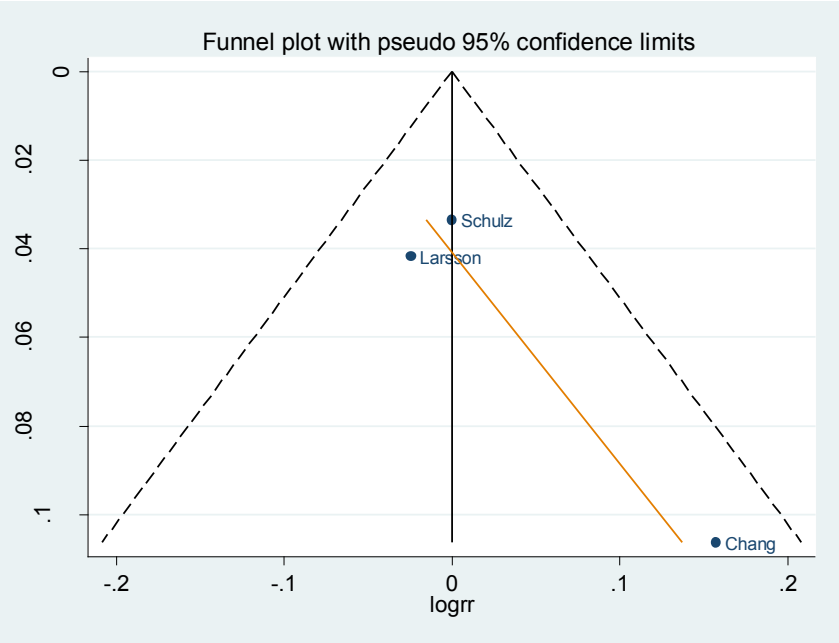
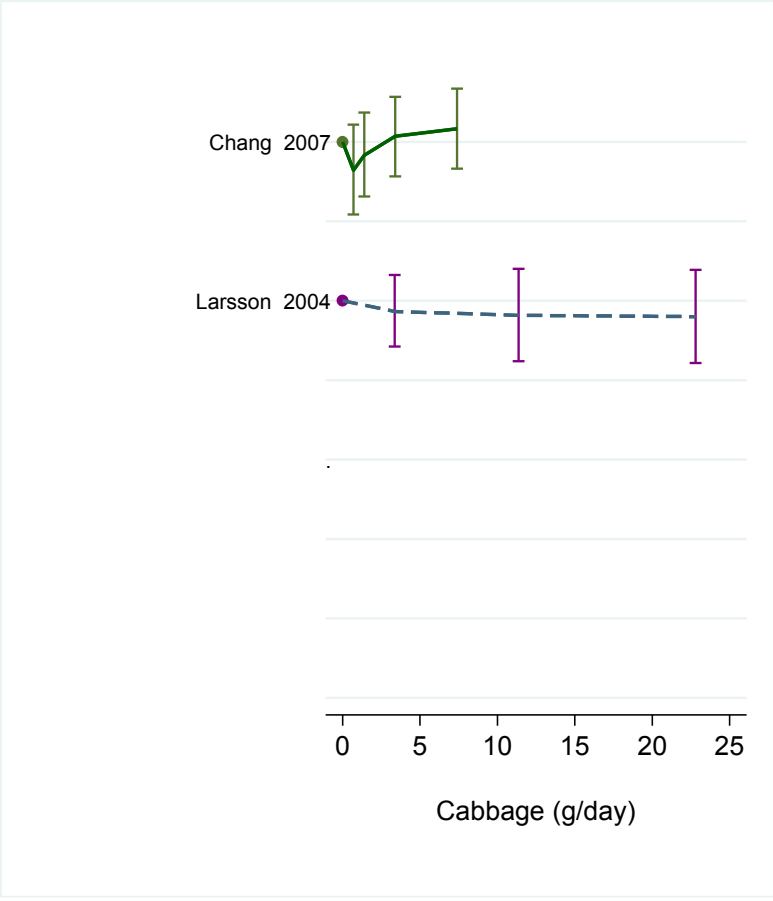


Figure 13 Dose-response graph of cabbage intake and ovarian cancer



2.2.2 Fruits

Methods

A total of 7 cohort studies have been published on fruit intake and ovarian cancer risk up to 2012, and there was only two new studies identified in the CUP. Dose-response analyses were conducted per 100 grams per day.

Main results

The summary RR per 100 grams per day was 1.05 (95% CI: 0.98-1.12, I^2=35.5%, $p_{heterogeneity}$=0.16). Egger's test for publication bias was not significant, p=0.55.

Heterogeneity

There was some evidence of moderate heterogeneity, I^2=35.5%, $p_{heterogeneity}$=0.15.

Published pooled analysis

A pooled analysis of 12 cohort studies including 560441 participants and 2130 cases found pooled RRs of 1.06 (95% CI: 0.92-1.21) for the highest versus the lowest quartile of total fruit intake (Koushik et al, 2005). For an increment in intake of 100 g/d, the pooled multivariate RR (95% CI) was 1.00 (0.97-1.02).

The EPIC study (Schulz et al, 2005) and the NIH-AARP Diet and Health Study (George et al, 2009) are the only studies identified in the SLR that were not included in the published pooled analysis. If the published results of EPIC and the NIH-AARP study are combined with those of the pooling project the RR per 100 gram/day increase is 1.01 (95% CI: 0.98-1.05).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating fruit intake to ovarian cancer was considered limited and no conclusion was possible.

Table 17 Studies on fruits identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
George, 2009	USA	NIH-AARP Diet and Health Study	514 cases	~8 years	1.04	0.79	1.37	1.8 vs. 0.4 cup equivalents/1000 kcal/d
Kiani, 2006	USA	Adventist Health Study	71 cases	Up to 16 years	0.46	0.20	1.04	>1/d vs. ≤5/wk

Table 18 Overall evidence on fruits and ovarian cancer

SLR	Summary of evidence
2005 SLR	Five studies reported on fruit intake and ovarian cancer, none of which found a significant association.
Continuous Update Project	Two cohort studies have been published and one small study found a non-significant inverse association, while the largest study found no significant association. A pooled analysis of 12 cohort studies reported a multivariate RR (95% CI) of 1.00 (0.97-1.02) for an increment in intake of 100 g/d.

Table 19 Summary of results of the dose-response meta-analysis of fruit intake and ovarian cancer

Ovarian cancer		
	SLR	Continuous Update Project
Studies (n)	4	7
Cases (n)	1400	2124
RR (95% CI)	1.08 (1.02-1.14)	1.05 (0.98-1.12)
Quantity	Per 1 serv/d	Per 100 g/d
Heterogeneity (I^2, p-value)	0%, p=not available	35.5, p=0.16
EPIC, NIH-AARP study and Pooling Project		
Cases (n)		3225
RR (95% CI)		1.01 (0.98-1.05)
Increment		100 g/d

Table 20 Inclusion/exclusion table for meta-analysis of fruit intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11685	George	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Distribution of cases and person-years, recalculation from cup equivalents to grams per day	
OVA11647	Kiani	2006	Prospective cohort study	Adventist Health Study	Incidence	No	Yes	Yes	Distribution of cases and person-years, recalculation from servings to grams	
OVA11850	Mommers	2005	Case-cohort study	The Netherlands Cohort study	Incidence	Yes	Yes	Yes		
OVA09823	Schulz	2005	Prospective cohort study	EPIC study	Incidence	Yes	Yes	No		Only continuous results presented
OVA09697	Larsson	2004	Prospective cohort study	Swedish Mammography Cohort Study	Incidence	Yes	Yes	Yes	Recalculated from servings to grams per day	
OVA01437	Fairfield	2001	Prospective cohort study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Recalculated from servings to grams per day	
OVA02880	Kushi	1999	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Recalculated from servings to grams per day, person-years	

Figure 14 Highest versus lowest forest plot of fruits and ovarian cancer

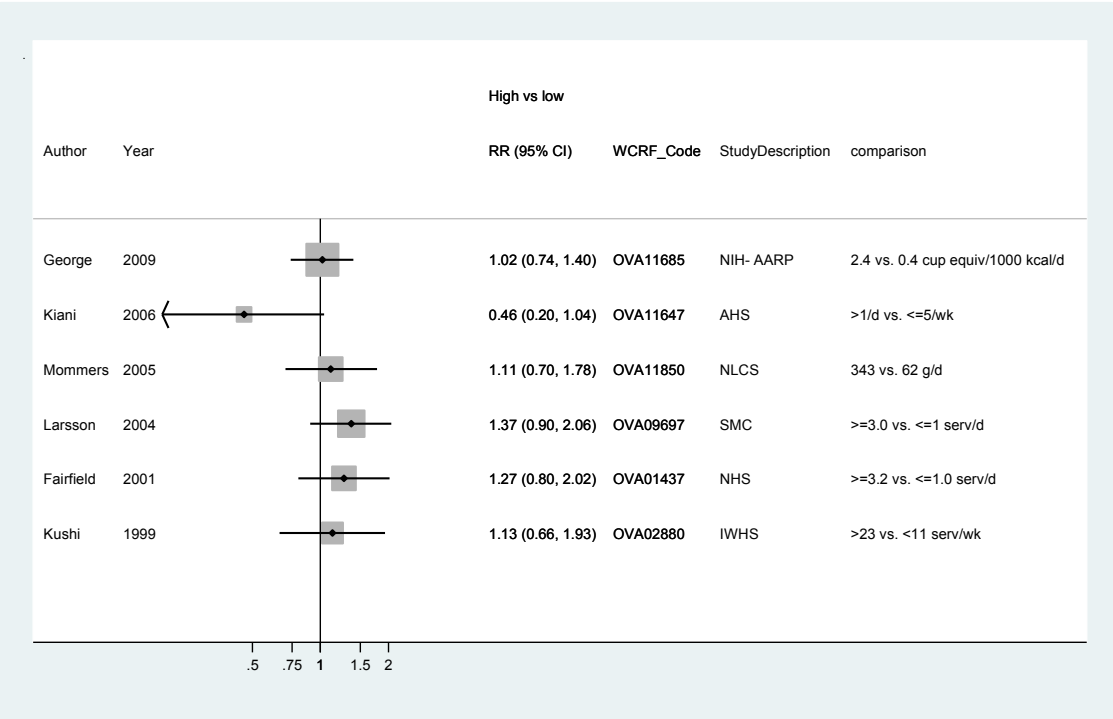


Figure 15 Dose-response meta-analysis of fruits and ovarian cancer, per 100 g/d

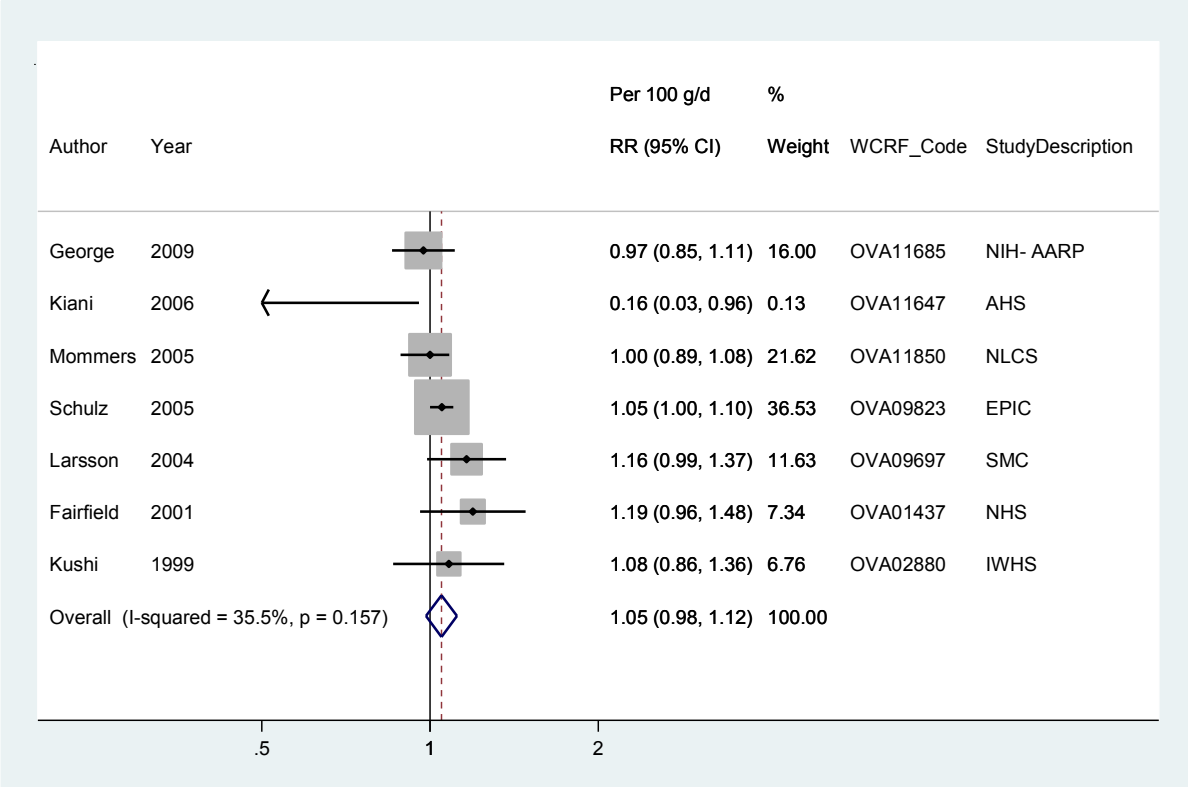


Figure 16 Funnel plot of fruits and ovarian cancer

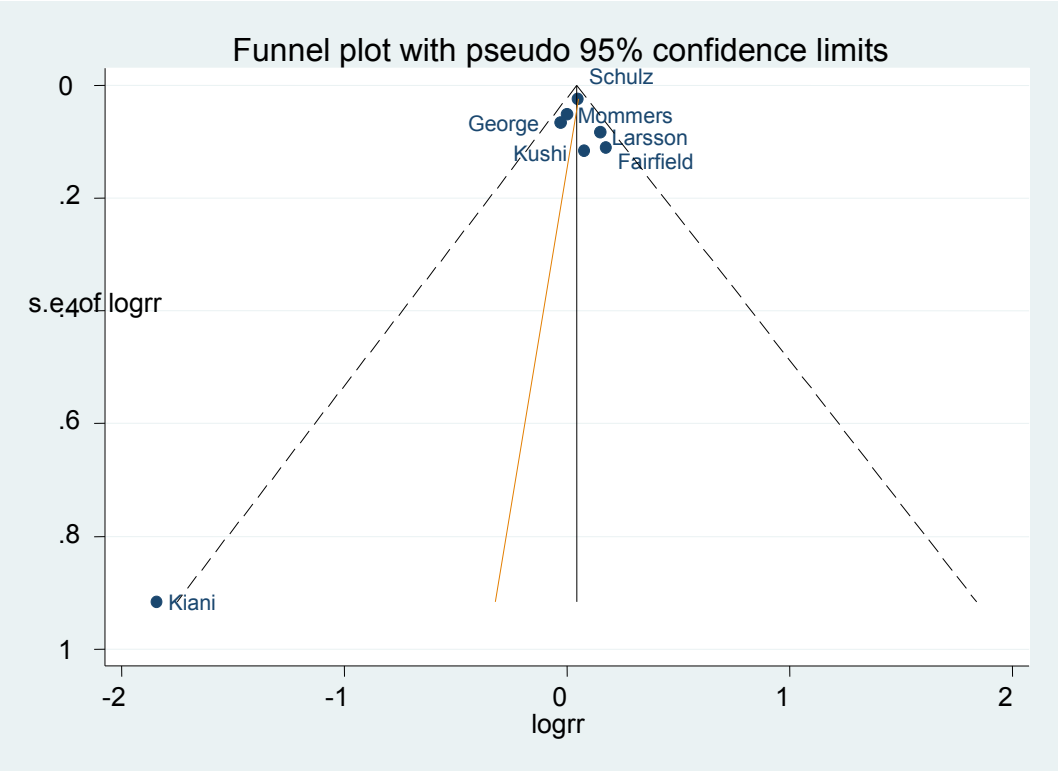
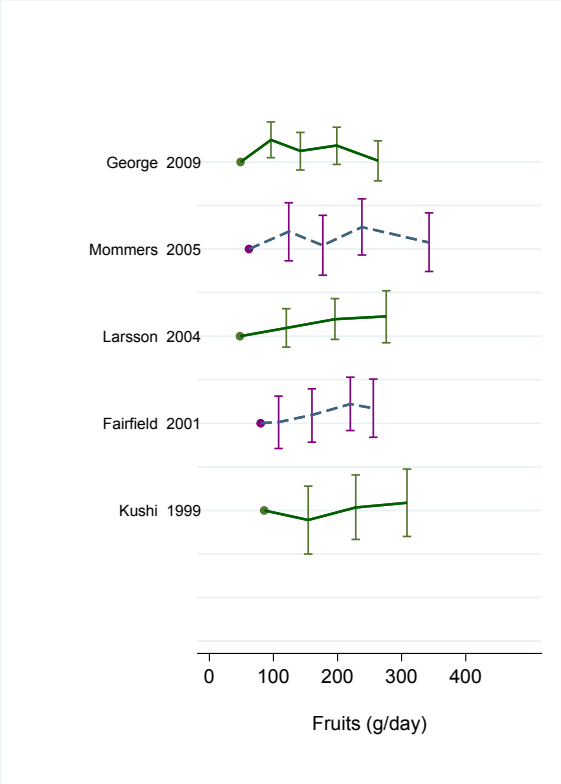


Figure 17 Dose-response graph of fruit intake and ovarian cancer



2.5.1.2 Processed meat

Methods

Four cohort studies have been published on processed meat and ovarian cancer; all four were identified in the Continuous Update Project. One study identified in the SLR reported no association of sausage intake with ovarian cancer (Larsson, 2005)
A serving size of 50 grams was used to convert intake frequency to grams per day in one study. The results of dose-response analyses are presented for an increment of 50 grams per day. One study (Cross et al, 2007) provided median serving size intake in g/1000 kcal, which was used in this analysis.

Main results

Four studies (one in ovarian cancer mortality) were included in meta-analysis. The summary RR per 50 g/d was 1.13 (95% CI: 0.88-1.46, I^2=0%, $P_{heterogeneity}$=0.76) for all studies combined (n=4). After exclusion of one study on ovarian cancer mortality, the pooled estimate was 1.14 (95% CI: 0.88-1.47, I^2=0%, $P_{heterogeneity}$=0.59) (n=3). In a sensitivity analysis the summary RR ranged from 1.03 (95% CI: 0.74-1.48) when excluding the National Institute of Health- American Association for Retired Persons to 1.21 (95% CI: 0.90-1.63) when excluding the Netherland Cohort Study.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies (I^2=0%, $P_{heterogeneity}$=0.76, Egger's test p=0.48)

Published meta-analysis

In a published meta-analysis of five prospective studies (Wallin et al, 2011), the summary RR of ovarian cancer for 100 grams per week increment of processed meat intake was 1.05 (95% CI: 0.98- 1.14; $P_{heterogeneity}$=0.67).Included in this meta-analysis was the study by Larsson et al, 2005 in Swedish women that reported only on sausage intake (RR per 100 g: 1.46 (95% CI: 0.82- 2.62)

In another published meta-analysis (Kolahdooz et al, 2010), the summary RR of ovarian cancer for highest vs. lowest processed meat intake for all the studies combined (three cohorts and four population-based case-control studies) was 1.19 (95% CI: 1.07-1.34; $P_{heterogeneity}$=0.88). The relative risks estimates were 1.26 (95% CI: 1.02-1.56; $P_{heterogeneity}$=0.93) for the three cohort studies and 1.17 (95% CI: 1.03-1.34; $P_{heterogeneity}$=0.58) for the four population-based case-control studies, respectively.

Table 21 Studies on processed meat identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Contrast
Gilsing, 2011	Netherlands	The Netherland Cohort Study	340	16.3	0.83 0.96	0.59 0.75	1.20 1.23	High vs low quintile Per 25 g/day increase
Schulz, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	581	6.3	1.25 1.05	0.81 0.91	1.92 1.21	>=42 g/day vs <17g/day Per 15.6 g/day increase
Cross, 2007	United States	National Institute of Health-American Association for Retired Persons	522	6.8	1.23	0.92	1.63	22.6 g/1000 kcal vs 1.6 g/1000 kcal
Sakauchi, 2007	Japan	Japan Collaborative Cohort study	57 deaths	13.3	0.91	0.30	2.76	>=-4 times/week vs <=1-2 times/week

Table 22 Overall evidence on processed meat and ovarian cancer

	Summary of evidence
SLR	No study on processed meat (processed meat, processed pork and pork products) was identified.
Continuous Update Project	Four prospective studies were identified. None of the studies reported a significant association of ovarian cancer and processed meat intake.

Table 23 Summary of results of the dose response meta-analysis on processed meat and ovarian cancer

Ovarian cancer*		
	SLR	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1530
Increment unit	-	Per 50 g/d
RR (95% CI)	-	1.13 (0.88-1.46)
Heterogeneity (I^2, p-value)		0%, p=0.76
Ovarian cancer incidence*		
	SLR	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1473
Increment unit	-	Per 50 g/d
RR (95% CI)	-	1.14 (0.88-1.47)
Heterogeneity (I^2, p-value)	-	0% p=0.59

*No meta-analysis was conducted in the 2nd report

Table 24 Inclusion/exclusion table for meta-analysis of processed meat and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP HvL forest plot	Estimated values	Exclusion reason
OVA11616	Gilsing	2011	Case-Cohort study	The Netherland Cohort Study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11639	Schulz	2007	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11686	Cross	2007	Prospective Cohort study	National Institute of Health-American Association for Retired Persons	Incidence	No	Yes	Yes	Reported median intake in g/1000 kcal was recalculated to g/energy intake by quintile	-
OVA11661	Sakauchi	2007	Prospective Cohort study	Japan Collaborative Cohort study	Mortality	No	Yes	Yes	Person/ years per category g/day per quintile and mid-exposure values	-

Figure 18 Highest versus lowest forest plot of processed meat and ovarian cancer

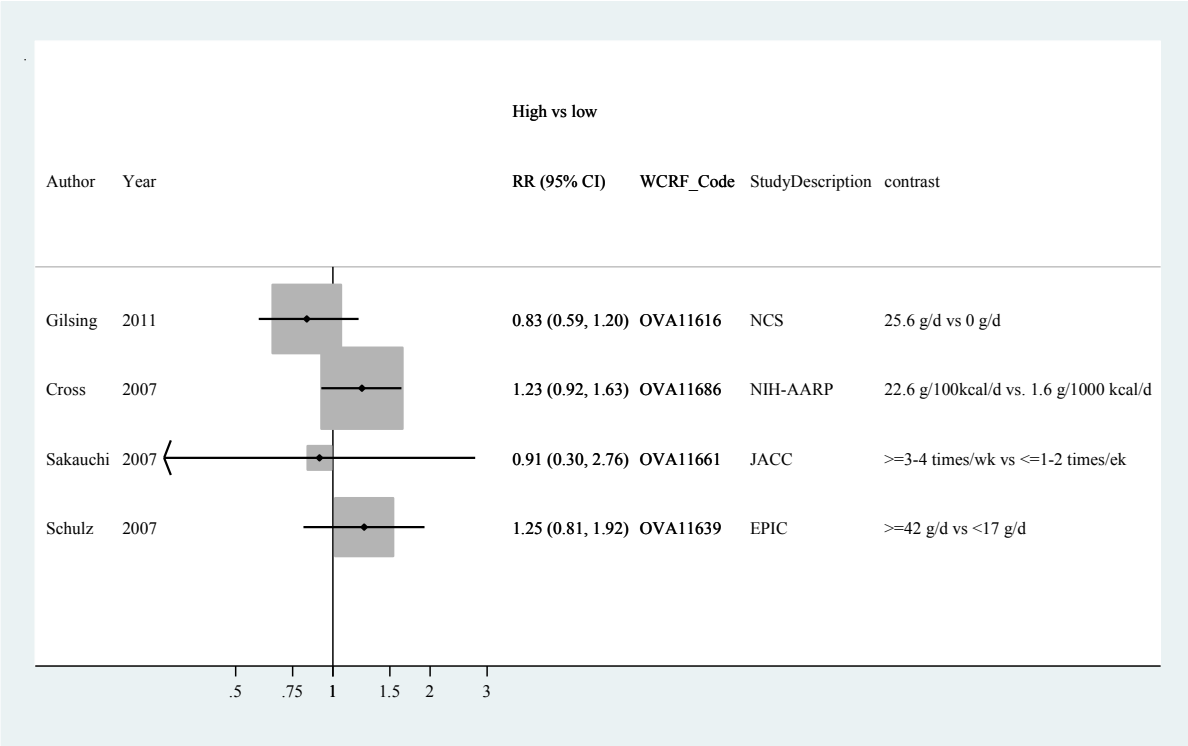


Figure 19 Dose-response meta-analysis of processed meat and ovarian cancer - per 50 g/d

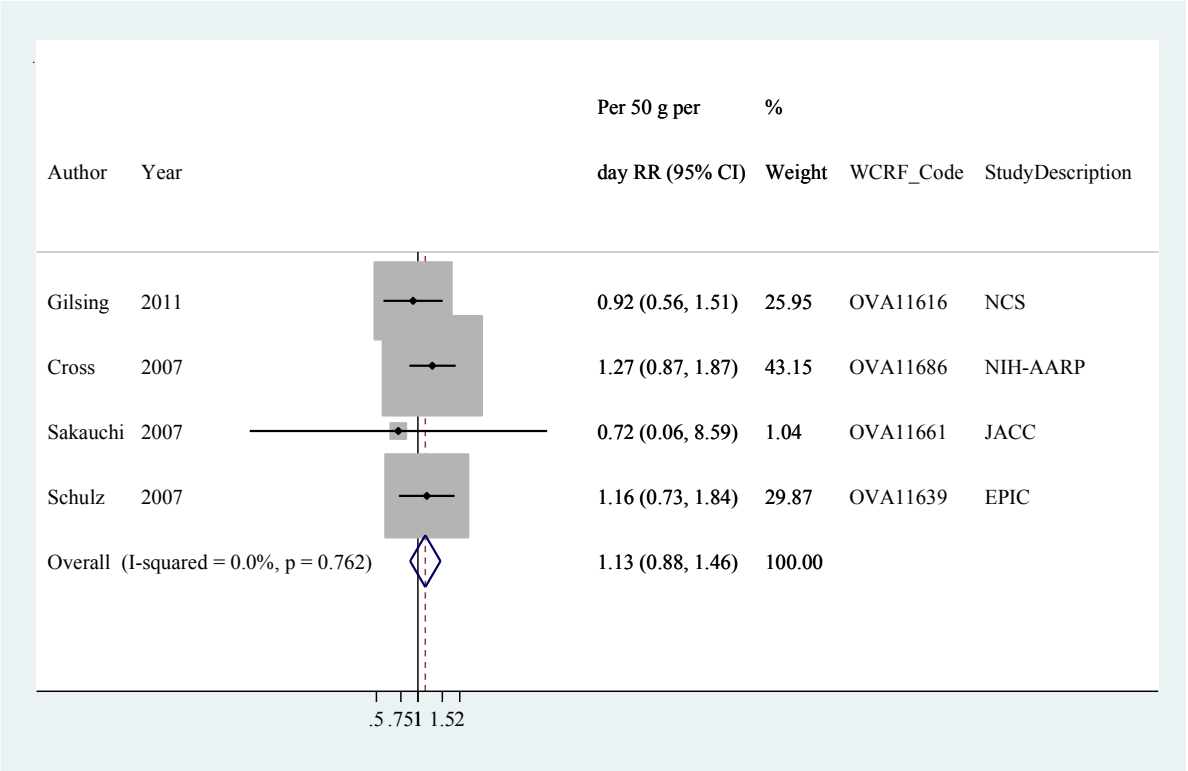


Figure 20 Funnel plot of processed meat and ovarian cancer

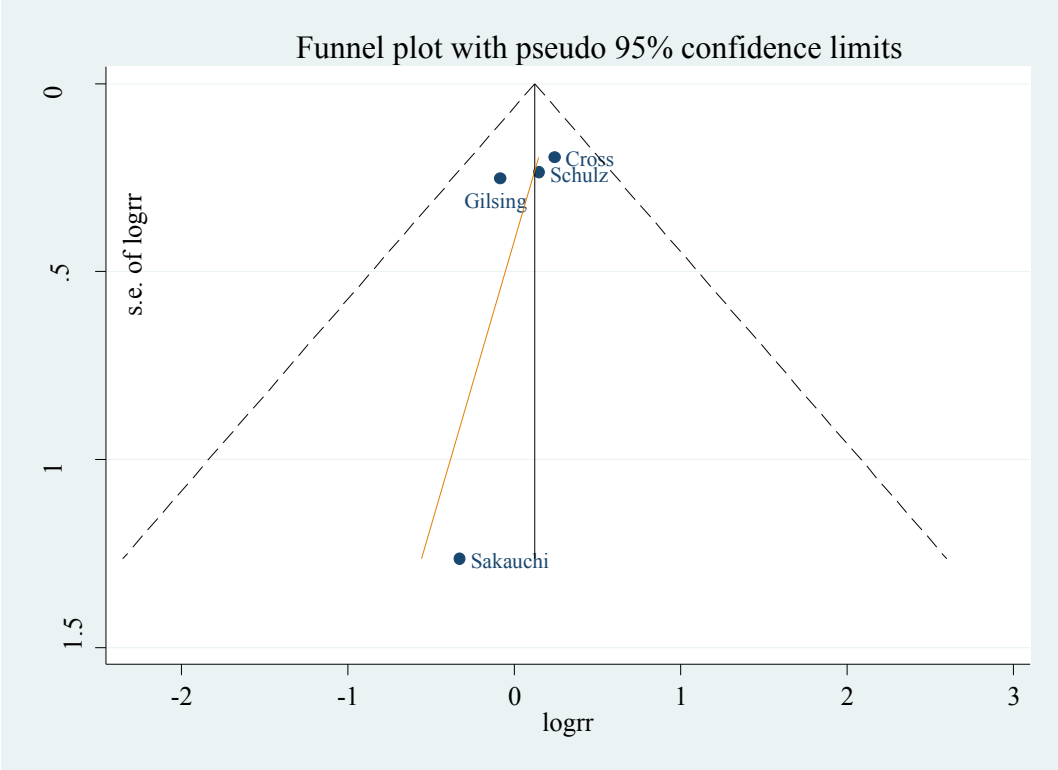
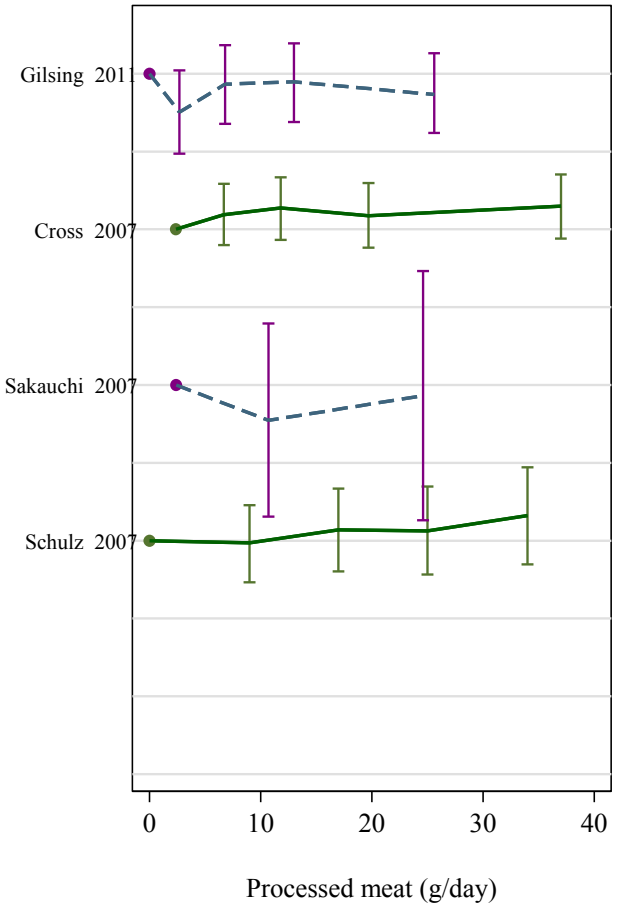


Figure 21 Dose-response graph of processed meat and ovarian cancer



2.5.1.3 Red meat

Methods

Five cohort studies have been published on red meat and ovarian cancer, three of which were identified in the Continuous Update Project and two during the SLR. Five studies could be included in CUP meta-analysis.

A serving size of 100 grams was used to convert intake frequency to grams per day. For one study (Bertone, 2002) a serving size of 85g was used, as informed in a latter publication (Pan, 2012). For Cross et al, 2007 a median serving size intake in g/1000 kcal, provided, this was used in this analysis.

The results of dose-response analyses are presented for an increment of 100 grams per day.

Main results

The summary RR per 100 g/d (85 g/d for Bertone, 2002; g/1000 kcal for Cross, 2007) was 1.03 (95% CI: 0.86-1.24, I^2=0%, $P_{heterogeneity}$ =0.56) for all studies combined. In influence analysis the summary RR ranged from 0.98 (95% CI: 0.79-1.22) when excluding the National Institute of Health- American Association for Retired Persons Study (Cross, 2007) to 1.13 (95% CI: 0.89-1.44) when excluding The Netherland Cohort Study (Gilsing, 2011).

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies (I^2=0%, $P_{heterogeneity}$ =0.56). There was no indication of publication bias with Egger's test (p=0.68). However, only five studies were identified.

Comparison with the Second Expert Report

Two studies were identified during the SLR, one of them showed a suggestive modest increased association of red meat intake and ovarian cancer risk.

Published meta-analysis

In a published meta-analysis of eight prospective studies (Wallin et al, 2011), the summary RR of ovarian cancer for 100 grams per week increment of red meat intake was 1.02 (95% CI: 0.99- 1.04; $P_{heterogeneity}$=0.972). This meta-analysis included studies that did not report separately on red meat. Included were a study by Kiani et al, 2006 in adventists, that investigated all meats combined (beef, pork, poultry, fish and any meat) (RR per 100 g increase: 1.05 (95% CI: 0.63-1.77); the study by Kushi et al, 1999 (IWHS) on all meats (RR per 100 g: 1.02 (95% CI: 0.98-1.07) and the study by Sakauchi et al, 2007 (JACC) that investigated separately on intake of pork, beef, ham and sausage, but not on red meat. In another published meta-analysis (Kolahdooz et al, 2010), the summary RR of ovarian cancer for highest vs. lowest red meat intake for all the studies included in the meta-analysis (three cohorts, four population-based case-control and three hospital-based case-control studies) was 1.16 (95% CI: 1.02-1.32; $P_{heterogeneity}$=0.07). The individual meta-analyses results were RR = 1.15; 95% CI: 0.97-1.36; $P_{heterogeneity}$=0.77, RR= 0.99; 95% CI: 0.78-1.24;

$P_{heterogeneity}$=0.15 and RR= 1.39; 95% CI: 1.19-1.62; $P_{heterogeneity}$=0.37; for the cohorts studies, population-based case-control studies and hospital-based case-control meta-analyses respectively.

Table 25 Studies on red meat identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Contrast
Gilsing, 2011	Netherlands	The Netherland Cohort Study	340	16.3	0.93 0.98	0.61 0.92	1.42 1.05	High vs low quintile of intake Per 25 g/day increase
Schulz, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	581	6.3	1.04 0.96	0.70 0.83	1.56 1.10	>=55 g/day vs<25g/day Per 18.2 g/day increase
Cross, 2007	United States	National Institute of Health-American Association for Retired Persons	522	6.8	1.19	0.89	1.59	62.7 g/1000 kcal vs 9.8 g/1000 kcal

Table 26 Overall evidence on red meat and ovarian cancer

	Summary of evidence
SLR	Two cohort studies were identified during the SLR. One US prospective cohort study (Bertone et al., 2002) found that frequent intake of all types of red meat (main dish of beef, pork and lamb) was suggestive of a modestly increased ovarian cancer risk (RR= 1.3; CI 0.93-1.82) with high red meat intake. The Sweden cohort reported no association with epithelial ovarian cancer (Larsson, 2005).
Continuous Update Project	Three prospective studies were identified. None of the studies reported a significant association of ovarian cancer and red meat intake.

Table 27 Summary of results of the dose response meta-analysis on red meat and ovarian cancer

Ovarian cancer*		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	2089
Increment unit	-	Per 100 g/d
RR (95% CI)	-	1.03 (0.86-1.24)
Heterogeneity (I^2, p-value)		0%, p=0.56

*No meta-analysis was conducted in the 2nd report

Table 28 Inclusion/exclusion table for meta-analysis of red meat and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP HvL forest plot	Estimated values	Exclusion reason
OVA11616	Gilsing	2011	Case-Cohort study	The Netherland Cohort Study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11639	Schulz	2007	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11686	Cross	2007	Prospective Cohort study	National Institute of Health-American Association for Retired Persons	Incidence	No	Yes	Yes	Reported median intake in g/1000 kcal was recalculated to g/energy intake by quintile	-
OVA10420	Larsson	2005	Prospective Cohort study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	-	-
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Person/ years per category, g/day per category and mid-exposure values	-

Figure 22 Highest versus Lowest forest plot of red meat consumption and ovarian cancer

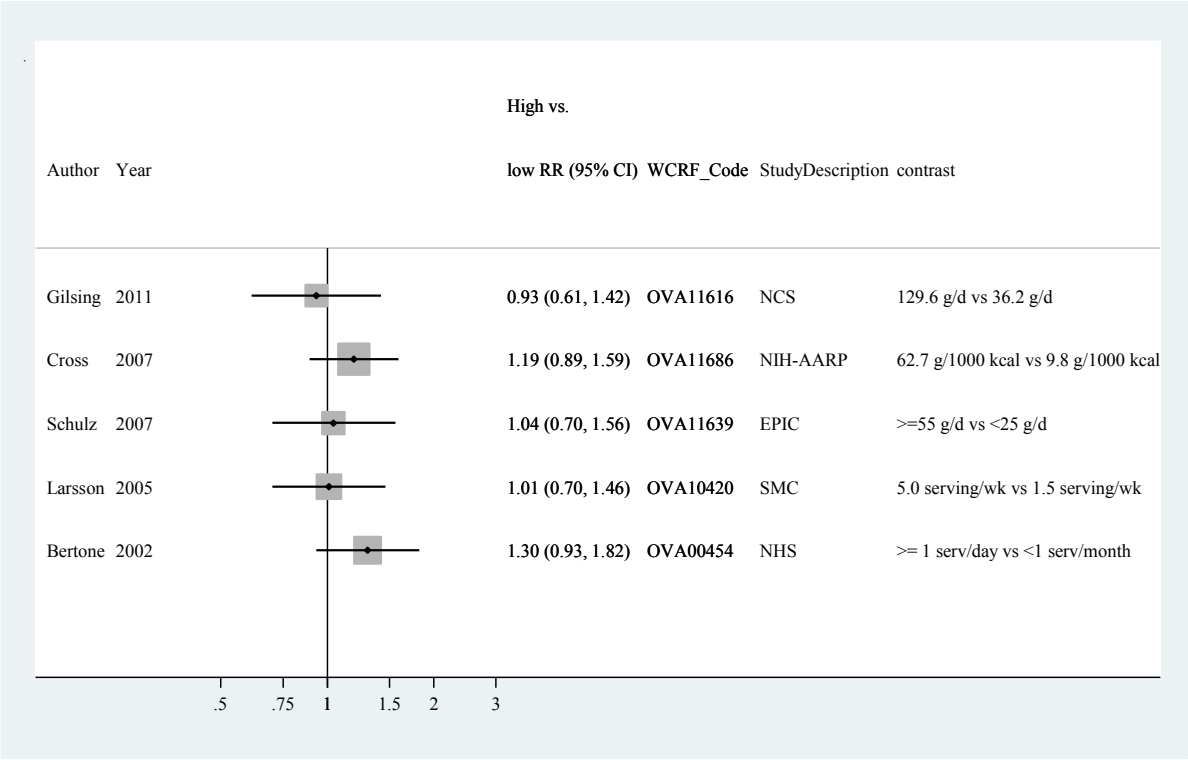


Figure 23 Dose-response meta-analysis of red meat consumption and ovarian cancer per 100 g/day

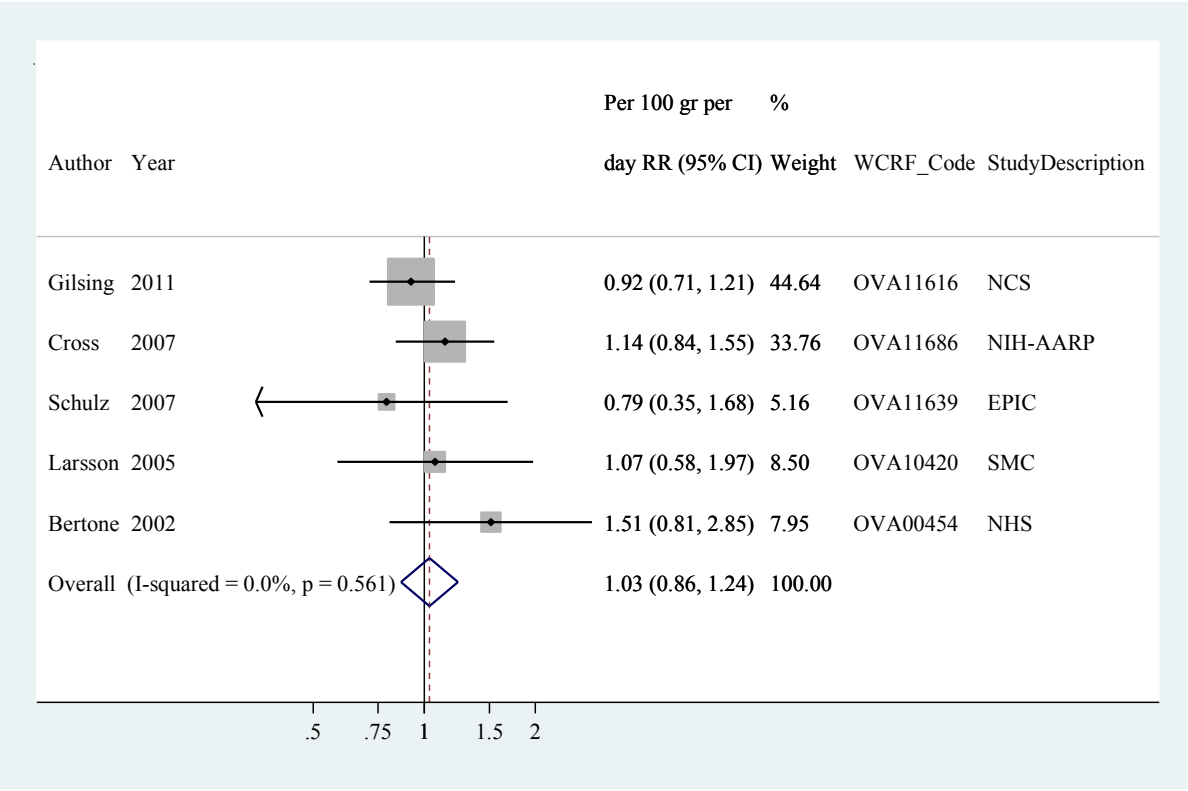


Figure 24 Funnel plot of red meat consumption and ovarian cancer

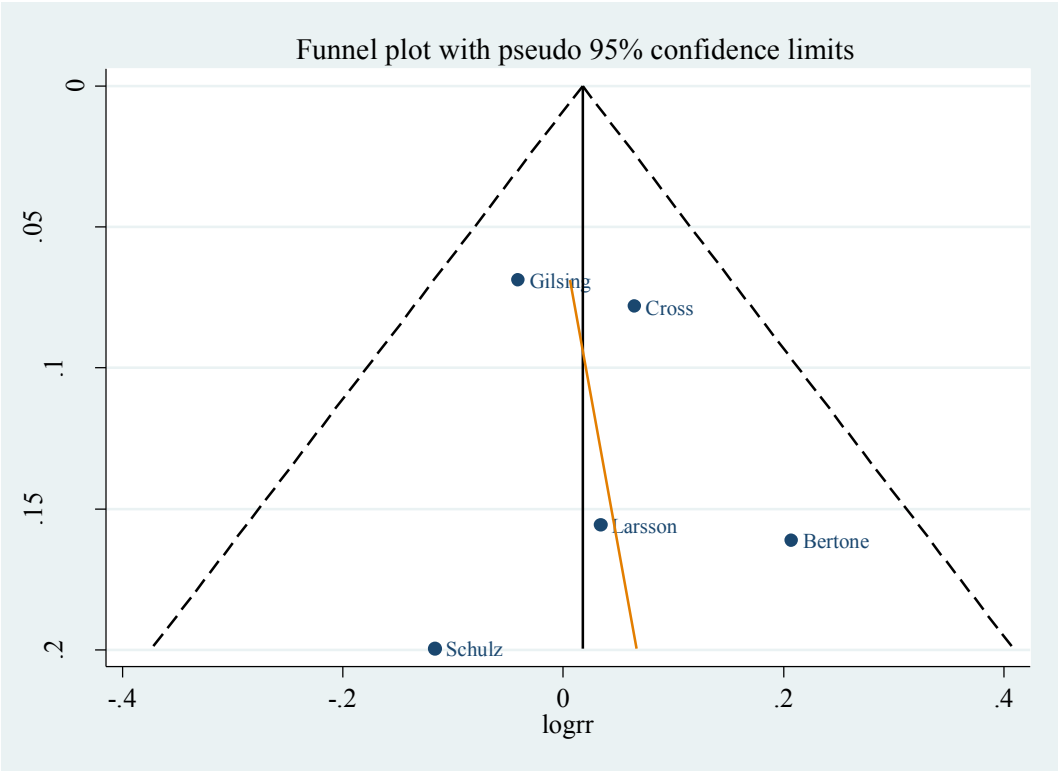


Figure 25 Dose-response graph of red meat and ovarian cancer

2.5.1.3.1 Beef

Methods

Three cohort studies have been published on beef and ovarian cancer; the three of them were identified in the Continuous Update Project.
A serving size of 120 grams was used to convert intake frequency to grams per day in two studies. The results of dose-response analyses are presented for an increment of 50 grams per day.

Main results

Three studies could be included in meta-analysis. The summary RR per 50 g/d was 1.15 (95% CI: 0.91-1.44, I^2=0%, $P_{heterogeneity}$ =0.94) for all studies combined. The overall results remained the same when one study with mortality as outcome was excluded from the analysis (RR= 1.14, 95% CI: 0.90-1.44; I^2= 0%, $P_{heterogeneity}$=0.98). In influence analysis the summary RR ranged from 1.14 (95% CI: 0.90-1.43) when excluding the Japan Collaborative Cohort study to 1.30 (95% CI: 0.43-3.9) when excluding the Netherland Cohort Study.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies (I^2=0%, $P_{heterogeneity}$=0.94). There was no indication of publication bias with Egger's test (p=0.46).

Table 29 Studies on beef identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Gilsing, 2011	Netherlands	The Netherland Cohort Study	340	16.3	1.15 1.07	0.81 0.95	1.64 1.20	Highest vs low quintile Per 25 g/day increase
Sakauchi, 2007	Japan	Japan Collaborative Cohort study	77	13.3	1.24	0.50	3.05	>=1-2 times/week vs Seldom
Kiani, 2006	USA	Adventist Health Study	71	16	1.09	0.50	2.38	>=1 time/week vs Never

Table 30 Overall evidence on beef and ovarian cancer

	Summary of evidence
SLR	No studies were found on beef intake and ovarian cancer risk.
Continuous Update Project	Three prospective studies were identified. None of the studies reported a significant association of ovarian cancer and beef intake.

Table 31 Summary of results of the dose response meta-analysis on beef and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	488
Increment unit	-	Per 50 g/d
RR (95% CI)	-	1.15 (0.91-1.44)
Heterogeneity (I^2, p-value)	-	0%, p=0.94
Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	411
Increment unit	-	Per 50 g/d
RR (95% CI)	-	1.14 (0.90-1.44)
Heterogeneity (I^2, p-value)		0%, p=0.98

*No meta-analysis was conducted in the 2nd report

Table 32 Inclusion/exclusion table for meta-analysis of beef and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP HvL forest plot	Estimated values	Exclusion reason
OVA11616	Gilsing	2011	Case-Cohort study	The Netherland Cohort Study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11661	Sakauchi	2007	Prospective Cohort study	Japan Collaborative Cohort study	Mortality	No	Yes	Yes	Person/ years per category g/day per category and mid-exposure values	-
OVA11647	Kiani	2006	Prospective Cohort study	Adventist Health Study	Incidence	No	Yes	Yes	Cases and person/ years per category g/day per category and mid-exposure values	-

Figure 26 Highest versus lowest forest plot of beef consumption and ovarian cancer

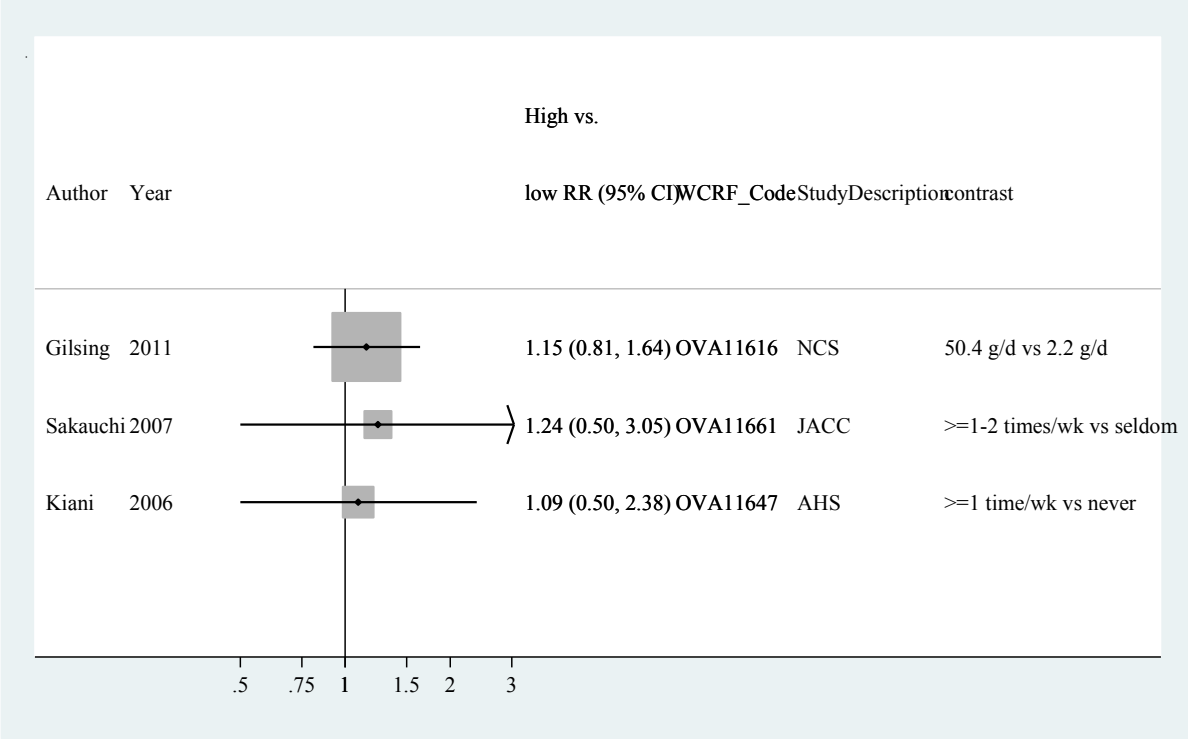


Figure 27 Dose-response meta-analysis of beef consumption and ovarian cancer – per 50 g/day

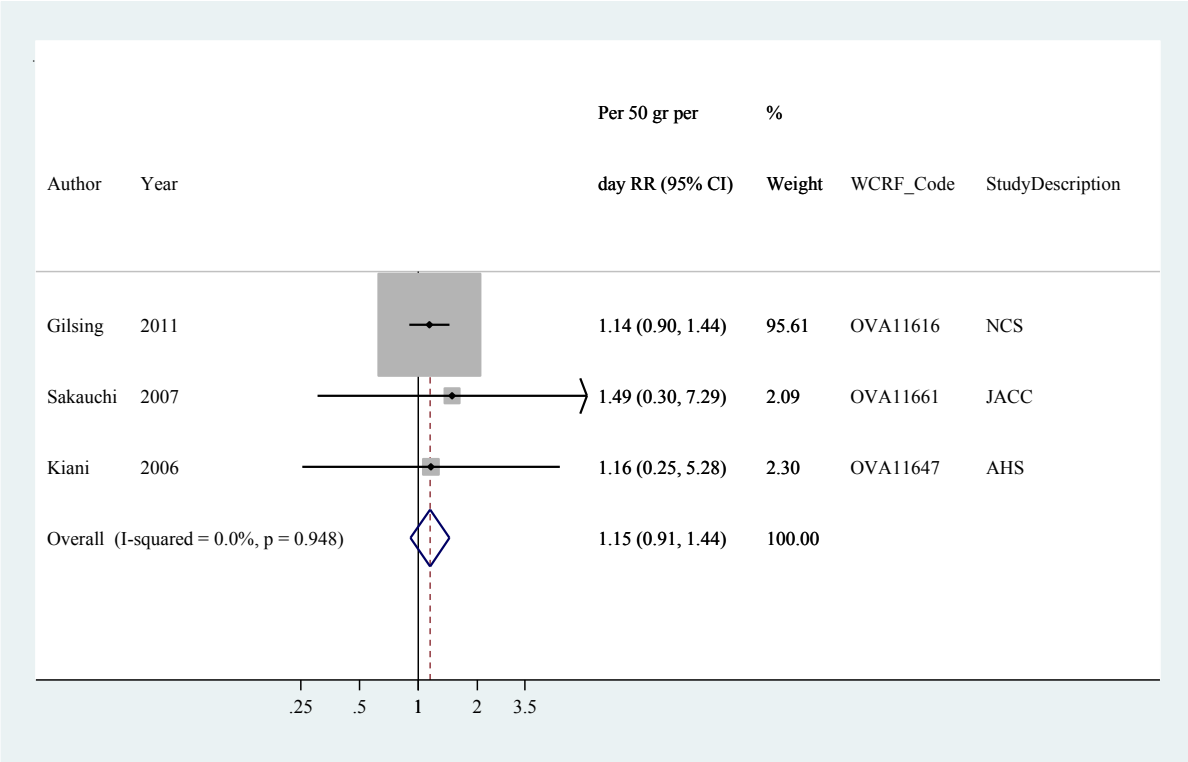


Figure 28 Funnel plot of beef consumption and ovarian cancer

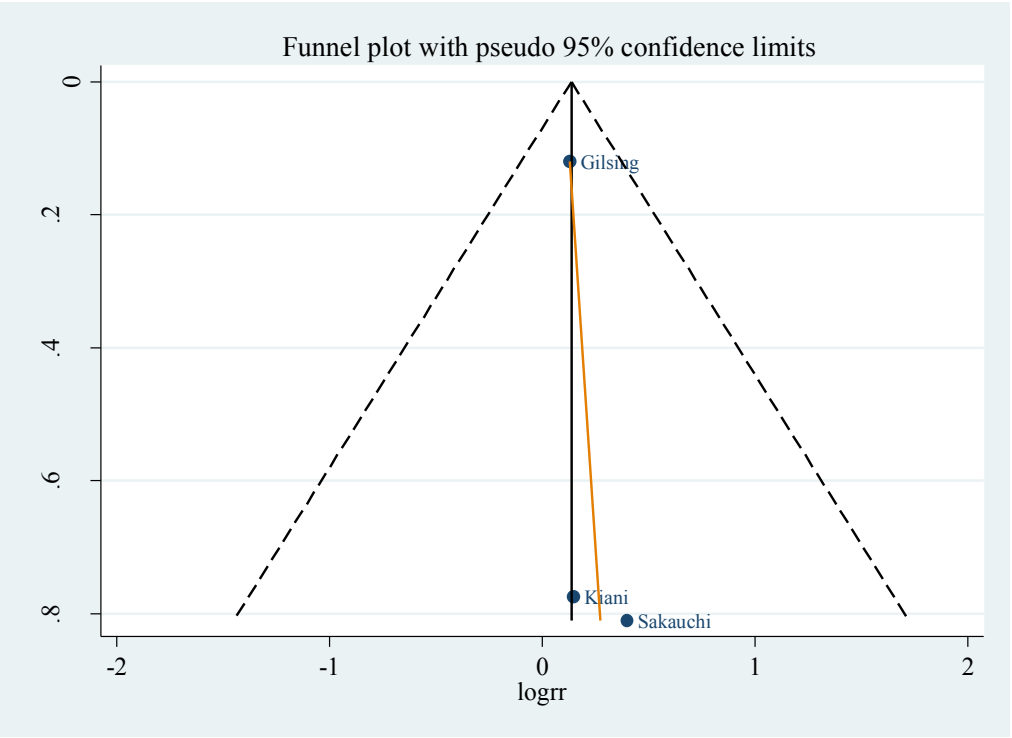
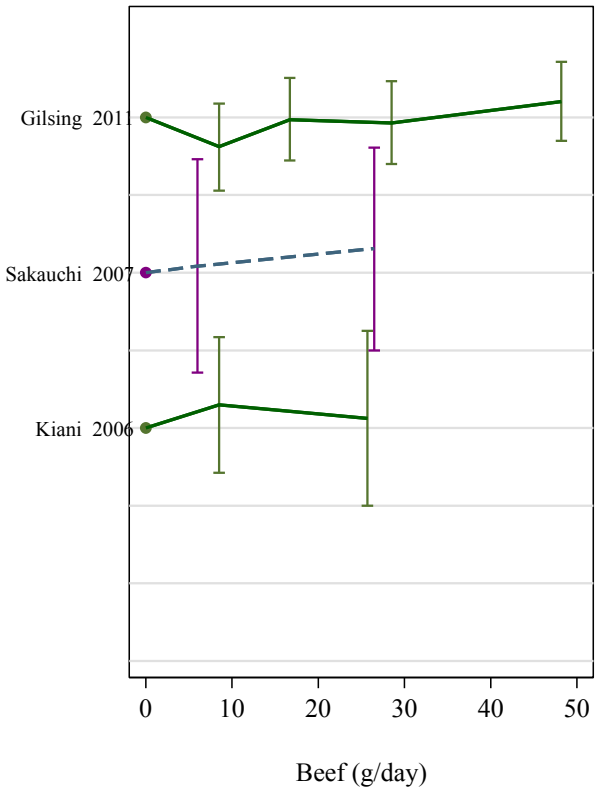


Figure 29 Dose-response graph of beef and ovarian cancer



2.5.1.4 Poultry

Methods

Up to December 2012, reports from five cohort studies were identified, four of them during the CUP. The CUP meta-analysis included five studies (four studies identified during the CUP and one study identified during the 2007 SLR). For the dose-response analyses results were converted to a common scale of exposure level (servings per day) of 120 grams per day. The results of dose-response analyses are presented for an increment of 25 grams per day.

Main results

Five studies could be included in meta-analysis. The summary RR per 25g/d was 1.00 (95% CI: 0.91-1.10, I^2=0%, $P_{heterogeneity}$ =0.93) for all studies combined. The overall results remained the same when one study with mortality as outcome was excluded from the analysis (RR= 1.00; 95% CI 0.90-1.10; I^2= 0%, $P_{heterogeneity}$=0.85). In influence analysis the summary RR ranged from 0.99 (95% CI: 0.89-1.0.9) when excluding the European Prospective Investigation into Cancer and Nutrition Study to 1.01 (95% CI: 0.90-1.13) when excluding the Netherland Cohort Study.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies (I^2=0%, $P_{heterogeneity}$=0.93). There was no indication of publication bias with Egger's test (p=0.11).

Published meta-analysis

In a published meta-analysis (Kolahdooz et al, 2010), the summary RR of ovarian cancer for highest vs. lowest poultry intake for all the studies included in the meta-analysis (three cohorts, four population-based case-control and two hospital-based case-control studies) was 0.90 (95% CI: 0.79-1.01; $P_{heterogeneity}$=0.52). The individual meta-analyses results did not differ from the main results (RR = 1.03; 95% CI: 0.84-1.27; $P_{heterogeneity}$=0.81, RR= 0.83; 95% CI: 0.67-1.02; $P_{heterogeneity}$=0.26 and RR= 0.81; 95% CI: 0.60-1.10; $P_{heterogeneity}$=0.82; for the cohorts studies, population-based case-control studies and hospital-based case-control meta-analyses respectively).

Table 33 Studies on poultry identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Gilsing, 2011	Netherlands	The Netherland Cohort Study	340	16.3	1.06 0.96	0.76 0.80	1.48 1.14	Highest vs low quintile Per 25 g/day increase
Sakauchi, 2007	Japan	Japan Collaborative Cohort study	77	13.3	1.13	0.40	3.17	>=1-2 times/week vs <=1-2 times/month
Schulz, 2007	Europe	European Prospective Investigation into Cancer and Nutrition Study	581	6.3	1.05 1.04	0.75 0.88	1.47 1.21	>=23 g/da vs<8 g/d Per 9.3 g/day intake
Kiani. 2006	USA	Adventist Health Study	71	16	1.23	0.66	2.32	>= 1 time/week vs Never

Table 34 Overall evidence on poultry and ovarian cancer

	Summary of evidence
SLR	One study was found on poultry intake and ovarian cancer risk. There was no association between poultry consumption and risk of ovarian cancer in this study
Continuous Update Project	Four prospective studies were identified. None of the studies reported a significant association of ovarian cancer and poultry intake. Overall, five studies were included in the CUP meta-analysis.

Table 35 Summary of results of the dose response meta-analysis on poultry and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1427
Increment unit	-	Per 25 g/d
RR (95% CI)	-	1.00 (0.91-1.10)
Heterogeneity (I^2, p-value)	-	0%, p=0.93
Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1350
Increment unit	-	Per 25 g/d
RR (95% CI)	-	1.00 (0.90-1.10)
Heterogeneity (I^2, p-value)		0%, p=0.85

*No meta-analysis was conducted in the 2nd report

Table 36 Inclusion/exclusion table for meta-analysis of poultry and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP HvL forest plot	Estimated values	Exclusion reason
OVA11616	Gilsing	2011	Case-Cohort study	The Netherland Cohort Study	Incidence	No	Yes	Yes	-	-
OVA11639	Schulz	2007	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition Study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11661	Sakauchi	2007	Prospective Cohort study	Japan Collaborative Cohort study	Mortality	No	Yes	Yes	Person/ years per category g/day per category and mid-exposure values	-
OVA11647	Kiani	2006	Prospective Cohort study	Adventist Health Study	Incidence	No	Yes	Yes	Cases and person/ years per category g/day per category and mid-exposure values	-
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Person/ years per category g/day per category and mid-exposure values	-

Figure 30 Highest versus lowest forest plot of poultry consumption and ovarian cancer

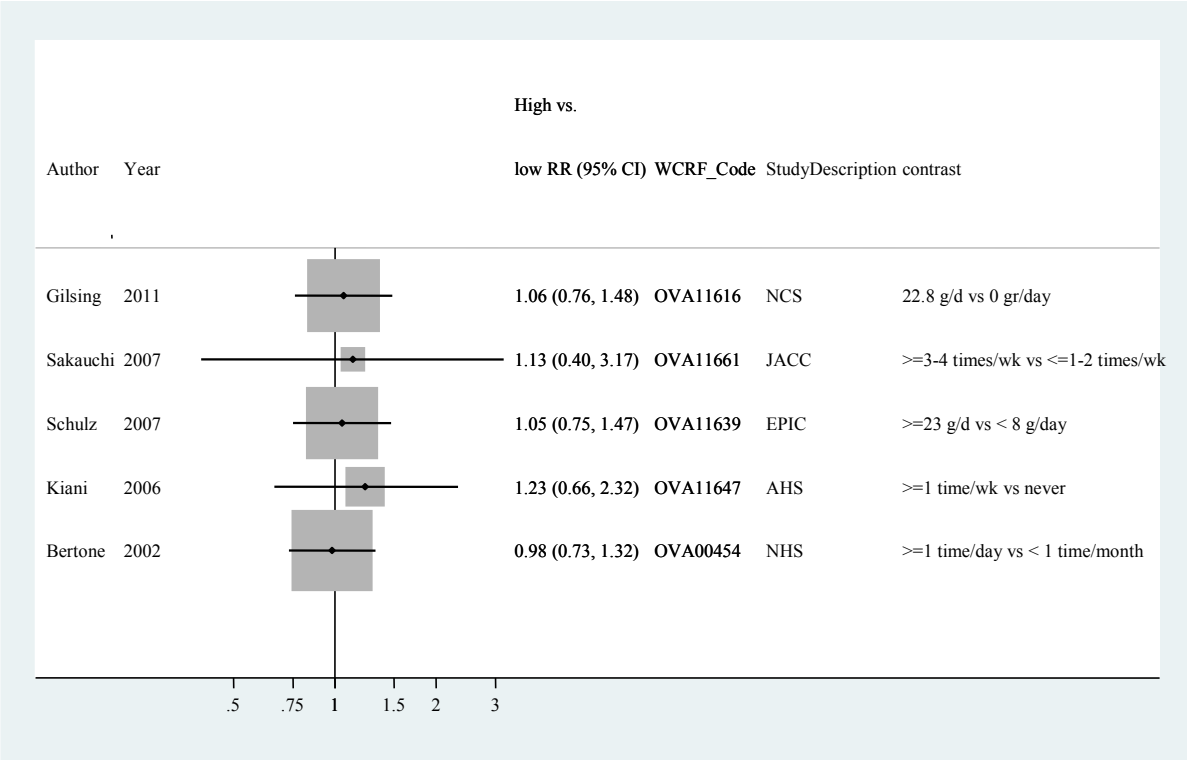


Figure 31 Dose-response meta-analysis of poultry consumption and ovarian cancer – per 25 g/day

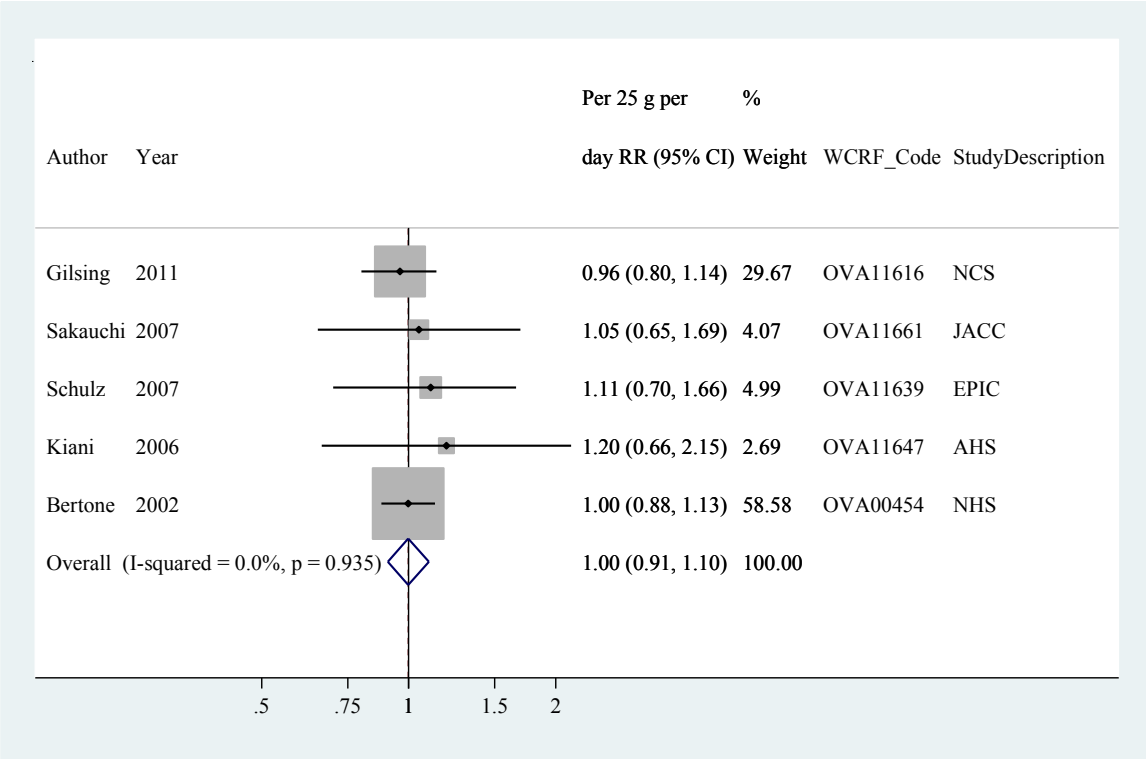


Figure 32 Funnel plot of poultry consumption and ovarian cancer

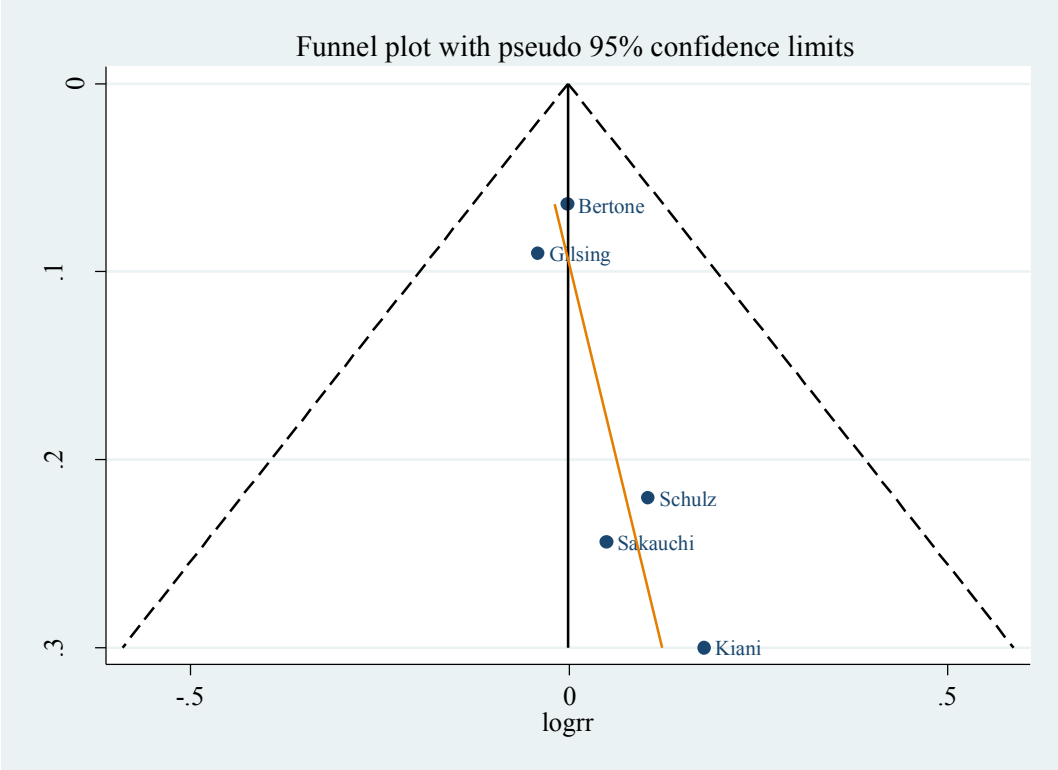
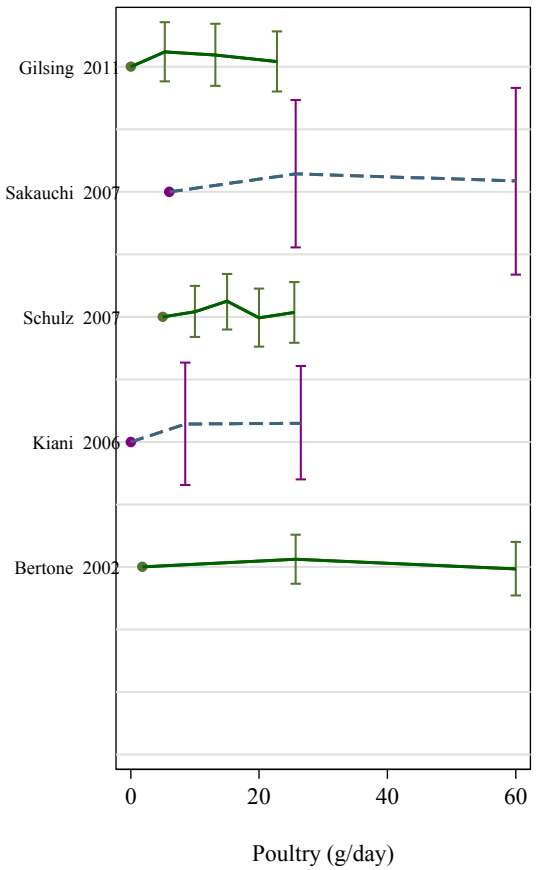


Figure 33 Dose-response graph of poultry and ovarian cancer



2.5.2 Fish

Methods

Five cohort studies on fish and ovarian cancer have been published up to December 2012. Four studies were identified during the CUP and one during the SLR for the Second Expert Report.

For the CUP dose-response analyses all results were converted to a common scale (grams per day) and 120 grams was used as standard serving or portion size for three studies that presented the intake only by frequency. One study presented results separately for dried fish and fresh fish (Sakauchi et al, 2007). Only the results for fresh fish were included in the meta-analysis. The dose-response analyses were presented for an increment of 25 grams per day.

Main results

The five studies identified were included in dose-response meta-analysis. The summary RR per 25g/day was 1.01 (95% CI: 0.91-1.13; I^2= 0%, $P_{heterogeneity}$=0.66). In influence analysis the RR ranged from 0.99 (95% CI: 0.88-1.12) when excluding the Japan Collaborative Cohort study (Sakauchi et al, 2007) that has mortality as outcome to 1.05 (95% CI: 0.92-1.20) when excluding the Netherland Cohort Study (Gilsing et al, 2011).

When including only the four studies that reported incidence results, the RR estimate was 1.00 (95% CI:0.88-1.12; I^2= 0%, $P_{heterogeneity}$=0.59)

In one study in Seventh-day Adventist, the highest fish intake level was only more than once per week (Kiani, 2006). After exclusion of this study from the analysis, the RR was 1.00 (95% CI: 0.89- 1.12).

One study investigated dried or salted fish in relation to ovarian cancer (Sakauchi et al, 2007) and reported a significant increased risk in women consuming dried or salted fish more than 3-4 times per week compared to consuming less than 1-2 times per week (RR=2.8; 95% CI: 1.14-6.89)

Heterogeneity

There was no evidence of heterogeneity (I^2= 0%, p=0.66) between studies. Egger's tests suggested no evidence of publication bias (p=0.15). However, the funnel plot suggests that the smallest study (Kiani, 2006) reported stronger relative risk estimates than other studies, although not statistically significant.

Published meta-analysis

In a published meta-analysis (Kolahdooz et al, 2010), the summary RR of ovarian cancer for highest vs. lowest fish intake for all the studies included in the meta-analysis (two cohorts, three population-based case-control studies and three hospital-based case-control studies) was 0.84 (95% CI: 0.68-1.03; $P_{heterogeneity}$=0.003). The individual meta-analyses results did not differ from the main results (RR = 1.00; 95% CI: 0.76-1.34; $P_{heterogeneity}$=0.55, RR= 0.88; 95% CI: 0.67-1.16; $P_{heterogeneity}$=0.09 and RR= 0.75; 95% CI: 0.46-1.21; $P_{heterogeneity}$=0.01 for the

cohorts studies, population-based case-control studies and hospital-based case-control meta-analyses respectively).

Table 37 Studies on fish intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Gilsing, 2011	Netherlands	The Netherland Cohort Study	340	16.3	1.01 0.91	0.71 0.74	1.43 1.12	>=20 g/day vs 0 Per 25 g/day increase
Schulz, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	581	6.3	0.90 1.01	0.56 0.85	1.43 1.20	>=44 g/day vs <17 per g/day Per 17 g/day increase
Sakauchi, 2007	Japan	Japan Collaborative Cohort study	77	13.3	1.33	0.59	2.98	Almost every day vs <=1-2 times/week
Kiani, 2006	USA	Adventist Health Study	71	16	1.39	0.73	2.62	>=1 times/week vs never

Table 38 Overall evidence on fish intake and ovarian cancer

	Summary of evidence
SLR	One study was identified. There was no association of fish consumption and risk of ovarian cancer in this study.
Continuous Update Project	Four cohort studies were identified. None reported significant associations between fish consumption and ovarian cancer. Overall, the CUP meta-analysis included five studies.

Table 39 Summary of results of the dose response meta-analysis on fish intake and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1357
Increment unit used	-	Per 25 g/day
Overall RR (95%CI)	-	1.01 (0.91-1.13)
Heterogeneity (I^2,p-value)	-	0%, p=0.66

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1280
Increment unit used	-	Per 25 g/day
Overall RR (95%CI)	-	1.00 (0.88-1.12)
Heterogeneity (I^2,p-value)	-	0%, p=0.59

*No meta-analysis was conducted in the 2nd report

Table 40 Inclusion/exclusion table for meta-analysis on fish intake and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11616	Gilsing	2011	Case-Cohort study	The Netherland Cohort Study	Incidence	No	Yes	Yes	----------	-
OVA11639	Schulz	2007	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11661	Sakauchi	2007	Prospective Cohort study	Japan Collaborative Cohort study	Mortality	No	Yes	Yes	Person/ years per category g/day per quintile and mid-exposure values	-
OVA11647	Kiani	2006	Prospective Cohort study	Adventist Health Study	Incidence	No	Yes	Yes	Cases and person/ years per category g/day per quintile and mid-exposure values	-
OVA10420	Larsson	2005	Prospective Cohort study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	------	-

Figure 34 Highest versus lowest forest plot of fish and ovarian cancer

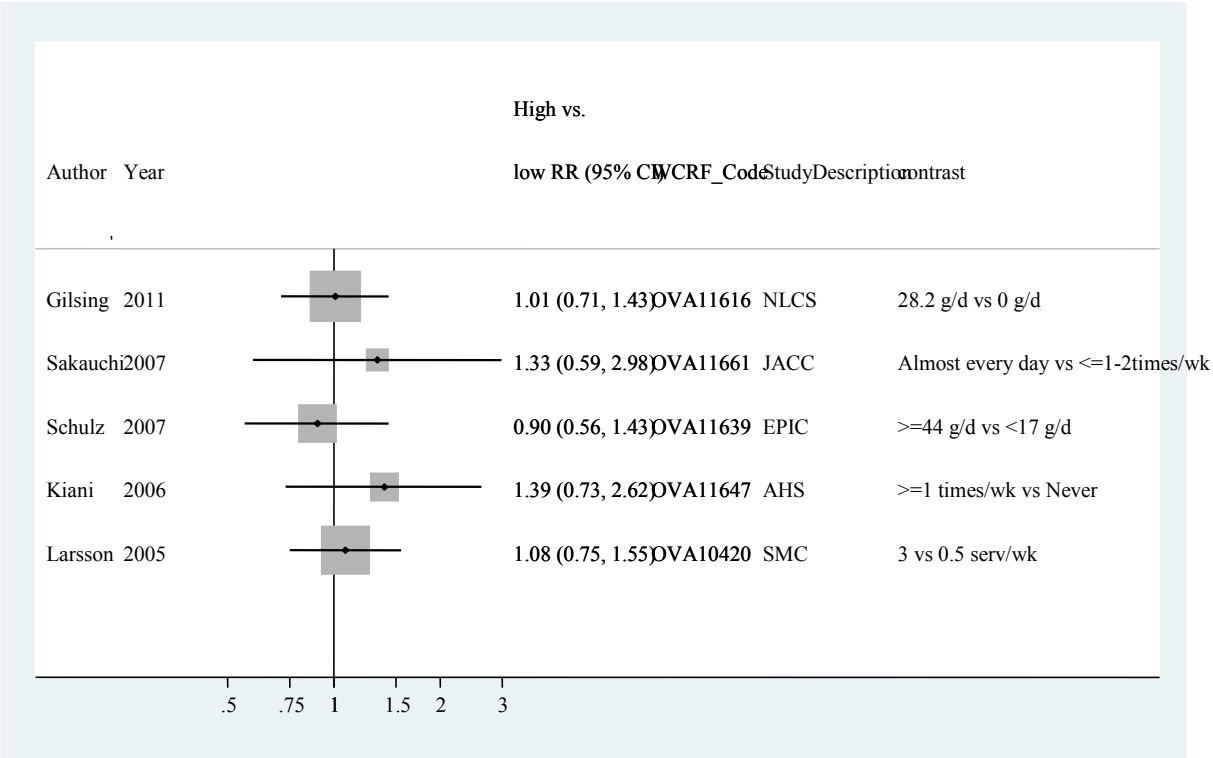


Figure 35 Dose-response meta-analysis of fish and ovarian cancer – per 25 gr/day

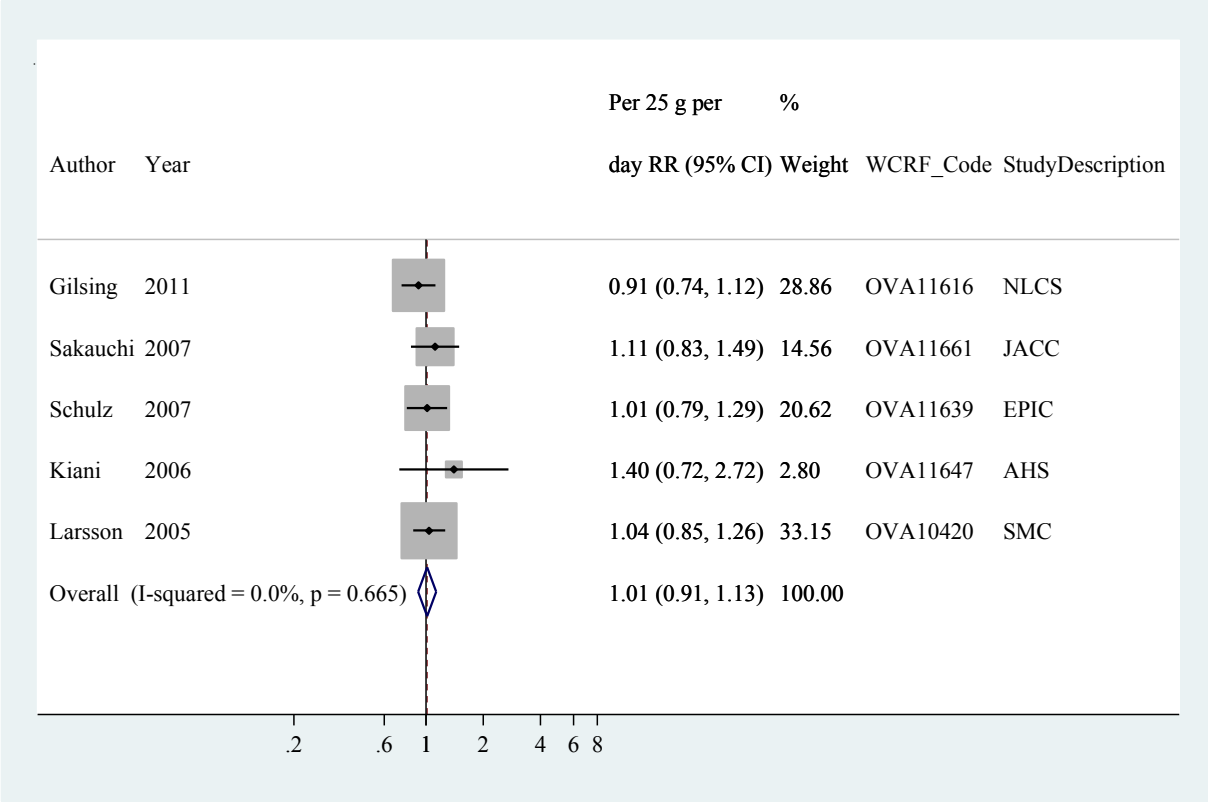


Figure 36 Funnel plot of fish and ovarian cancer

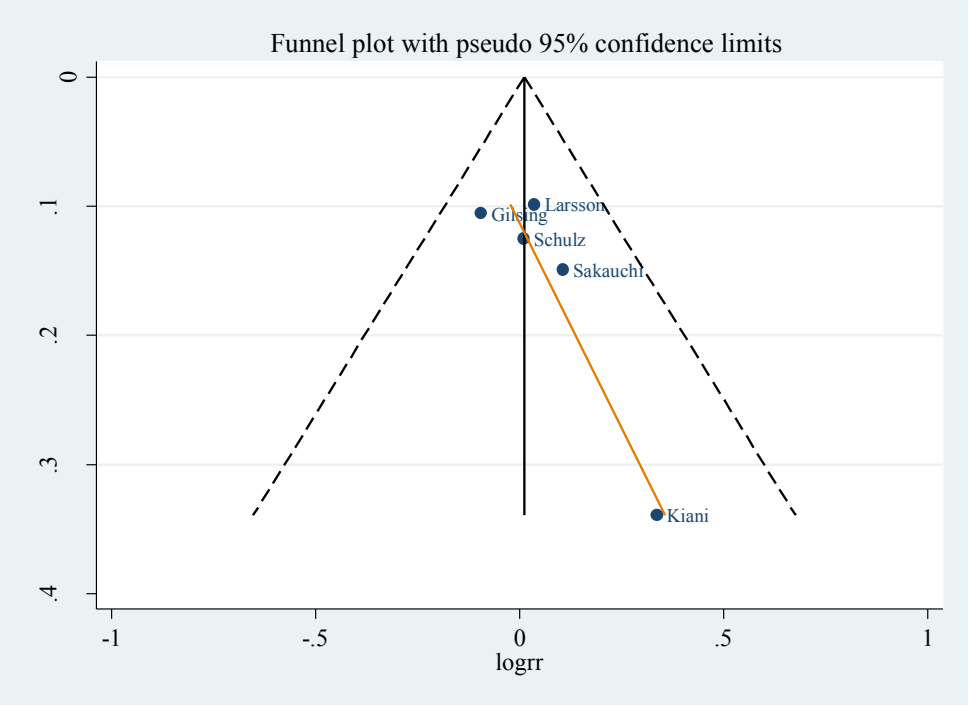
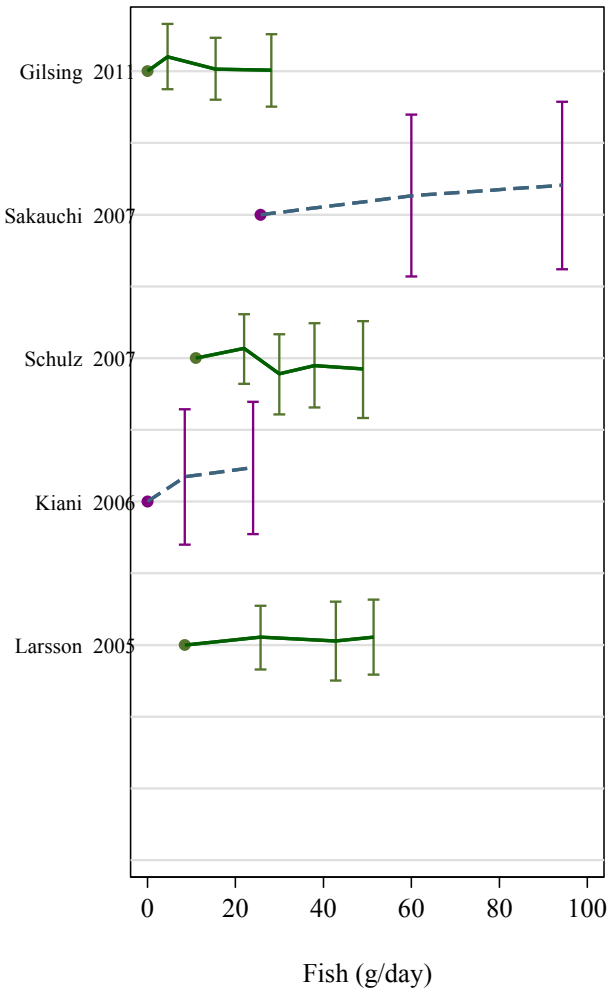


Figure 37 Dose-response graph of fish and ovarian cancer



2.5.4 Eggs

Methods

Up to December 2012, reports from eight cohort studies were identified, four of which were identified during the CUP. The dose-response meta-analysis for ovarian cancer performed in the previous SLR report included two studies. In the updated meta-analysis, six studies (three studies identified during the CUP and three studies identified during the 2007 SLR) were included. For the dose-response analyses all results were converted to a common scale of exposure level (servings per day) of 55 grams, which was used as an average serving size. The dose-response results are presented for an increment of 25 g/day.

Main results

The summary RR per 25 g/day was 1.13 (95% CI: 0.89-1.44; I^2= 51.1%, $P_{heterogeneity}$=0.069) for all studies combined. The overall results remained the same when one study with mortality as outcome was excluded from the analysis (RR= 1.20; 95% CI: 0.95-1.52; I^2= 46.3%, $P_{heterogeneity}$=0.114). In influence analysis, the RR ranged from 1.05 (95% CI: 0.85-1.30) when excluding the Iowa Women's Health Study (Kushi et al, 1999) to 1.19 (95% CI: 0.94-1.51) when excluding the Japan Collaborative Cohort study (Sakauchi et al, 2007).

Heterogeneity

Substantial heterogeneity was observed (I^2= 51.1%, p=0.069). Egger's tests did not show evidence of publication bias (p= 0.47).

Comparison with the Second Expert Report

A borderline significant association was observed in the SLR. The CUP results found no evidence of association of eggs intake with ovarian cancer risk.

Published meta-analysis

In a published pooled analysis of 12 prospective studies of dietary fat, cholesterol and egg intake and ovarian cancer (Genkinger et al, 2006), egg consumption was not associated with ovarian cancer risk (pooled multivariate RR = 1.18; 95% CI: 0.89–1.57, $P_{heterogeneity}$ = 0.87, comparing intake of >50 grams per day of eggs to < 6.25 g/day of eggs). When examined continuous intake, higher intakes of eggs were associated with a slightly higher risk of ovarian cancer (pooled multivariate RR for a 50 g/day increment = 1.11, 95% CI: 0.99–1.24).

When the Japan Collaborative Cohort study (Sakauchi et al, 2007) and the European Prospective Investigation into Cancer and Nutrition Study (Schulz et al, 2007) were pooled with the studies included in the Genkinger et al, 2006 Pooling Project of Cohort Studies of Diet and Cancer, the pooled RR estimate for an increase of 50g/d of eggs was 1.06 (95% CI: 0.85, 1.32; $P_{heterogeneity}$=0.33)

Table 41 Studies on eggs consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Sakauchi, 2007	Japan	Japan Collaborative Cohort study	77	13.3	0.65	0.30	1.41	almost everyday vs <=1-2/times week
Schulz, 2007	Europe	European Prospective Investigation into Cancer and Nutrition Study	581	6.3	1.19 0.97	0.85 0.87	1.67 1.08	<16g/day vs >=9g/day Per 6.6 g/day increase
Chang, 2007	USA	California Teachers Study	280	8.1	0.78	0.53	1.15	Highest vs lowest quintile of intake
Kiani. 2006	USA	Adventist Health Study	56	16	1.02	0.50	2.10	>2 times/week vs Never

Table 42 Overall evidence on eggs consumption and ovarian cancer

	Summary of evidence
SLR	Four studies addressed the relationship between eggs consumption and ovarian cancer risk. The two studies that were included only in the high versus low analysis reported a significant increased risk. The other two studies were included in the dose-response meta-analysis and the pooled RR: 1.10 (1.00-1.21) for each additional serving per day of eggs.
Continuous Update Project	Four cohort studies were identified; three could be included in the meta-analysis. None of the studies found an association between eggs consumption and ovarian cancer. Overall, six studies were included in the CUP meta-analysis. In the pooled analysis of 12 cohort studies, the RR for a 50 g/day increment was 1.11 (95% CI: 0.99-1.24).

Table 43 Summary of results of the dose response meta-analysis of eggs consumption and ovarian cancer

Ovarian cancer		
	SLR	Continuous Update Project
Studies (n)	2	6
Cases (n)	427	1499
Increment unit used	serving/day	Per 25g/day
Overall RR (95%CI)	1.10 (1.00-1.21)	1.13 (0.89-1.44)
Heterogeneity (I^2,p-value)	72.2%	51.1%, p=0.069

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1422
Increment unit used	-	Per 25g/day
Overall RR (95%CI)	-	1.20 (0.95-1.52)
Heterogeneity (I^2,p-value)	-	46.3%, p=0.114

*No meta-analysis was conducted in the Second Expert Report

Table 44 Inclusion/exclusion table for meta-analysis of eggs consumption and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11661	Sakauchi	2007	Prospective Cohort study	Japan Collaborative Cohort study	Mortality	No	Yes	Yes	Person/ years per category g/day per category and mid-exposure values	-
OVA11639	Schulz	2007	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition Study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study	Incidence	No	No	Yes	------	Only high versus low reported
OVA11647	Kiani	2006	Prospective Cohort study	Adventist Health Study	Incidence	No	Yes	Yes	Cases and person/ years per category g/day per category and mid-exposure values	-
OVA10420	Larsson	2005	Prospective Cohort study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	--------	-
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Person/ years per category g/day per category and mid-exposure values	-
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category g/day per category and mid-exposure values	-
OVA05024	Snowdon	1985	Prospective Cohort study	Seventh-Day Adventist- 1960	Mortality	Yes	No	Yes	---------	Two categories of exposure (high vs. low).

Figure 38 Highest versus lowest forest plot of egg consumption and ovarian cancer

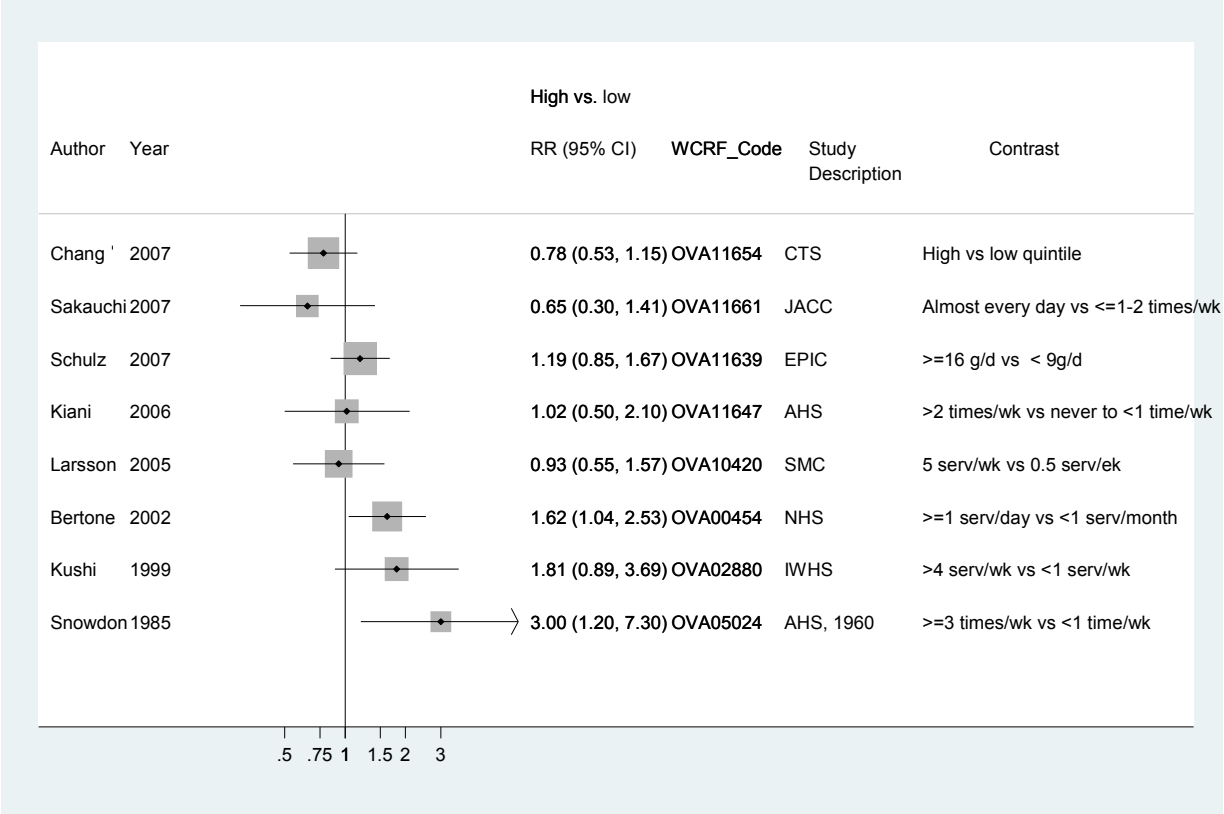


Figure 39 Dose-response meta-analysis of eggs and ovarian cancer - per 25 g/d

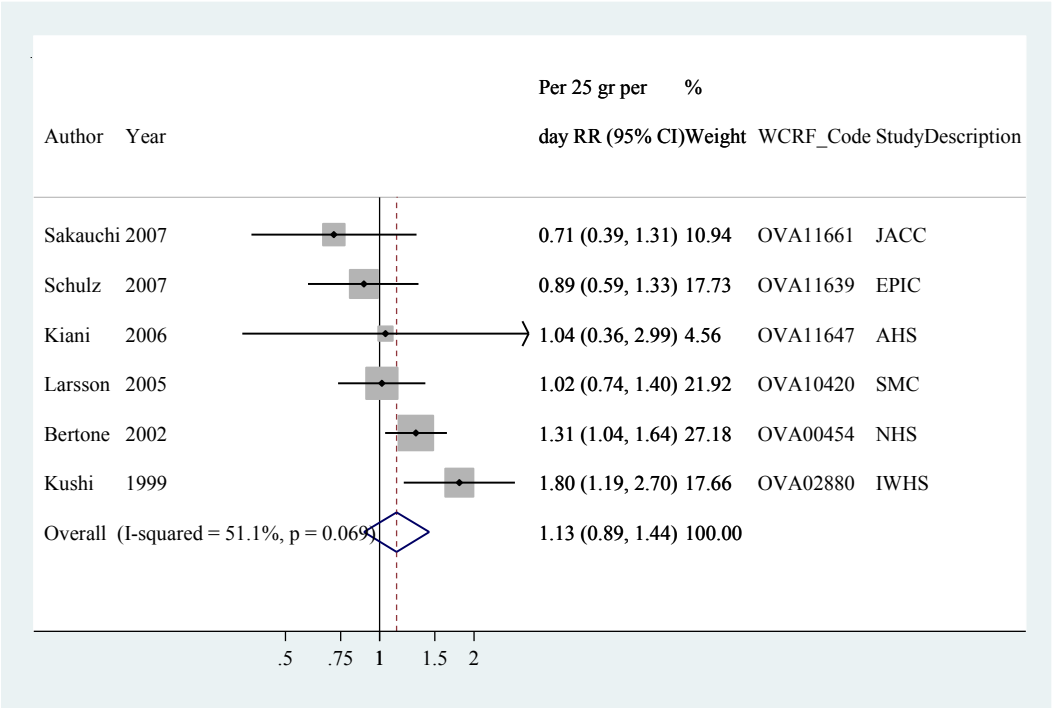


Figure 40 Funnel plot of egg consumption and ovarian cancer

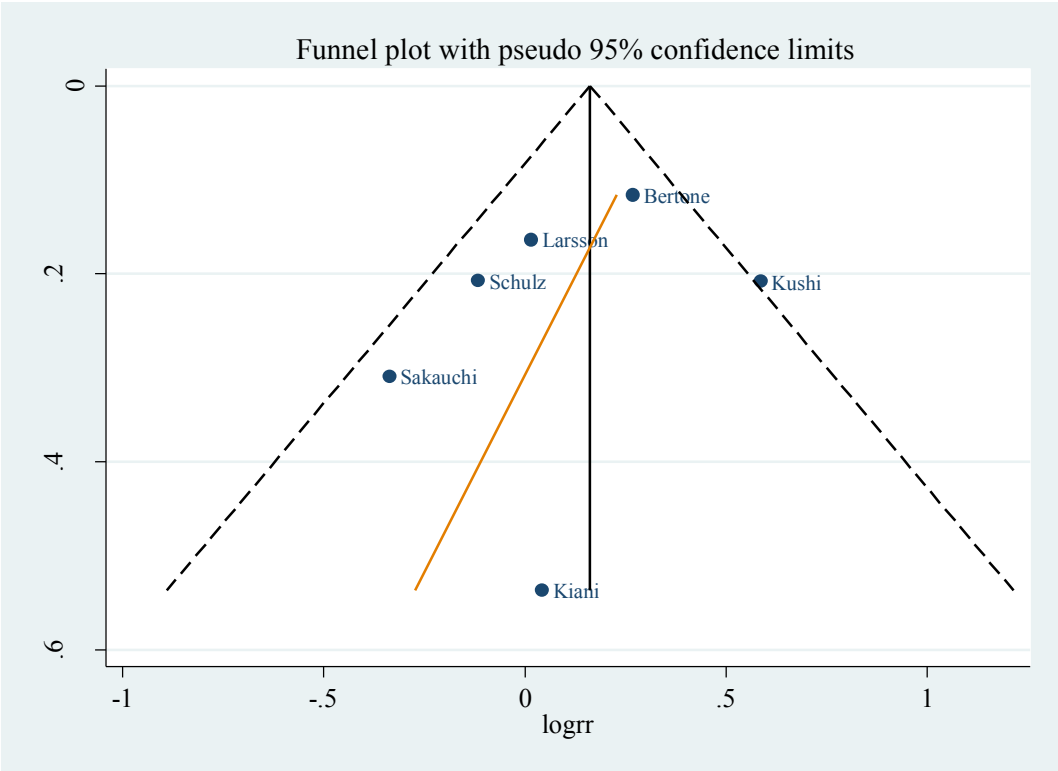
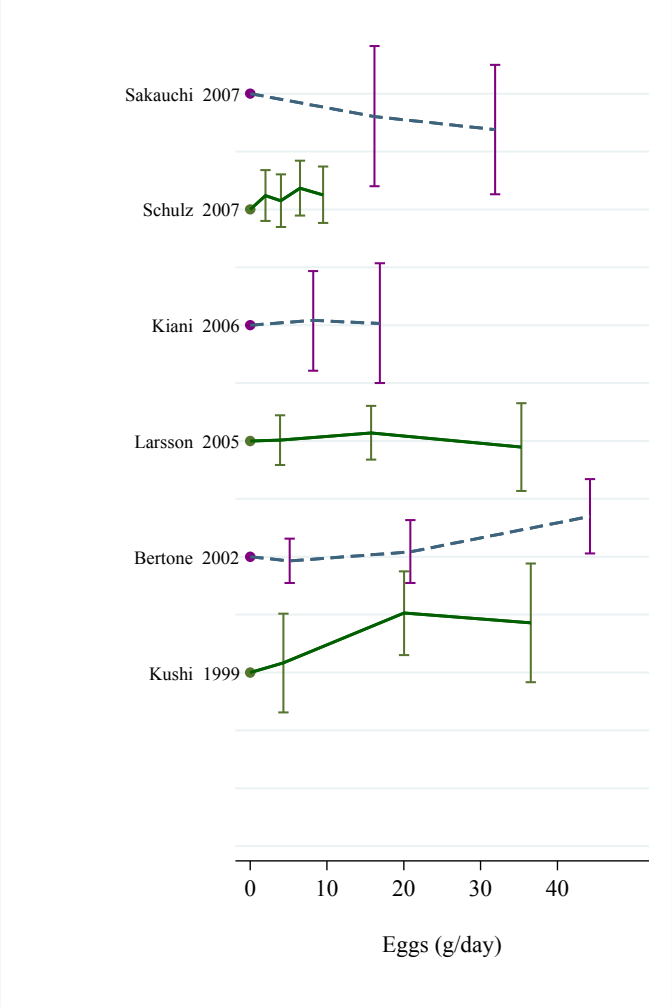


Figure 41 Dose-response graph of egg and ovarian cancer



2.7 Dairy products

Methods

A total of 6 cohort studies have been published on dairy products and ovarian cancer risk up to 2012, four of which were identified in the CUP. Dose-response analyses were conducted per 200 g/d.

Main results

The summary RR per 200 g/d of dairy products was 1.06 (95% CI: 0.92-1.23, I^2=66.1%, $p_{heterogeneity}$=0.02). There was no evidence of publication bias with Egger's test, p=0.79.

Heterogeneity

There was high heterogeneity, I^2=66.1%, $p_{heterogeneity}$=0.02.

Published meta-analyses

A meta-analysis of eight case-control studies found a summary RR of 1.25 (95% CI: 0.76-2.08) for high vs. low dairy product intake and ovarian cancer risk (Qin et al, 2005).

A meta-analysis of five case-control studies and two cohort studies found a summary RR = 1.17 (95% CI: 0.85-1.60, I^2=64.7%, $p_{heterogeneity}$=0.009) for all studies, and 1.66 (95% CI: 1.19-2.31, I^2=0%, $p_{heterogeneity}$=0.81) for the two cohort studies (Larsson et al, 2006).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited and inconclusive evidence for an association between milk and dairy products and ovarian cancer.

Table 45 Studies on dairy products identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Park, 2009	USA	NIH-AARP Diet and Health Study	515	7 years	1.03	0.77	1.37	1.6 vs. 0.2 serv/1000 kcal
Schulz, 2007	Europe	EPIC Study	581	~6.3 years	0.58 0.89	0.26 0.63	1.29 1.24	≥209 vs. <131 g/d Per 39.4 g/d
Chang, 2007	USA	California Teachers Study	280	8.1 years	0.84	0.56	1.26	Q5 vs. Q1
Koralek, 2006	USA	Breast Cancer Detection Demonstration Project	146	8.3 years	0.42	0.20	0.89	≥7 vs. 0 serv/d

Table 46 Overall evidence on dairy products and ovarian cancer

SLR	Summary of evidence
2005 SLR	Two cohort studies reported on dairy products and ovarian cancer. Both studies showed positive associations between dairy products and ovarian cancer risk, which was significant in one of the studies.
Continuous Update Project	Four additional studies reported on dairy products and ovarian cancer risk, with two studies showing non-significant and significant inverse associations and the two remaining studies reporting no significant association.

Table 47 Summary of results of the dose-response meta-analysis of dairy products and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1647
RR (95% CI)	-	1.06 (0.92-1.23)
Quantity	-	Per 200 g/d
Heterogeneity (I^2, p-value)	-	66.1%, p=0.02

*No meta-analysis was conducted in the 2nd report

Table 48 Inclusion/exclusion table for meta-analysis of dairy products and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11694	Park	2009	Prospective study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Distribution of cases/person-years	
OVA11639	Schulz	2007	Prospective study	EPIC study	Incidence	No	Yes	Yes	Midpoints	
OVA11654	Chang	2007	Prospective study	California Teachers Study	Incidence	No	No	Yes	-	Only high vs. low comparison reported
OVA11662	Koralek	2006	Prospective study	Breast Cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Distribution of person-years	
OVA10870	Larsson	2004	Prospective study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	
OVA02880	Kushi	1999	Prospective study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	

Figure 42 Highest versus lowest forest plot of dairy products and ovarian cancer

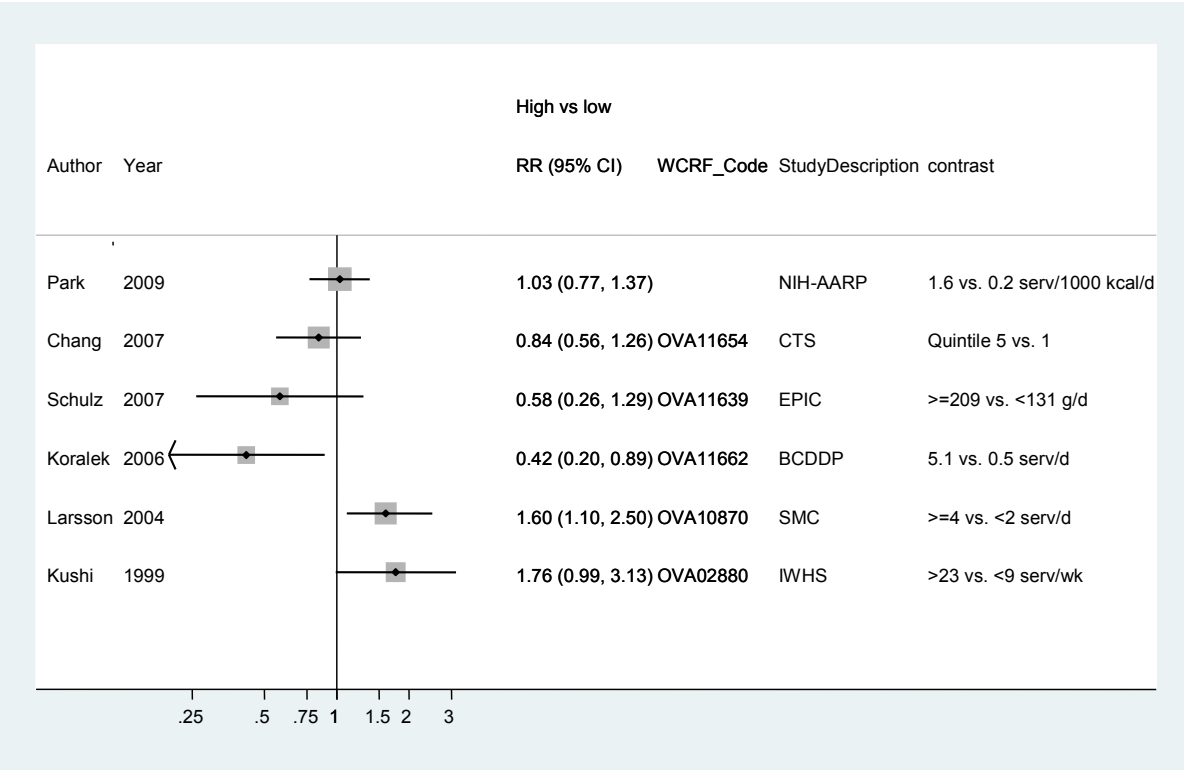


Figure 43 Dose-response meta-analysis of dairy products and ovarian cancer, per 200 g/d

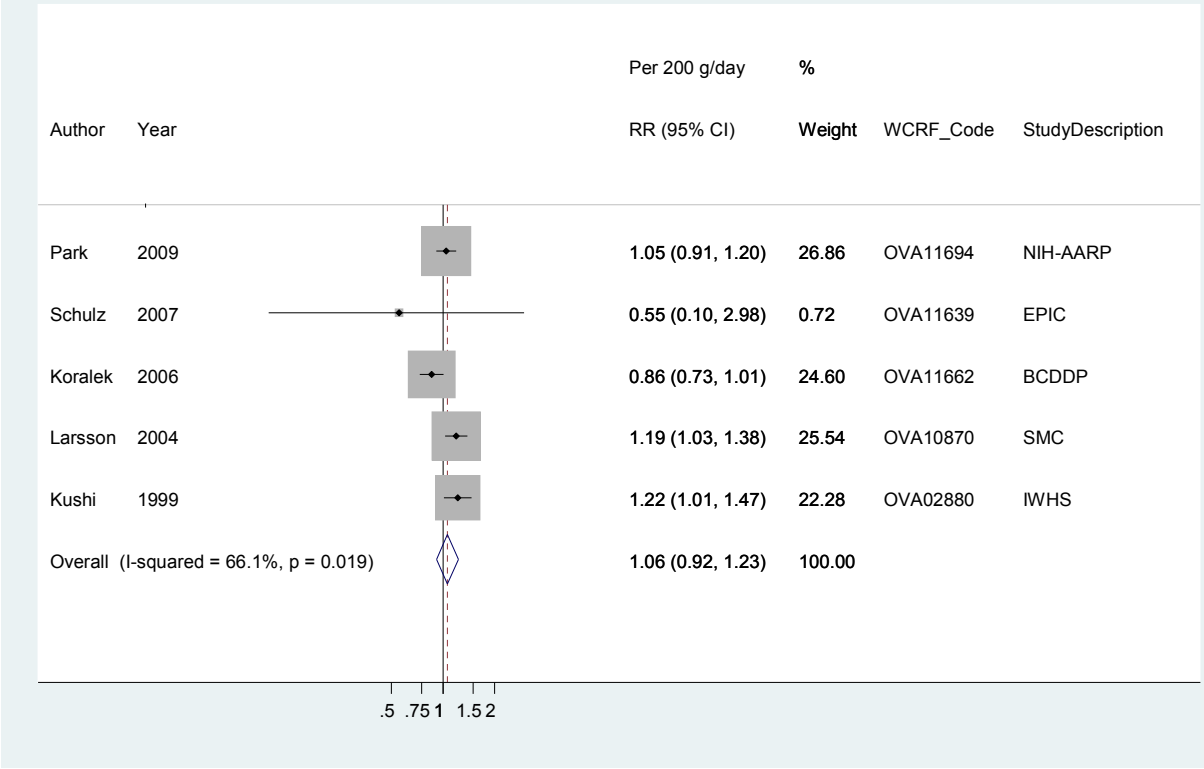


Figure 44 Funnel plot of dairy products and ovarian cancer

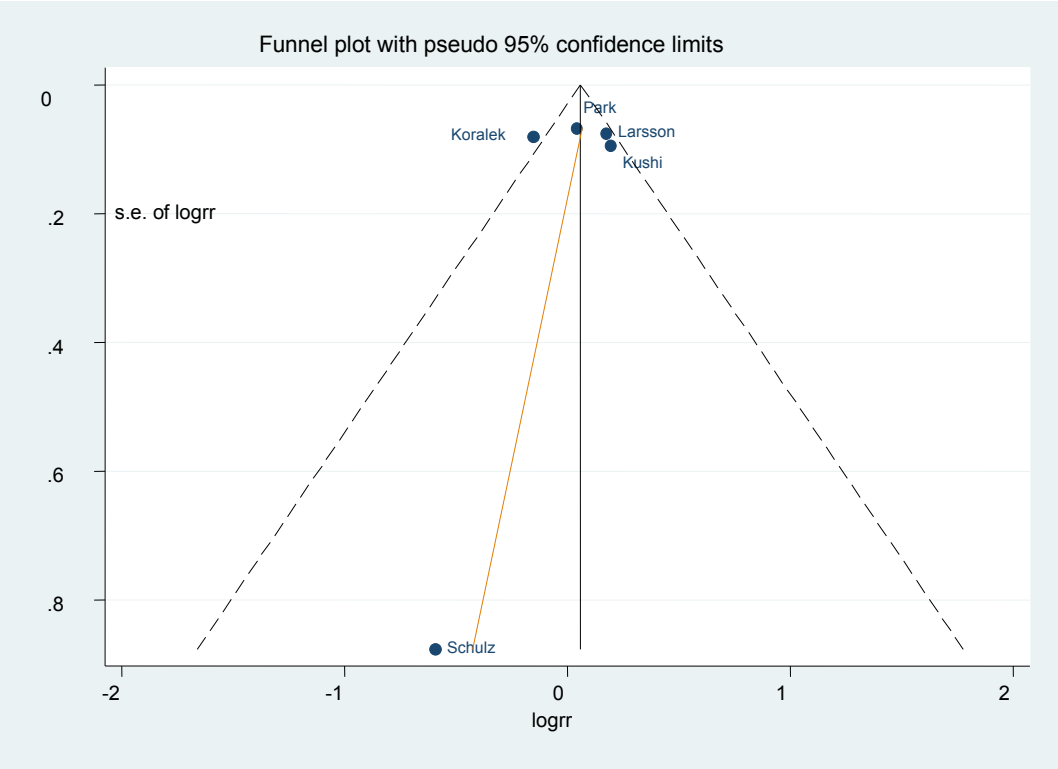
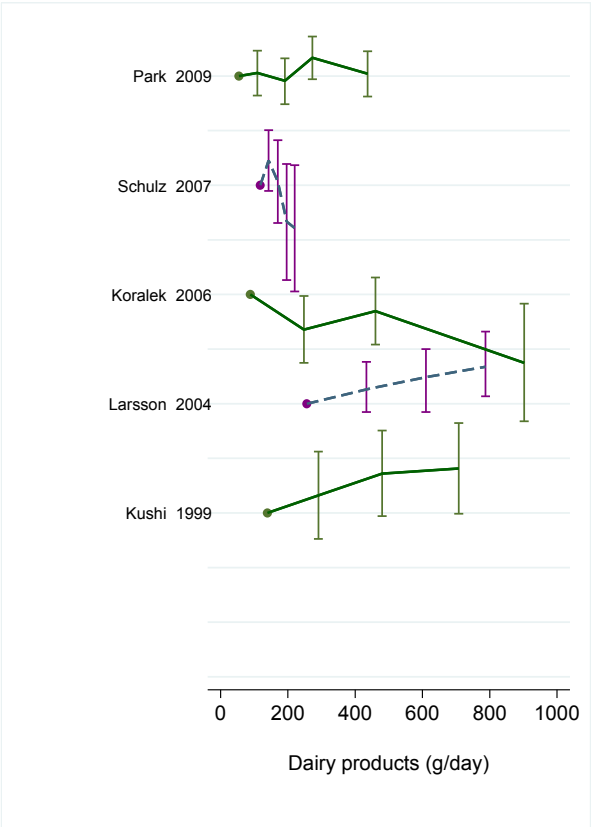


Figure 45 Dose-response graph of dairy products and ovarian cancer



2.7.1 Milk

A total of 8 cohort studies have been published on milk and ovarian cancer risk up to 2012, four of which were identified in the CUP. Dose-response analyses were conducted per 200 g/d.

Main results

The summary RR per 200 g/d of milk was 1.01 (95% CI: 0.93-1.09, I^2=0%, $p_{heterogeneity}$=0.47). There was no evidence of publication bias with Egger's test, p=0.68.

Heterogeneity

There was no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.47.

Published pooled analysis and meta-analyses

A meta-analysis of six case-control studies found a summary RR of 0.81 (95% CI: 0.61-1.07) for high vs. low milk intake and ovarian cancer risk (Qin et al, 2005).

A meta-analysis of seven case-control studies and one cohort study found no association between milk intake and ovarian cancer risk, summary RR = 0.87 (95% CI: 0.68-1.10, I^2=73.1%, $p_{heterogeneity}$<0.001) for all studies (Larsson et al, 2006).

A pooled analysis of 12 cohort studies found no association between milk intake and ovarian cancer risk, pooled RR=1.11 (95% CI: 0.87-1.41, $p_{heterogeneity}$=0.30) for ≥500 vs. 0 g/d (Genkinger et al, 2006). The relative risk for an increment of 250 g/day was 1.02 (95% CI: 0.97-1.08).

If the results of the EPIC study (Schutlz et al, 2007) and the JACC (Sakauchi et al, 2007) are pooled with the summary results of the pooled analysis of 12 cohorts (Genkinger et al, 2006), the relative risk estimate for an increase of 200 g/day is 1.02 (95% CI= 0.97-1.06).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating milk and dairy products to ovarian cancer risk was limited and no conclusion was possible.

Table 49 Studies on milk identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Sakauchi, 2007	Japan	Japan Collaborative Cohort Study	77	13.3 years	1.67	0.66	4.23	Almost every day vs. ≤1-2/mo
Schulz, 2007	Europe	EPIC Study	581	~6.3 years	0.93	0.70	1.25	≥264 vs. <55 g/d
Chang, 2007	USA	California Teachers Study	280	8.1 years	0.84	0.56	1.26	Q5 vs. Q1
Koralek, 2006	USA	Breast Cancer Detection Demonstration Project	146	8.3 years	1.21	0.61	2.44	14.0 vs. 0 serv/wk
Ursin, 1990	Norway	NA	11	11.5	5.92	0.72	49.32	≥2 vs <1 glass/d

Table 50 Overall evidence on milk and ovarian cancer

SLR	Summary of evidence
2005 SLR	Four cohort studies reported on milk and ovarian cancer. Three studies showed non-significant positive associations between milk and ovarian cancer risk and one study showed a borderline positive association.
Continuous Update Project	Four additional studies reported on milk and ovarian cancer risk and all the studies found no significant association. The pooled analysis of 12 cohort studies reported a RR for 250 g/day increase of 1.02 (95% CI: 0.97-1.08).

*One multi-cancer study that was missed by the SLR is included here

Table 51 Summary of results of the dose-response meta-analysis of milk and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1647
RR (95% CI)	-	1.01 (0.93-1.09)
Quantity	-	Per 200 g/d
Heterogeneity (I^2, p-value)	-	0%, p=0.47

*No meta-analysis was conducted in the 2nd report

Table 52 Inclusion/exclusion table for meta-analysis of milk and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11661	Sakauchi	2007	Prospective study	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Distribution of person-years, midpoints	
OVA11639	Schulz	2007	Prospective study	EPIC study	Incidence	No	Yes	Yes	Midpoints	
OVA11654	Chang	2007	Prospective study	California Teachers Study	Incidence	No	No	Yes		Only high vs. low comparison reported
OVA11662	Koralek	2006	Prospective study	Breast Cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Distribution of person-years	
OVA09788	Mommers	2006	Prospective study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
OVA10870	Larsson	2004	Prospective study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	
OVA11491	Fairfield	2004	Prospective study	Nurses' Health Study	Incidence	Yes	No	Yes		Only high vs. low comparison
OVA11697	Ursin	1990	Prospective study	NA	Incidence	No*	No	No	Confidence intervals	Only high vs. low comparison

*The study was missed in the SLR for ovarian cancer in the 2nd Expert Report (it is a paper on multiple cancer sites)

Figure 46 Highest versus lowest forest plot of milk and ovarian cancer

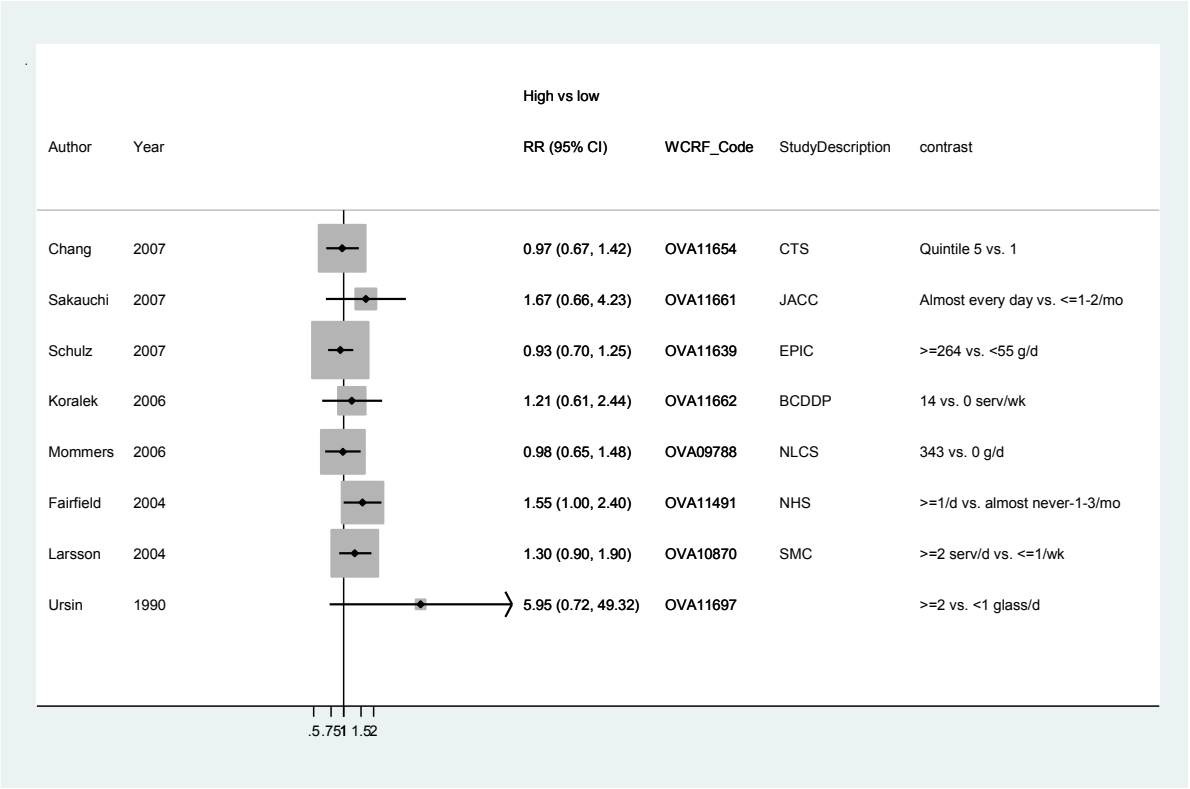


Figure 47 Dose-response meta-analysis of milk and ovarian cancer, per 200 g/d

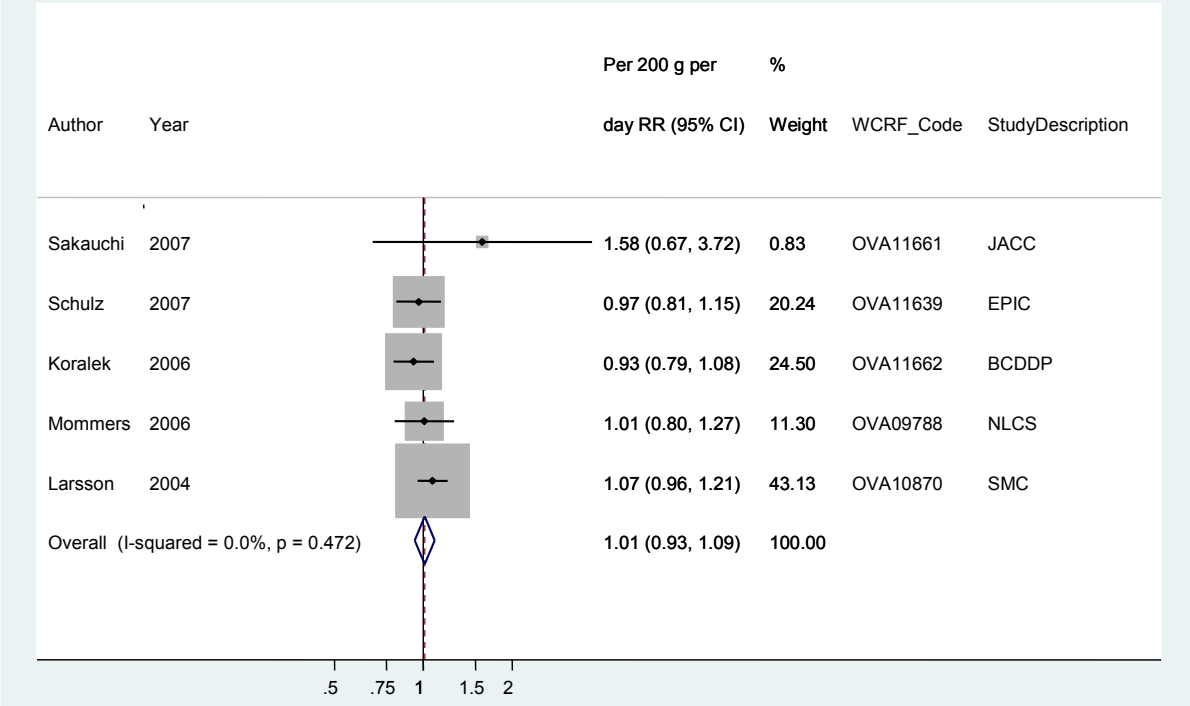


Figure 48 Funnel plot of milk and ovarian cancer

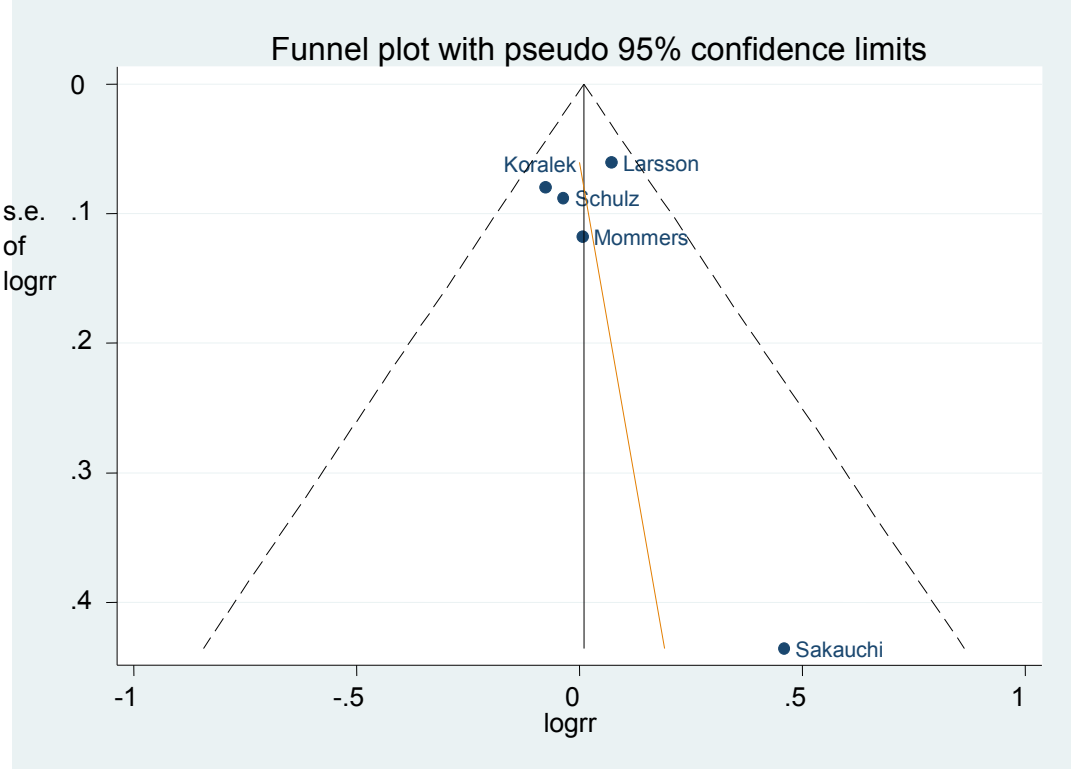
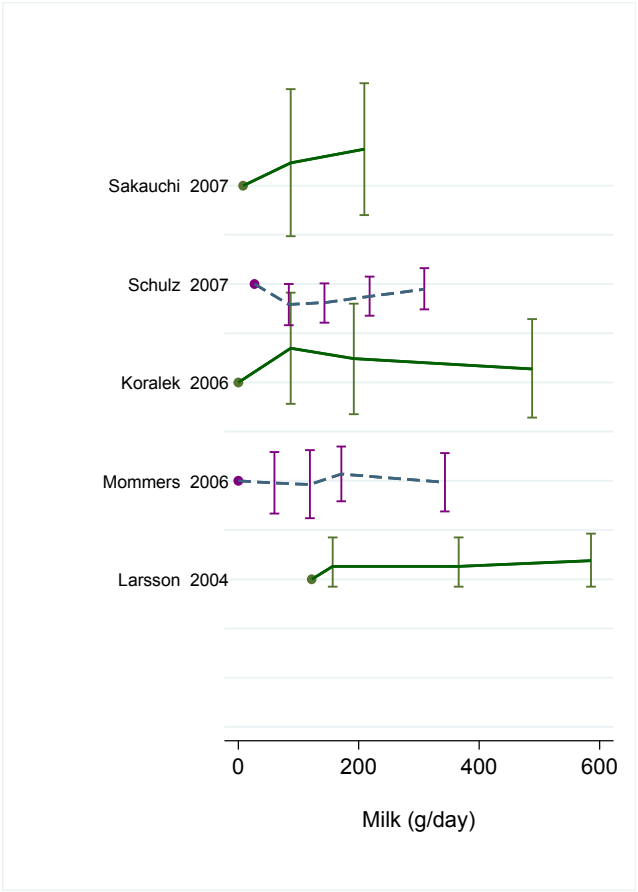


Figure 49 Dose-response graph of milk and ovarian cancer



2.7.1.1 Whole milk

Methods

A total of 4 cohort studies have been published on whole milk and ovarian cancer risk up to 2012 (one study only reported on serous ovarian cancer), two of which were identified in the CUP. Dose-response analyses were conducted per 200 g/d.

Main results

The summary RR per 200 g/d of whole milk was 1.04 (95% CI: 0.88-1.23, I^2=0%, $p_{heterogeneity}$=0.60).

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.60.

Published pooled analysis and meta-analyses

A meta-analysis of eight case-control studies found a summary RR of 1.22 (95% CI: 0.94-1.59) for high vs. low whole milk consumption and ovarian cancer risk (Qin et al, 2005).

A meta-analysis of seven case-control studies and two cohort studies found a positive association between whole milk intake and ovarian cancer risk, summary RR = 1.25 (95% CI: 1.01-1.56, I^2=51.7%, $p_{heterogeneity}$=0.04) for all studies, and 1.17 (95% CI: 0.81-1.68, I^2=0%, $p_{heterogeneity}$=0.96) for the two cohort studies (Larsson et al, 2006).

A pooled analysis of 12 cohort studies (11 included in the analysis) found no association between ≥250 vs. 0 g/d of whole milk intake and ovarian cancer risk, pooled RR=0.95 (95% CI: 0.73-1.24, $p_{heterogeneity}$=0.10) (Genkinger et al, 2006). The relative risk for an increase of 250 g/day was 0.98 (95% CI: 0.88-1.10) ptrend= 0.09. All the studies included in the CUP meta-analysis were included in this pooled analysis.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited and inconclusive evidence for an association between milk and dairy products and ovarian cancer (no judgement specifically on whole milk).

Table 53 Studies on whole milk identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Kiani, 2006	USA	Adventist Health Study	71	~16 years	1.48	0.74	2.98	≥1/day vs. never
Koralek, 2006	USA	Breast Cancer Detection Demonstration Project	146	8.3 years	0.80	0.39	1.63	12.7 vs. 0 serv/wk

Table 54 Overall evidence on whole milk and ovarian cancer

SLR	Summary of evidence
2005 SLR	Two cohort studies reported on whole milk and ovarian cancer. Both studies showed no significant association between whole milk and ovarian cancer risk.
Continuous Update Project	Two additional studies reported on whole milk and ovarian cancer risk and found no significant association. In a pooled analysis of 11 cohort studies, the relative risk for an increase of 250 g/day was 0.98 (95% CI: 0.88-1.10).

Table 55 Summary of results of the dose-response meta-analysis of whole milk and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	518
RR (95% CI)	-	1.04 (0.88-1.23)
Quantity	-	Per 200 g/d
Heterogeneity (I^2, p-value)	-	0%, p=0.60

*No meta-analysis was conducted in the 2nd report

Table 56 Inclusion/exclusion table for meta-analysis of whole milk and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11647	Kiani	2006	Prospective study	Adventist Health Study	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA11662	Koralek	2006	Prospective study	Breast Cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Distribution of person-years	
OVA10870	Larsson	2004	Prospective study	Swedish Mammography Cohort	Incidence	Yes	No	No	-	Reported only on serous ovarian cancer
OVA11491	Fairfield	2004	Prospective study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Midpoints, distribution of person-years	

Figure 50 Highest versus lowest forest plot of whole milk and ovarian cancer

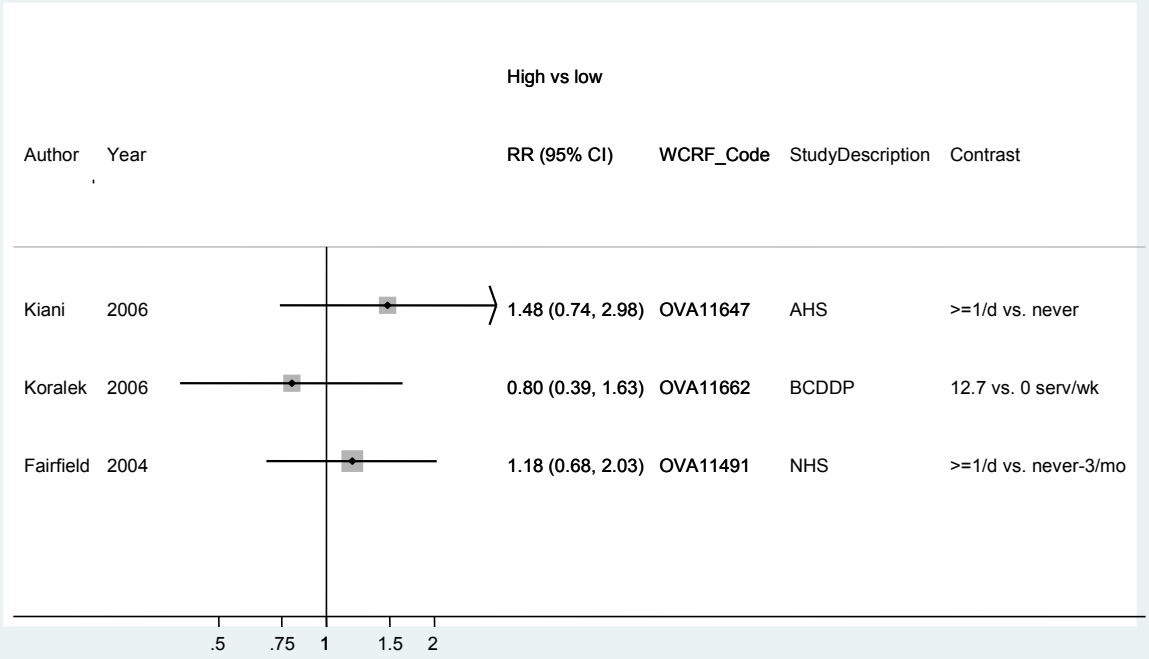


Figure 51 Dose-response meta-analysis of whole milk and ovarian cancer, per 200 g/d

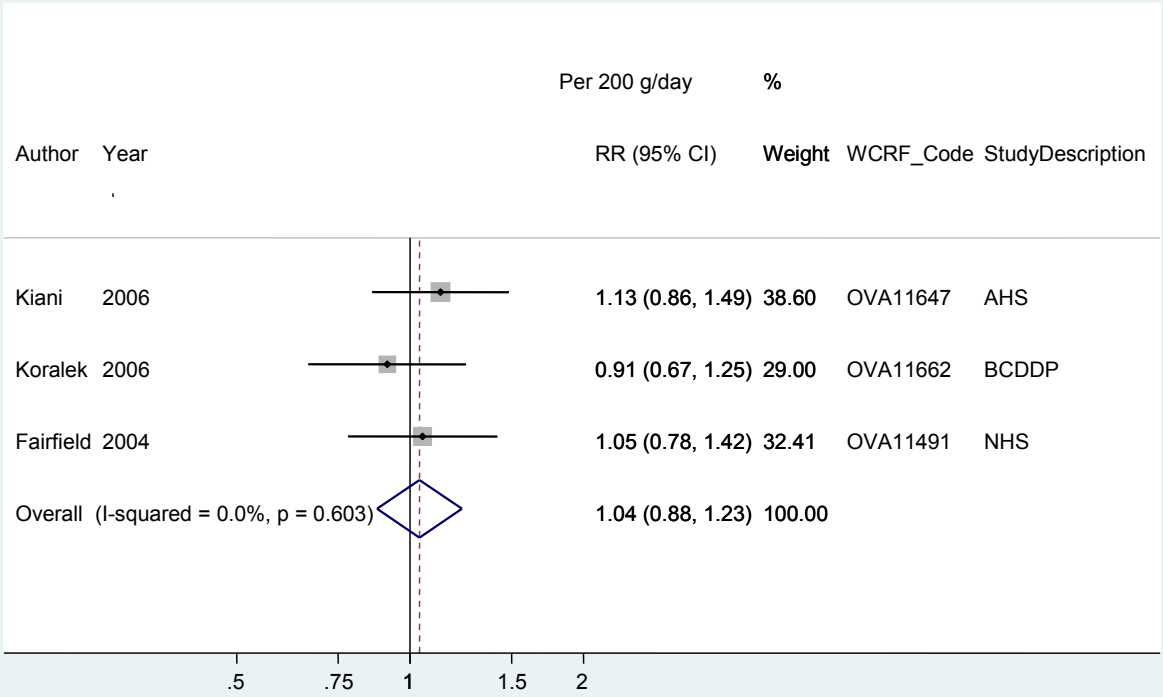
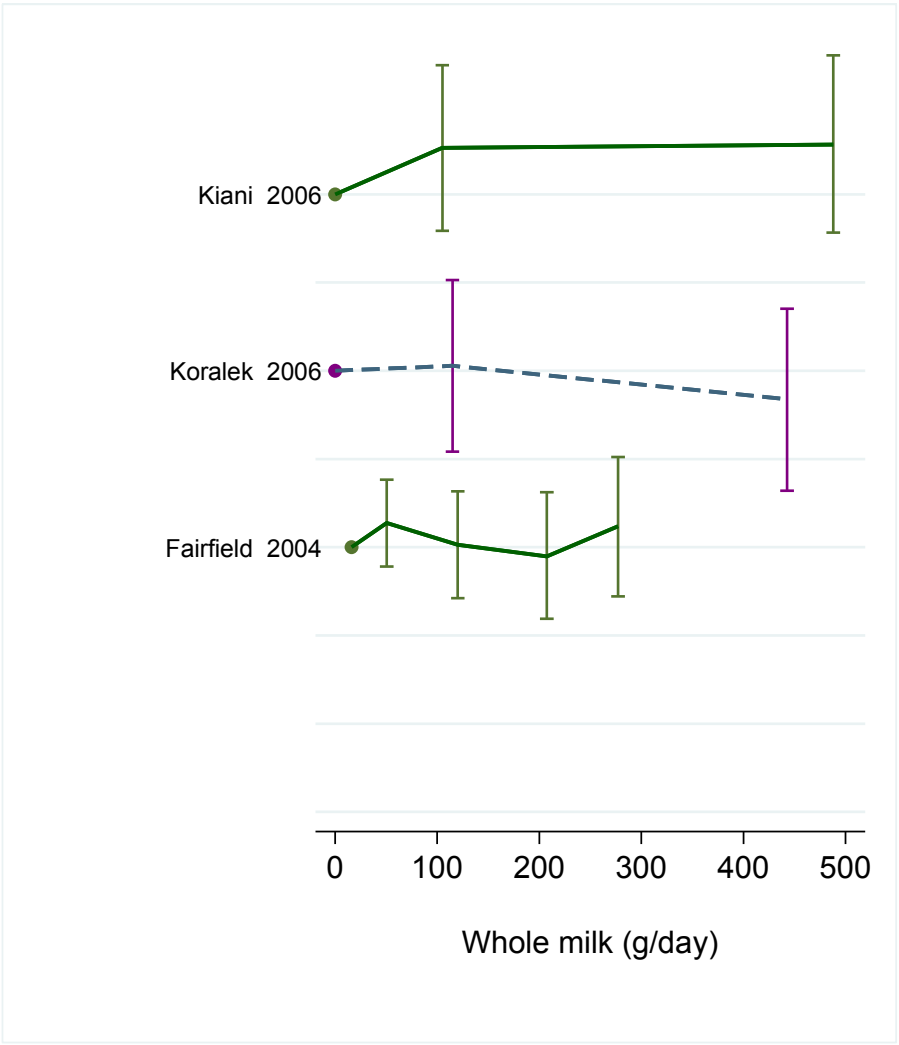


Figure 52 Dose-response graph of whole milk and ovarian cancer



2.7.2 Cheese

Methods

A total of 8 cohort studies (9 publications) have been published on cheese and ovarian cancer risk up to 2012, four of which were identified in the CUP. Dose-response analyses were conducted per 50 g/d.

Main results

The summary RR per 50 g/d of cheese was 1.03 (95% CI: 0.83-1.28, I^2=24.1%, $p_{heterogeneity}$=0.24). There was no evidence of publication bias with Egger's test, p=0.64.

Heterogeneity

There was some evidence of low heterogeneity, I^2=24.1%, $p_{heterogeneity}$=0.24.

Published pooled analysis and meta-analyses

A meta-analysis of five case-control studies and two cohort studies found a summary RR of 0.93 (95% CI: 0.75-1.17) for high vs. low cheese intake and ovarian cancer risk (Qin et al, 2005).

A meta-analysis of seven case-control studies and three cohort studies found no association between cheese intake and ovarian cancer risk, summary RR = 0.95 (95% CI: 0.80-1.12, I^2=33.1%, $p_{heterogeneity}$=0.14) for all studies (Larsson et al, 2006) and summary RR=1.04 (95% CI: 0.60-1.81, I^2=70.6%, $p_{heterogeneity}$=0.03) for cohort studies.

A pooled analysis of 12 cohort studies (11 studies in the analysis) found a pooled RR=1.30 (95% CI: 0.96-1.78, $p_{heterogeneity}$=0.74) for ≥50 vs. 0 g/d of cheese (Genkinger et al, 2006) and the RR for an increment of 25 g/day was 1.02 (95% CI: 0.93-1.11).

If the results of the EPIC study (Schultz et al, 2007) and the JACC (Sakauchi et al, 2007) are pooled with the summary results of the pooled analysis of 12 cohorts (Genkinger et al, 2006), the relative risk estimate for an increase of 25 g/day is 1.03 (95% CI= 0.94-1.11).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited and inconclusive evidence for an association between milk and dairy products and ovarian cancer (no judgement specifically on cheese).

Table 57 Studies on cheese identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Sakauchi, 2007	Japan	Japan Collaborative Cohort Study	77	13.3 years	1.66	0.65	4.25	≥1-2/wk vs. seldom
Schulz, 2007	Europe	EPIC Study	581	~6.3 years	1.18 1.04	0.77 0.91	1.80 1.18	≥44 vs. <19 g/d Per 15.6 g/d
Kiani, 2006	USA	Adventist Health Study	71	~16 years	1.68	0.82	3.44	>2/wk vs. never to <1/wk
Koralek, 2006	USA	Breast Cancer Detection Demonstration Project	146	8.3 years	0.87	0.50	1.53	5.0 vs. 0 serv/wk

Table 58 Overall evidence on cheese and ovarian cancer

SLR	Summary of evidence
2005 SLR	Four cohort studies reported on cheese and ovarian cancer and found no significant associations between cheese intake and ovarian cancer risk.
Continuous Update Project	Four additional studies reported on cheese and ovarian cancer risk and all studies found no significant association. The pooled analysis of 11 cohort studies found a RR for an increment of 25 g/day of 1.02 (95% CI: 0.93-1.11).

Table 59 Summary of results of the dose-response meta-analysis of cheese intake and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	8
Cases (n)	-	1833
RR (95% CI)	-	1.03 (0.83-1.28)
Quantity	-	Per 50 g/d
Heterogeneity (I^2, p-value)	-	24.1%, p=0.24

*No meta-analysis was conducted in the 2nd report

Table 60 Inclusion/exclusion table for meta-analysis of cheese and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11661	Sakauchi	2007	Prospective study	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Distribution of person-years, midpoints	
OVA11639	Schulz	2007	Prospective study	EPIC study	Incidence	No	Yes	Yes	Midpoints	
OVA11647	Kiani	2006	Prospective study	Adventist Health Study	Incidence	No	Yes	Yes	Distribution of person-years, midpoints	
OVA11662	Koralek	2006	Prospective study	Breast Cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Distribution of person-years	
OVA09788	Mommers	2006	Prospective study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
OVA11491	Fairfield	2004	Prospective study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Distribution of person-years, midopoints	
OVA10870	Larsson	2004	Prospective study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	
OVA00454	Bertone	2002	Prospective study	Nurses' Health Study	Incidence	Yes	No	No		Overlap with Fairfield et al, 2004 (OVA11491)
OVA02880	Kushi	1999	Prospective study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	

Figure 53 Highest versus lowest forest plot of cheese and ovarian cancer

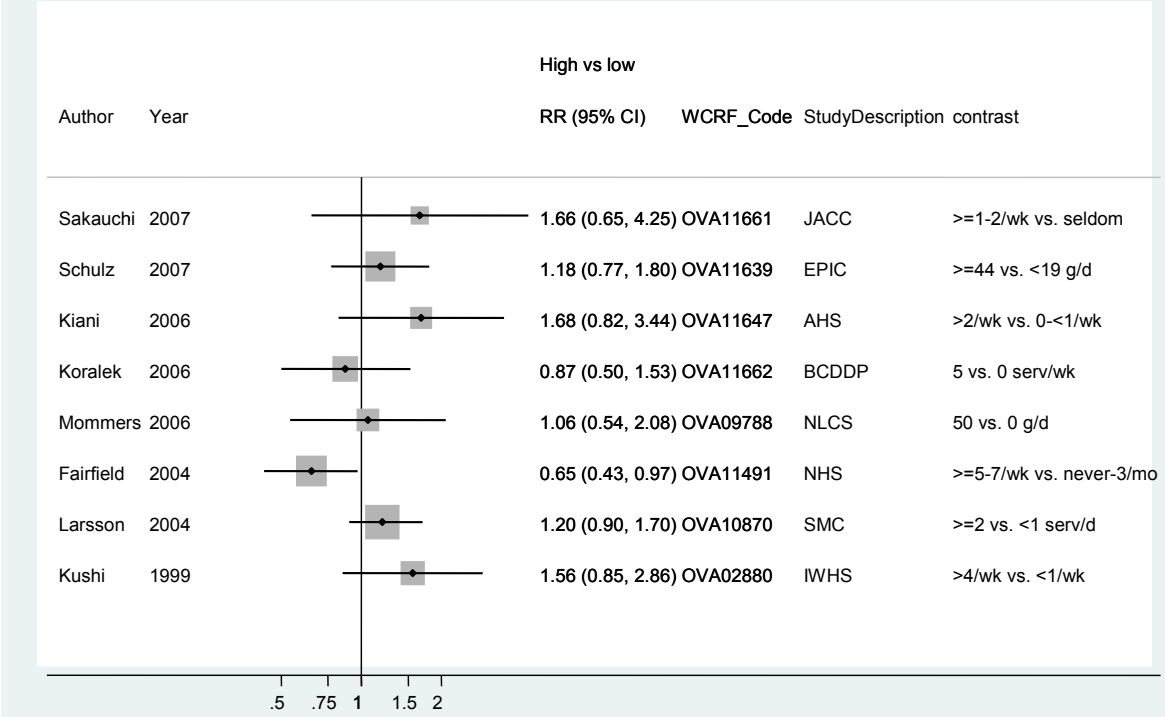


Figure 54 Dose-response meta-analysis of cheese and ovarian cancer, per 50 g/d

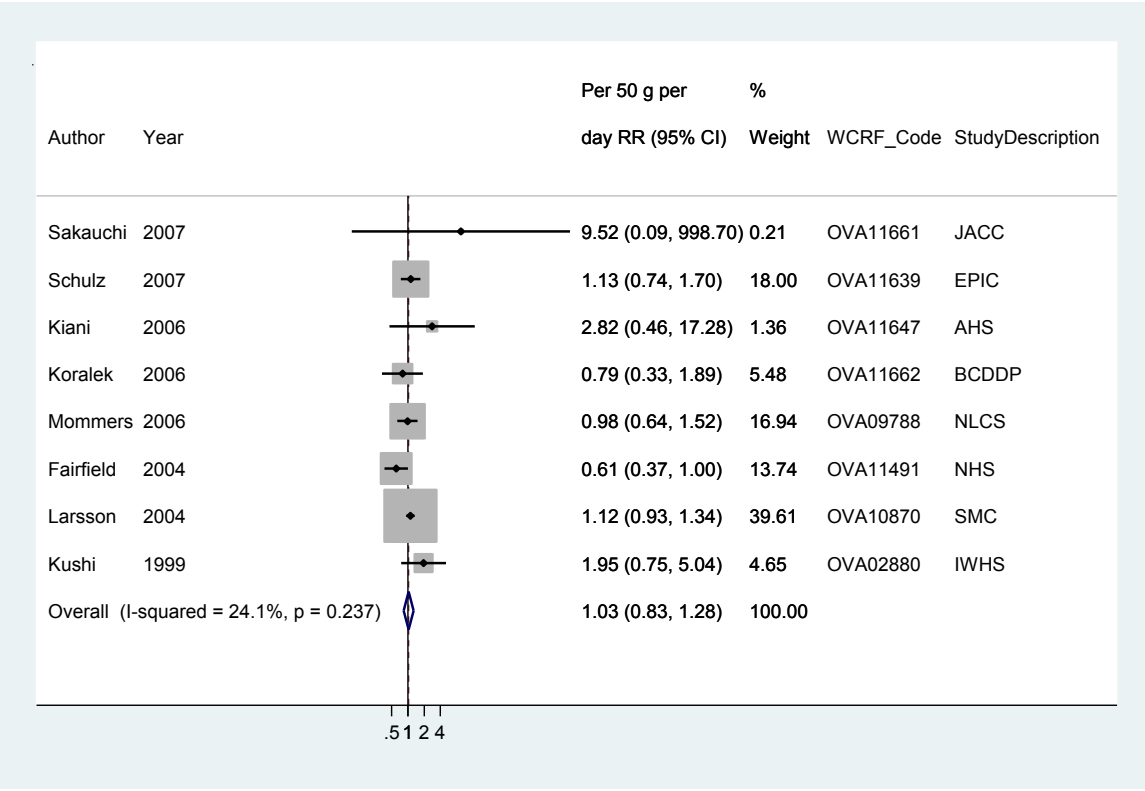


Figure 55 Funnel plot of cheese and ovarian cancer

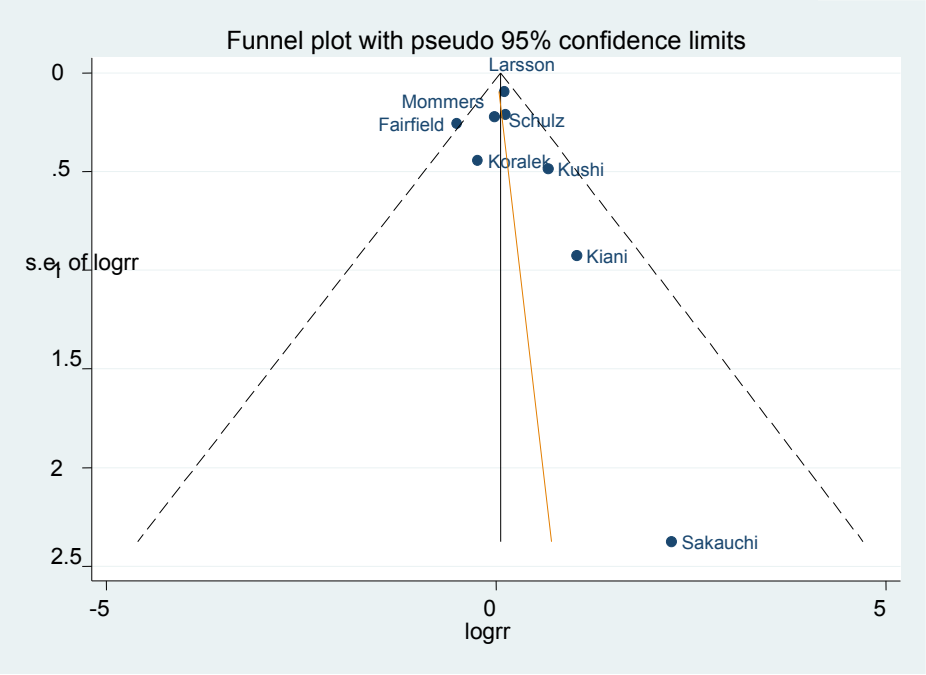
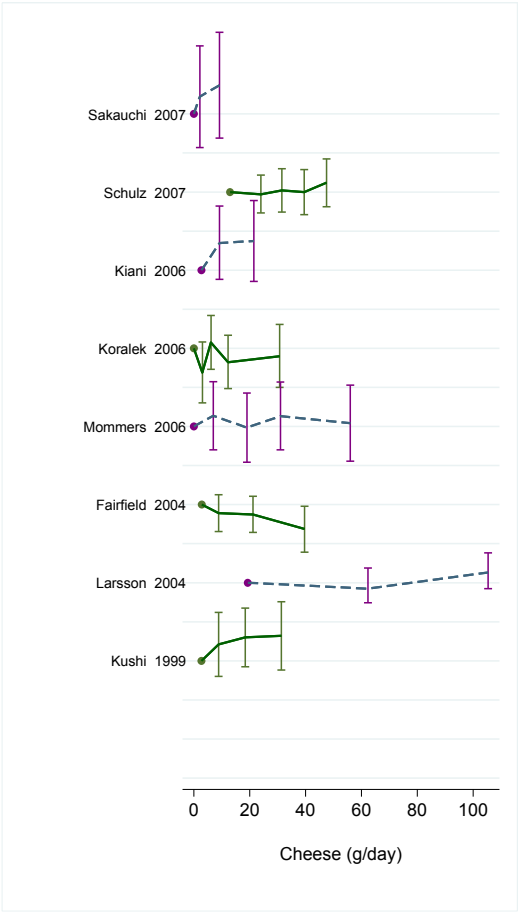


Figure 56 Dose-response graph of cheese and ovarian cancer



2.7.3 Yogurt

Methods

A total of 5 cohort studies have been published on yogurt and ovarian cancer risk up to 2012, two of which were identified in the CUP. Dose-response analyses were conducted per 200 g/d.

Main results

The summary RR per 200 g/d of yogurt was 1.06 (95% CI: 0.91-1.24, I^2=0%, $p_{heterogeneity}$=0.55). There was no evidence of publication bias with Egger's test, p=0.61.

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.55.

Published pooled analysis and meta-analyses

A meta-analysis of six case-control studies found a summary RR of 1.11 (95% CI: 0.97-1.26) for high vs. low yogurt intake and ovarian cancer risk (Qin et al, 2005).

A meta-analysis of seven case-control studies and two cohort studies found no association between yogurt intake and ovarian cancer risk, summary RR = 1.13 (95% CI: 0.96-1.33, I^2=11.6%, $p_{heterogeneity}$=0.34) for all studies, and 0.95 (95% CI: 0.69-1.30, I^2=0%, $p_{heterogeneity}$=0.41) for the two cohort studies (Larsson et al, 2006).

A pooled analysis of 12 cohort studies (9 studies included in the analysis) found no association between yogurt intake and ovarian cancer risk, pooled RR=1.04 (95% CI: 0.86-1.24, $p_{heterogeneity}$=0.75) for ≥114 vs. 0 g/d (Genkinger et al, 2006). The RR for an increment of 227 g/day was 0.91 (95% CI: 0.77-1.07).

If the results of the EPIC study (Schutlz et al, 2007) and the JACC (Sakauchi et al, 2007) are pooled with the summary results of the pooled analysis of 12 cohorts (Genkinger et al, 2006), the relative risk estimate for an increase of 200 g/day is 0.94 (95% CI= 0.81-1.07).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited and inconclusive evidence for an association between milk and dairy products and ovarian cancer (no judgement specifically on yogurt).

Table 61 Studies on yogurt identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Sakauchi, 2007	Japan	Japan Collaborative Cohort Study	77	13.3 years	1.66	0.71	3.91	≥1-2/wk vs. seldom
Schulz, 2007	Europe	EPIC Study	581	~6.3 years	0.90 1.06	0.69 0.96	1.19 1.17	≥83 vs. <6 g/d Per 44.6 g/d

Table 62 Overall evidence on yogurt and ovarian cancer

SLR	Summary of evidence
2005 SLR	Three cohort studies reported on yogurt and ovarian cancer and found no significant associations between yogurt intake and ovarian cancer risk.
Continuous Update Project	Two additional studies reported on yogurt and ovarian cancer risk and found no significant association. A pooled analysis of 9 cohort studies found no association between yogurt intake and ovarian cancer risk.

Table 63 Summary of results of the dose-response meta-analysis of yogurt intake and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1477
RR (95% CI)	-	1.06 (0.91-1.24)
Quantity	-	Per 200 g/d
Heterogeneity (I^2, p-value)	-	0%, p=0.55

*No meta-analysis was conducted in the 2nd report

Table 64 Inclusion/exclusion table for meta-analysis of yogurt and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11661	Sakauchi	2007	Prospective study	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Distribution of person-years, midpoints	
OVA11639	Schulz	2007	Prospective study	EPIC study	Incidence	No	Yes	Yes	Midpoints	
OVA09788	Mommers	2006	Prospective study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	-	
OVA10870	Larsson	2004	Prospective study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	
OVA11491	Fairfield	2004	Prospective study	Nurses' Health Study	Incidence	Yes	Yes	Yes	-	

Figure 57 Highest versus lowest forest plot of yogurt and ovarian cancer

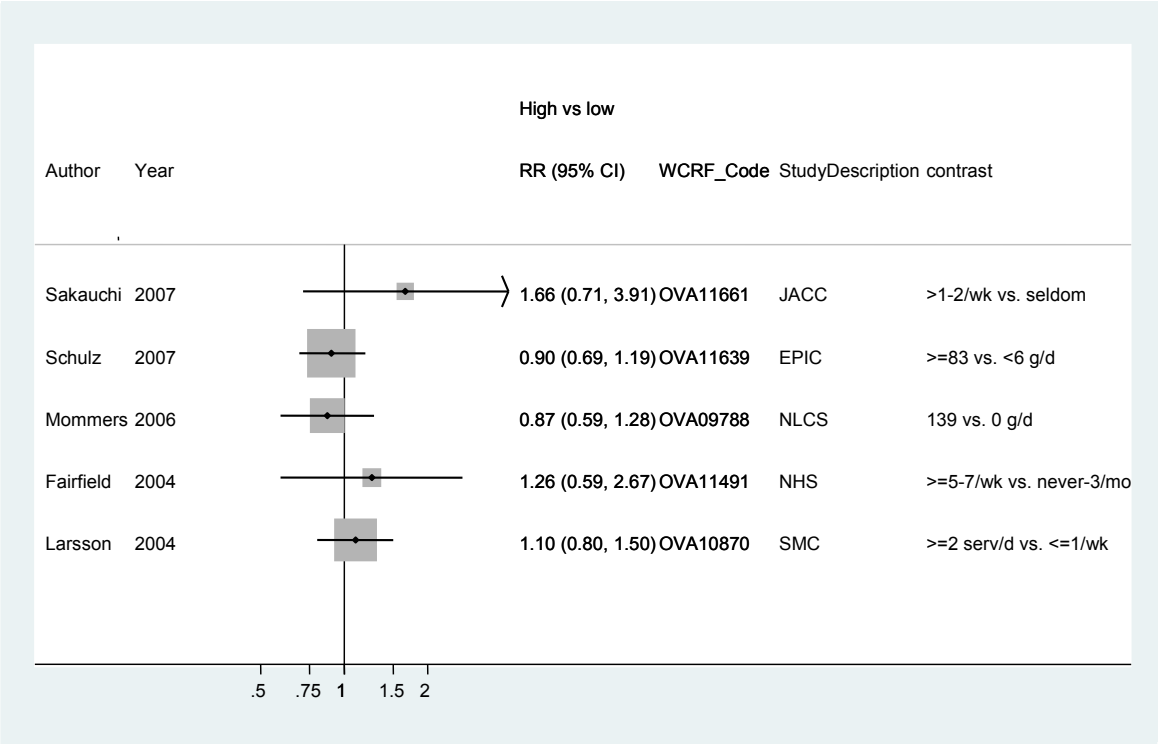


Figure 58 Dose-response meta-analysis of yogurt and ovarian cancer, per 200 g/d

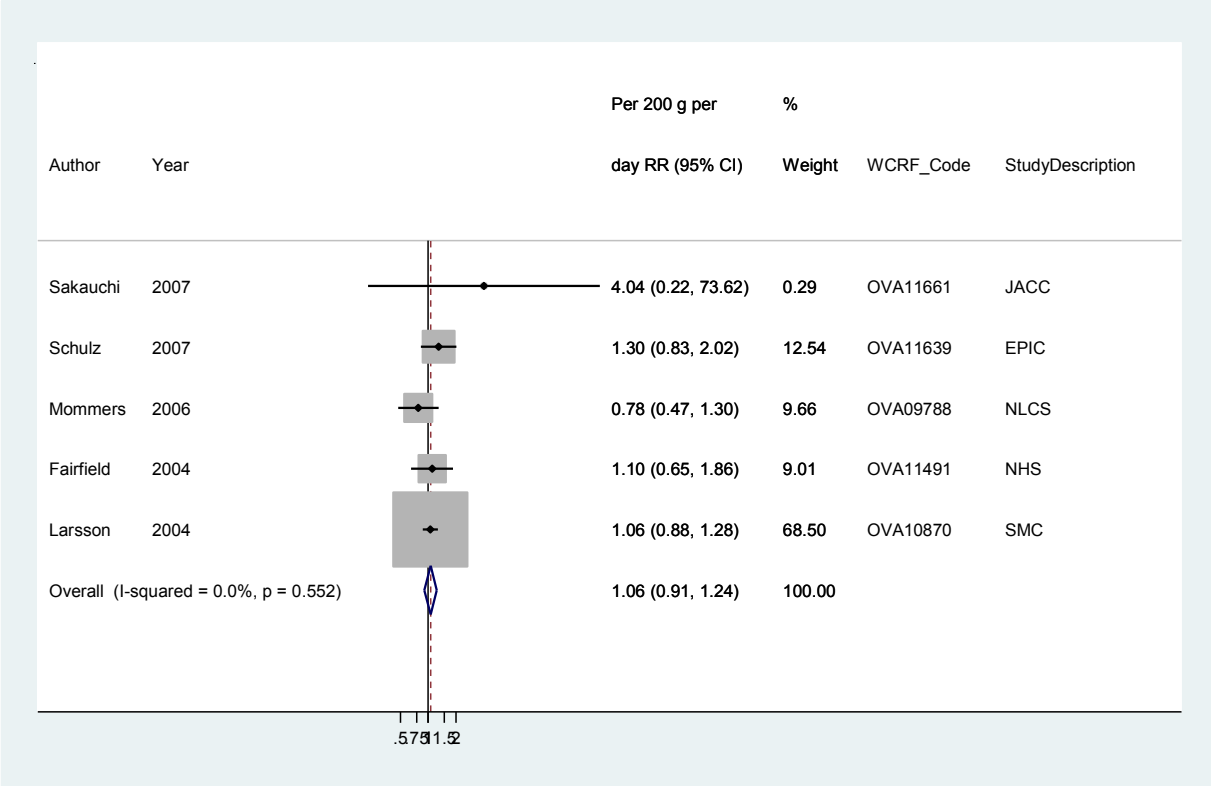


Figure 59 Funnel plot of yogurt and ovarian cancer

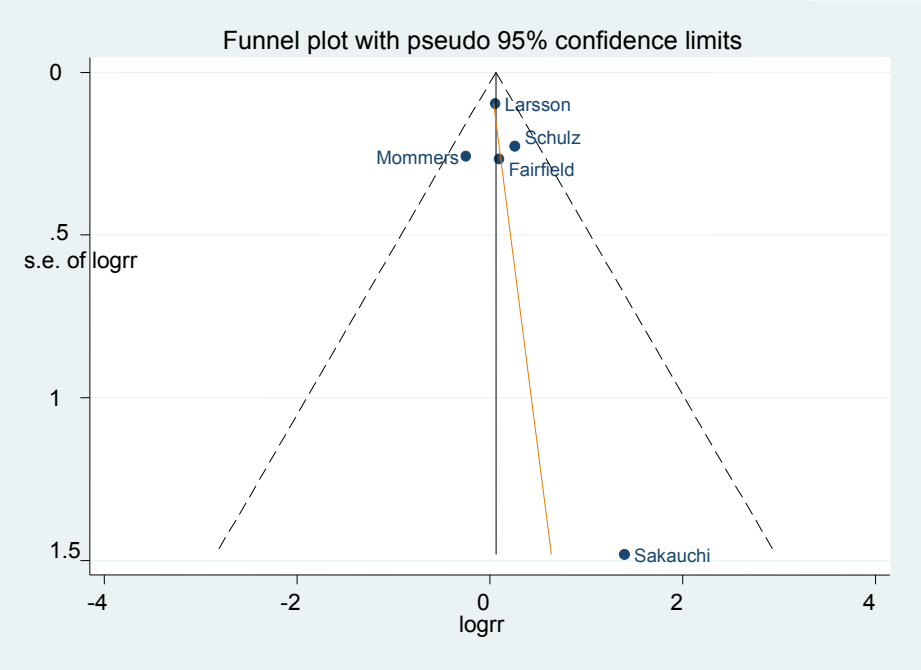
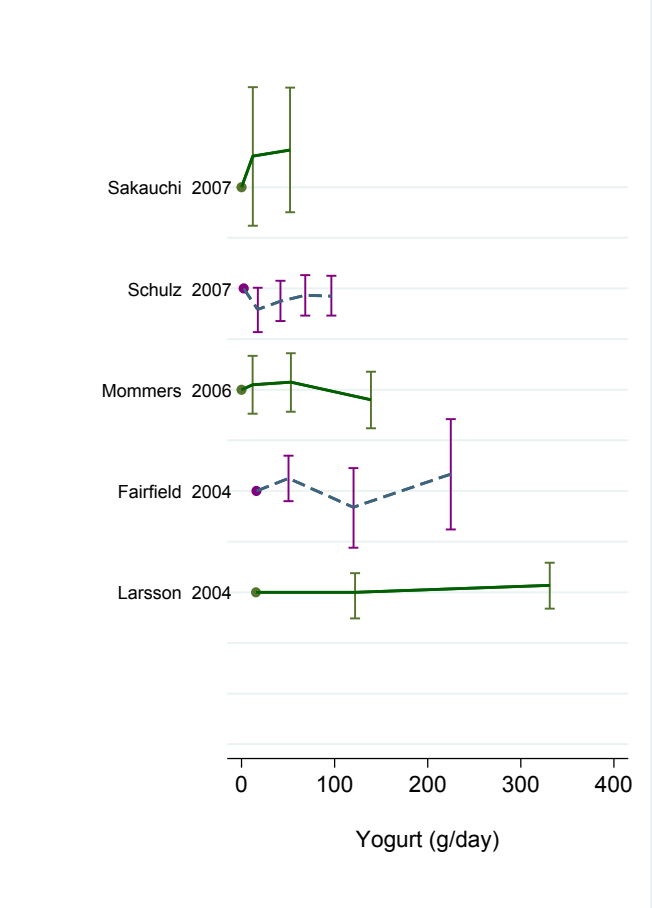


Figure 60 Dose-response graph of yogurt and ovarian cancer



3 Beverages

3.6.1 Coffee

Methods

Up to December 2012, reports from ten cohort studies were identified, eight of which were identified during the CUP (including a paper on multi-cancer missed by the SLR) and two during the SLR. The CUP meta-analysis included nine studies (seven studies identified during the CUP and two studies identified during the 2007 SLR). For the dose-response analyses results were converted to a common scale (servings per day) of 200 ml, which was used as an average serving size. The dose-response results are presented for an increment of 200 ml/day.

Main results

The summary RR per 200 ml/day was 1.02 (95% CI: 0.98-1.06; I^2= 28.8%, $P_{heterogeneity}$=0.188) for all studies combined. The overall results remained the same when one study with mortality as outcome (Snowdon et al, 1984) was excluded from the analysis (RR: 1.02; CI: 0.98-1.06). In influence analysis, the RR ranged from 1.01 (95% CI: 0.97-1.05) when excluding the Canadian National Breast Screening Study (Silvera et al, 2007) to 1.04 (95% CI: 1.00-1.07) when excluding the Nurses' Health Study (Tworoger et al, 2008).

Heterogeneity

Low heterogeneity was observed (I^2=28.8%, p=0.188). Egger's tests did not show evidence of publication bias (p=0.44).

Comparison with the Second Expert Report

Two studies were identified during the SLR, none of them showed an association with coffee consumption and ovarian cancer. One study was missed by the search and it is included in this report.

Published meta-analyses

In a published meta-analysis of prospective studies the summary RR of ovarian cancer for highest vs. lowest quintile of coffee intake was 1.13 (95% CI: 0.89-1.43), based on 7 studies. There was substantial heterogeneity (I^2=50.9%; p=0.057) (Braem, 2012).

In another meta-analysis on ovarian cancer and coffee intake, the summary RR estimate for the highest versus the lowest intake -including seven case-control studies- was 1.15 (95% CI; 0.89 -1.47) and there was evidence of substantial heterogeneity (I-squared = 60.2%, P = 0.005); the summary estimate was 1.32 (95% CI: 0.99-1.77) for four prospective cohort studies and there was no evidence of heterogeneity (Steevens, 2007). No dose-response analyses were conducted.

Table 65 Studies on coffee consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Braem, 2012	Europe	European Prospective Investigation into Cancer and Nutrition	1244	11.7	1.05	0.75	1.46	Quintile 5 vs. quintile 1
Nilsson, 2010	Sweden	Västerbotten Intervention Project	71	15	1.41	0.53	3.74	>=4 occasions/d vs. <1 occasion/d
Tworoger, 2008	USA	Nurse's Health Study	507	15.1	0.75	0.55	1.02	>=3 cups/d vs. none
Lueth, 2008	USA	Iowa Women's Health Study	266	18	1.28	0.76	2.16	>=5 cups/d vs. 0cups/d
Chang, 2007	USA	The California Teachers Study	280	8.1	1.02	0.55	1.90	Highest vs. lowest quintile
Silvera, 2007	Canada	Canadian National Breast Screening Study	264	16.4	1.62	0.95	2.75	>=4 cups/d vs. none
Steevens, 2007	Netherlands	The Netherlands Cohort Study on Diet and Cancer	280	13.3	1.08 1.04	0.75 0.97	1.57 1.12	>=5cups/d vs. 0-<1 cups/d Coffee increment (1cup/d)
Snowdon, 1984	USA	Adventist Health Study, 1960	51 (deaths)	21	1.20	0.60	2.50	>=2 cups/d vs. <1 cup/d

Table 66 Overall evidence on coffee consumption and ovarian cancer

	Summary of evidence
SLR	Two studies addressed the relationship between coffee intake and ovarian cancer risk. None of them reported significant associations
Continuous Update Project	Eight cohort studies were identified during the CUP. One additional (multi-cancer mortality) study that was missed by the SLR, showed a non-significant increase in risk. Overall, nine studies could be included in the meta-analysis

Table 67 Summary of results of the dose response meta-analysis of coffee consumption and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	9
Cases (n)	-	3208
Increment unit used	-	Per 200ml/day
Overall RR (95%CI)	-	1.02 (0.98-1.06)
Heterogeneity (I^2,p-value)	-	28.8%, p=0.188
Ovarian cancer incidence		
Studies (n)	-	8
Cases (n)	-	3159
Increment unit used	-	Per 200ml/day
Overall RR (95%CI)	-	1.02 (0.98-1.06)
Heterogeneity (I^2,p-value)	-	36.8%, p=0.135

*No meta-analysis was conducted in the 2nd report

Table 68 Inclusion/exclusion table for meta-analysis of coffee consumption and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11676	Braem	2012	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence EOC (borderline and invasive)	No	Yes	Yes	Average median intake per quintile in each participating country	-
OVA11693	Nilsson	2010	Prospective Cohort study	Västerbotten Intervention Project	Incidence	No	Yes	Yes	Person/ years per category and mid-exposure values	-
OVA11633	Tworoger	2008	Prospective Cohort study	Nurse's Health Study	Incidence EOC	No	Yes	Yes	Mid-exposure values	-
OVA11650	Lueth	2008	Prospective Cohort study	Iowa Women's Health Study	Incidence EOC	No	Yes	Yes	Mid-exposure values	-
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study	Incidence	No	No	Yes	-	Two categories of exposure (high vs. low).
OVA11659	Silvera,	2007	Prospective Cohort study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA11648	Steevens,	2007	Case-cohort study	The Netherlands Cohort Study on Diet and Cancer	Incidence EOC	No	Yes	Yes	Rescale of RR for continuous increase	-
OVA09965	Larsson	2005	Prospective Cohort study	Swedish Mammography Cohort	Incidence invasive EOC	Yes	Yes	Yes	Rescale of RR for continuous increase	-
OVA09682	Stensvold	1994	Prospective Cohort study	Norway, 1977	Incidence	Yes	Yes	Yes	Rescale of RR for continuous increase	-
OVA11692	Snowdon	1984	Prospective Cohort study	Adventist Health Study, 1960	Mortality	New	Yes	Yes	Person/ years per category and mid-exposure values. Sample size was obtained from article OVA05024	-

Figure 61 Highest versus lowest forest plot of coffee consumption and ovarian cancer

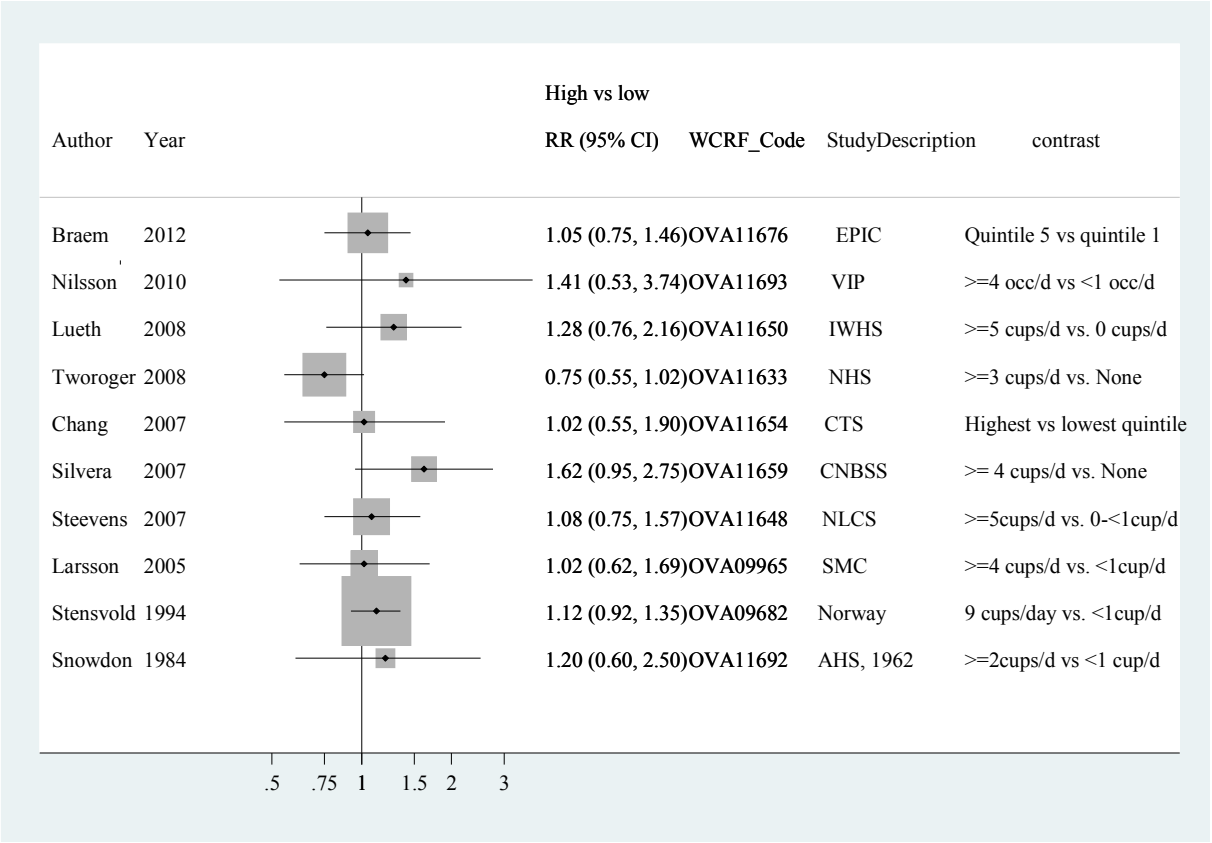


Figure 62 Dose-response meta-analysis of coffee and ovarian cancer - per 200ml/d

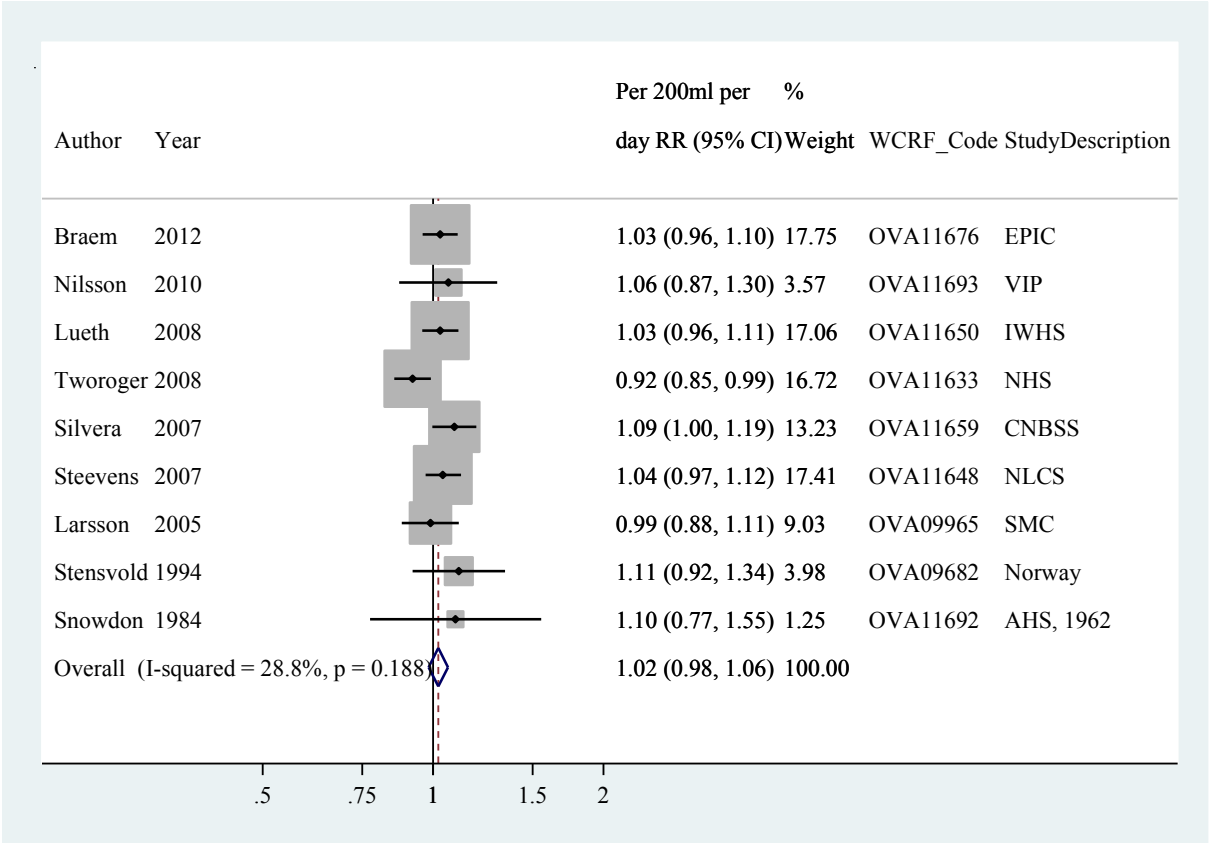


Figure 63 Funnel plot of coffee consumption and ovarian cancer

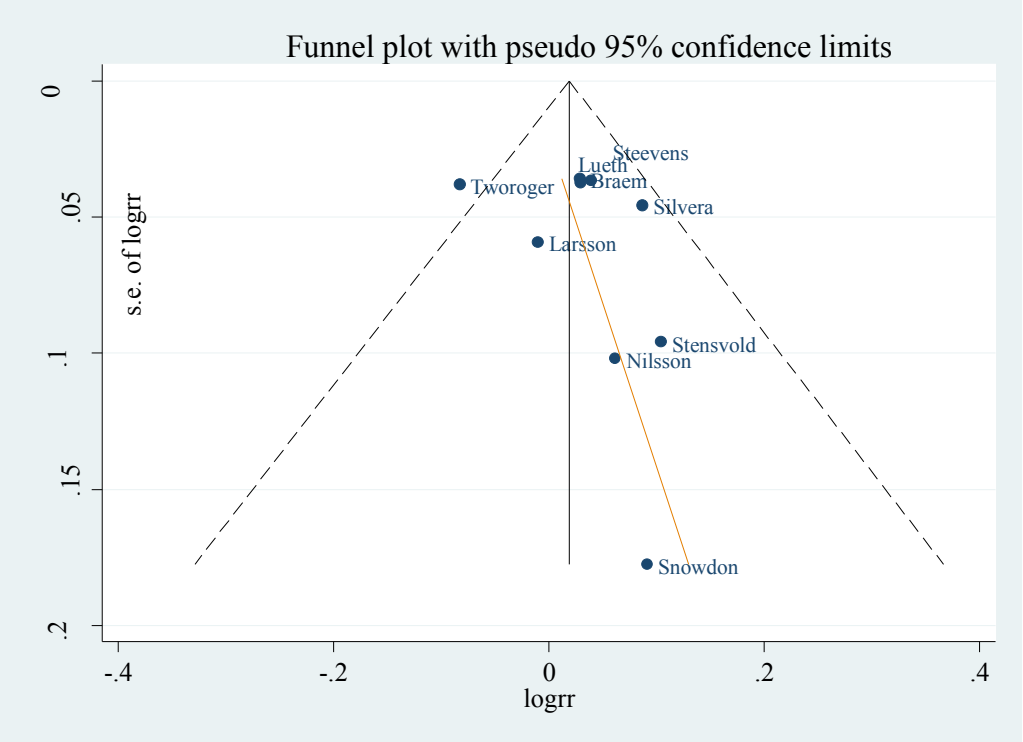
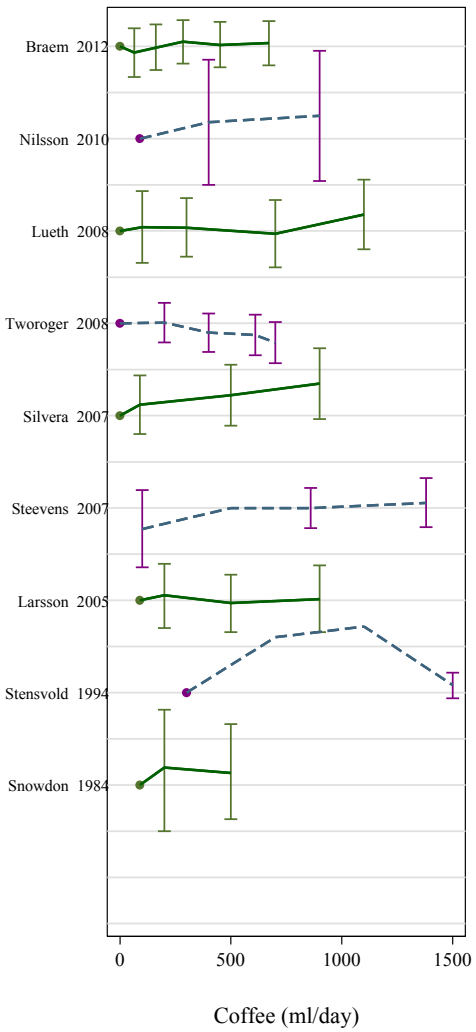


Figure 64 Dose-response graph of coffee and ovarian cancer



3.6.2 Tea

Methods

Up to December 2012, reports from seven cohort studies on tea intake were identified, five of which (six publications) were identified during the CUP. The CUP meta-analysis included six studies (four studies identified during the CUP and two studies identified during the 2007 SLR). For the dose-response analyses results were converted to a common scale of exposure level (servings per day) of 200 ml, which was used as an average serving size for all studies except one study (Zheng et al, 1996) that provided an average serving size of 237ml/day, which was used for this study. The dose-response results are presented for an increment of 200 ml/day.

Main results

The summary RR per 200 ml/day was 0.96 (95% CI: 0.91-1.00; I^2= 17.6%, $P_{heterogeneity}$=0.30) for all studies combined. In influence analysis, the RR ranged from 0.94 (95% CI: 0.89-0.99) when excluding the Canadian National Breast Screening Study (Silvera et al, 2007) to 0.96 (95% CI: 0.92-1.00) when excluding the study the Swedish Mammography Cohort study (Larsson et al, 2005).

Heterogeneity

Low heterogeneity was observed (I^2=17.6%, p=0.30). Egger's tests did not show evidence of publication bias (p=0.77).

Comparison with the Second Expert Report

Two studies were identified during the SLR, one of them found a significant protective association between tea consumption and epithelial ovarian cancer.

Published meta-analyses

In a published meta-analysis of prospective studies the summary RR of ovarian cancer for highest vs. lowest tea intake was 0.88 (95% CI: 0.71-1.09), based on six studies. There was low heterogeneity (I^2=31.8%; p=0.197), (Braem, 2012). In another meta-analysis on ovarian cancer, the summary RR estimate for the highest versus the lowest intake including seven case-control studies was 0.93 (95% CI; 0.76 -1.14) and there was evidence of substantial heterogeneity (I-squared = 66.5%, P = 0.006); the summary estimate was 0.71 (95% CI: 0.55-0.93) for five prospective cohort studies and there was mild heterogeneity (I-squared = 21.9%, P = 0.275); (Steevens, 2007). No dose-response analyses were conducted.

Table 69 Studies on tea consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Braem, 2012	Europe	European Prospective Investigation into Cancer and Nutrition	1244	11.7	1.07	0.78	1.46	Quintile 5 vs quintile 1
Tworoger, 2008	USA	Nurse's Health Study	507	15.1	0.96	0.70	1.30	>=2cups/d vs. <=1cup/d
Chang, 2007	USA	The California Teachers Study	280	8.1	1.27	0.79	2.06	Highest vs. lowest quintile ok intake
Silvera, 2007	Canada	Canadian National Breast Screening Study	264	16.4	1.07	0.64	1.79	>=4cups/d vs. none
Gates, 2007	USA	Nurses' Health Study	347	14.2	0.63	0.40	0.99	>=2serv/d vs. <1 serv./wk
Steevens, 2007	Netherlands	The Netherlands Cohort Study on Diet and Cancer	280	13.3	0.65 0.94	0.41 0.89	1.03 1.00	>=5cups/d vs. 0-<1 cups/d Tea increment (1cup/d)

Table 70 Overall evidence on tea consumption and ovarian cancer

	Summary of evidence
SLR	Two cohort studies were identified during the SLR. One prospective cohort study on Iowa post-menopausal women (Zheng et al., 1996) found no association between non-herbal tea consumption and ovarian cancer incidence. The Sweden cohort found a significant protective association with epithelial ovarian cancer (Larsson, 2005).
Continuous Update Project	Five cohort studies were identified; four of which could be included in the meta-analysis. Overall, six studies were included in the meta-analysis

Table 71 Summary of results of the dose response meta-analysis of tea consumption and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	6
Cases (n)	-	2703
Increment unit used	-	Per 200 ml/day
Overall RR (95%CI)	-	0.96 (0.91-1.00)
Heterogeneity (I^2,p-value)	-	17.6%, p=0.30

*No meta-analysis was conducted in the second report

Table 72 Inclusion/exclusion table for meta-analysis of tea consumption and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11676	Braem	2012	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence EOC (borderline and invasive)	No	Yes	Yes	Average median intake per quintile in each participating country	
OVA11633	Tworoger	2008	Prospective Cohort study	Nurse's Health Study	Incidence EOC	No	Yes	Yes	Mid-exposure values	
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study	Incidence	No	No	Yes	-	Two categories of exposure (high vs. low).
OVA11659	Silvera	2007	Prospective Cohort study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	
OVA11638	Gates	2007	Prospective Cohort study	Nurse's Health Study	Incidence	No	No	No	-	Superseded by Tworoger, 2008, OVA11633
OVA11648	Steevens	2007	Case-cohort study	The Netherlands Cohort Study on Diet and Cancer	Incidence EOC	No	Yes	Yes	Rescale of RR for continuous increase	
OVA09751	Larsson	2005	Prospective Cohort study	Swedish Mammography Cohort	Incidence invasive EOC	Yes	Yes	Yes	Mid-exposure values	
OVA06053	Zheng	1996	Prospective Cohort study	Iowa Women's Health Study	Incidence EOC	Yes	Yes	Yes	Person/ years per category ml/day per category and mid-exposure values	

Figure 65 Highest versus lowest forest plot of tea consumption and ovarian cancer

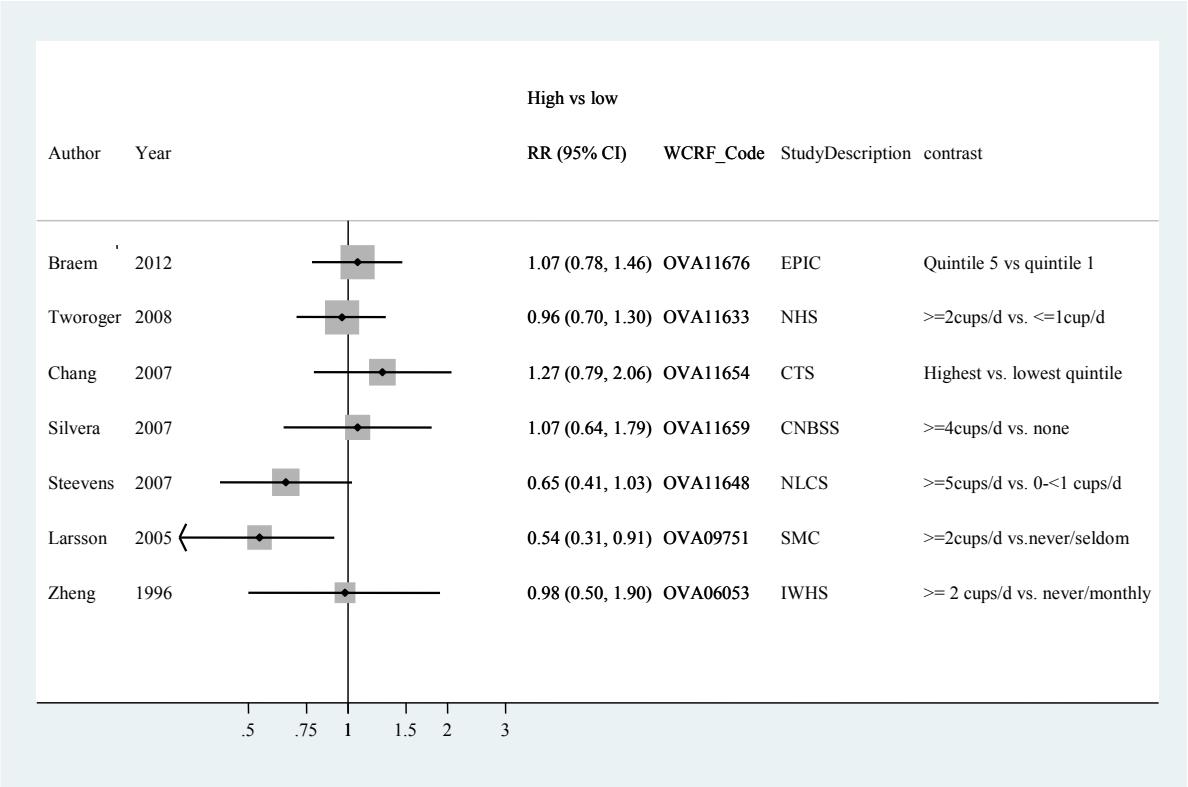


Figure 66 Dose-response meta-analysis of tea and ovarian cancer - per 200ml/d

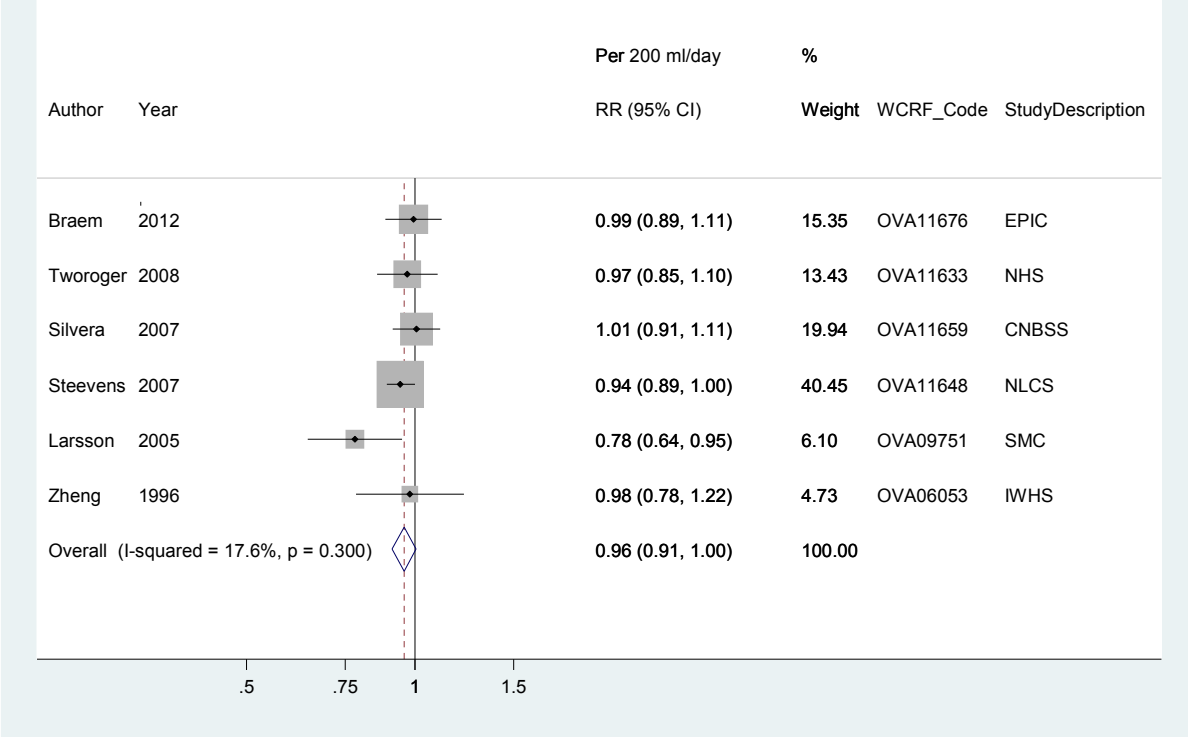


Figure 67 Funnel plot of tea consumption and ovarian cancer

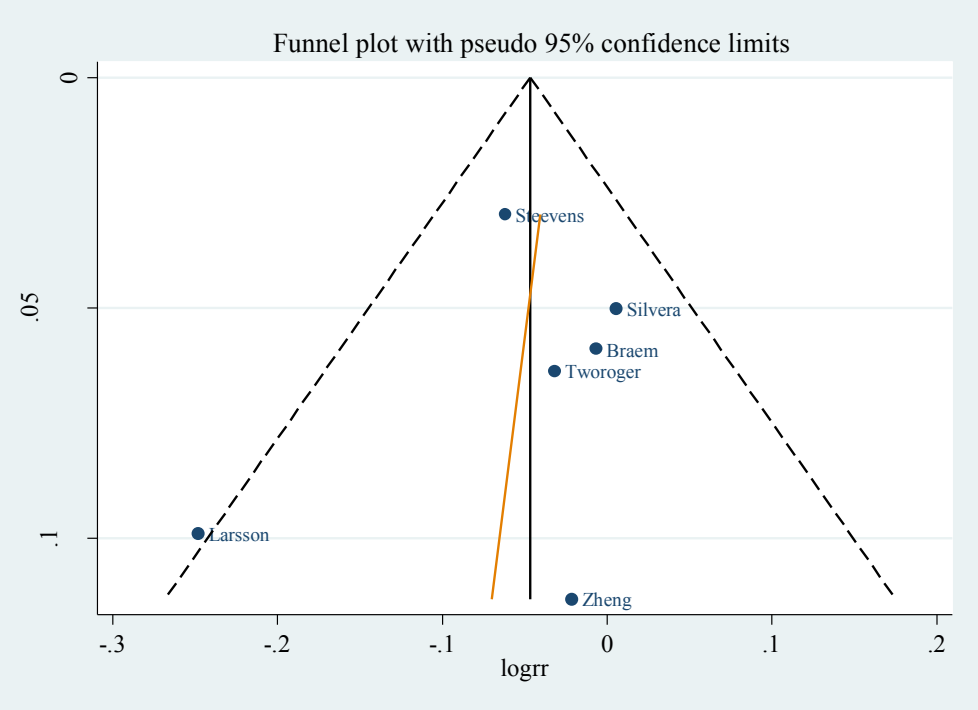
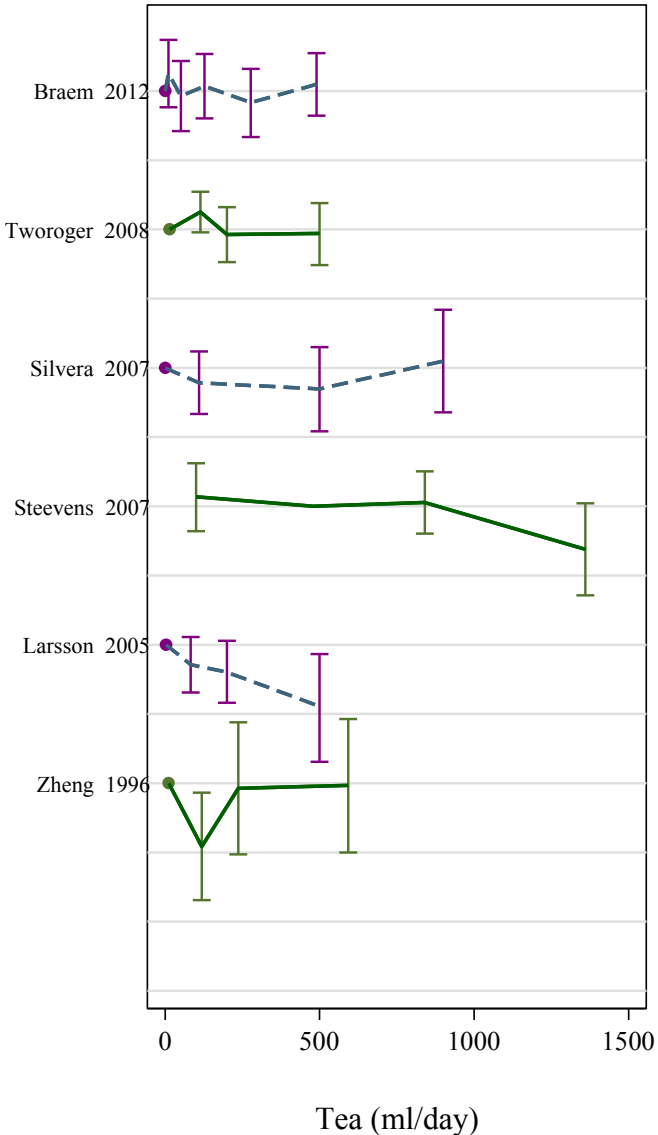


Figure 68 Dose-response graph of tea and ovarian cancer



4.4.2 Acrylamide

Methods

A total of 3 cohort studies have been published on dietary acrylamide intake and ovarian cancer risk up to 2012, all of which were identified in the CUP. Dose-response analyses were conducted per 10 μg per day. A subgroup analysis was conducted among never smokers to investigate the role of confounding from smoking.

Main results

The summary RR per 10 μg per day was 1.07 (95% CI: 0.94-1.21, I^2=43%, $p_{heterogeneity}$=0.18). When the analysis was restricted to never smokers the summary RR was 1.14 (95% CI: 1.00-1.30, I^2=0%, $p_{heterogeneity}$=0.64).

Heterogeneity

There was moderate evidence of heterogeneity, I^2=42.7%, $p_{heterogeneity}$=0.18 and when restricted to never smokers there was no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.64.

Published meta-analysis

A meta-analysis of dietary acrylamide intake and ovarian cancer risk reported a summary RR of 1.01 (0.94-1.08) per 10 μg per day increase in intake based on results from one case-control study and two cohort studies (Pelucchi, 2011).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was no evidence (no studies were identified) relating acrylamide to ovarian cancer risk.

Table 73 Studies on acrylamide identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Wilson, 2010	USA	Nurses' Health Study	416	26 years	1.25 1.19	0.88 0.66	1.77 2.15	25.1 vs. 8.7 µg/d, all 25.1 vs. 8.7 µg/d, never smokers
Larsson, 2009	Sweden	Swedish Mammography Cohort study	368	17.5 years	0.86 1.17 0.97	0.63 0.72 0.49	1.16 1.89 1.93	32.5 vs. 16.9 µg/d, long-term intake ≥29.2 vs. <20.5 µg/d, 10-year follow-up ≥29.2 vs. <20.5 µg/d, never smokers, 10-year follow-up
Hogervorst, 2007	Nether-lands	Netherlands Cohort study	300	11.3 years	1.78 2.22	1.10 1.20	2.88 4.08	36.8 vs. 9.5 µg/d, all 36.8 vs. 9.5 µg/d, never smokers

Table 74 Overall evidence on acrylamide and ovarian cancer

SLR	Summary of evidence
2005 SLR	No cohort studies reported on dietary acrylamide and ovarian cancer.
Continuous Update Project	Three cohort studies had reported on dietary acrylamide and ovarian cancer. Two studies reported no significant association and one study reported a positive significant association for the highest vs lowest category that was stronger in never smokers

Table 75 Summary of results of the dose-response meta-analysis of dietary acrylamide and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1084
RR (95% CI)	-	1.07 (0.94-1.21)
Quantity	-	Per 10 µg/d
Heterogeneity (I^2, p-value)	-	43%, p=0.18

*No meta-analysis was conducted in the 2nd report

Table 76 Summary of results of the dose-response meta-analysis of dietary acrylamide and ovarian cancer in never smokers

Ovarian cancer	
	Continuous Update Project in never smokers
Studies (n)	3
Cases (n)	360
RR (95% CI)	1.14 (1.00-1.30)
Quantity	Per 10 μg/d
Heterogeneity (I^2, p-value)	0%, p=0.64

Table 77 Inclusion/exclusion table for meta-analysis of dietary acrylamide and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11619	Wilson	2010	Prospective cohort	Nurses' Health Study	Incidence	No	Yes	Yes	-	-
OVA11617	Larsson	2009	Prospective cohort	Swedish Mammography Cohort	Incidence	No	Yes	Yes	-	-
OVA11622	Hogervorst	2007	Case cohort	Netherlands Cohort Study	Incidence	No	Yes	Yes	-	-

Figure 69 Highest versus lowest forest plot of dietary acrylamide and ovarian cancer

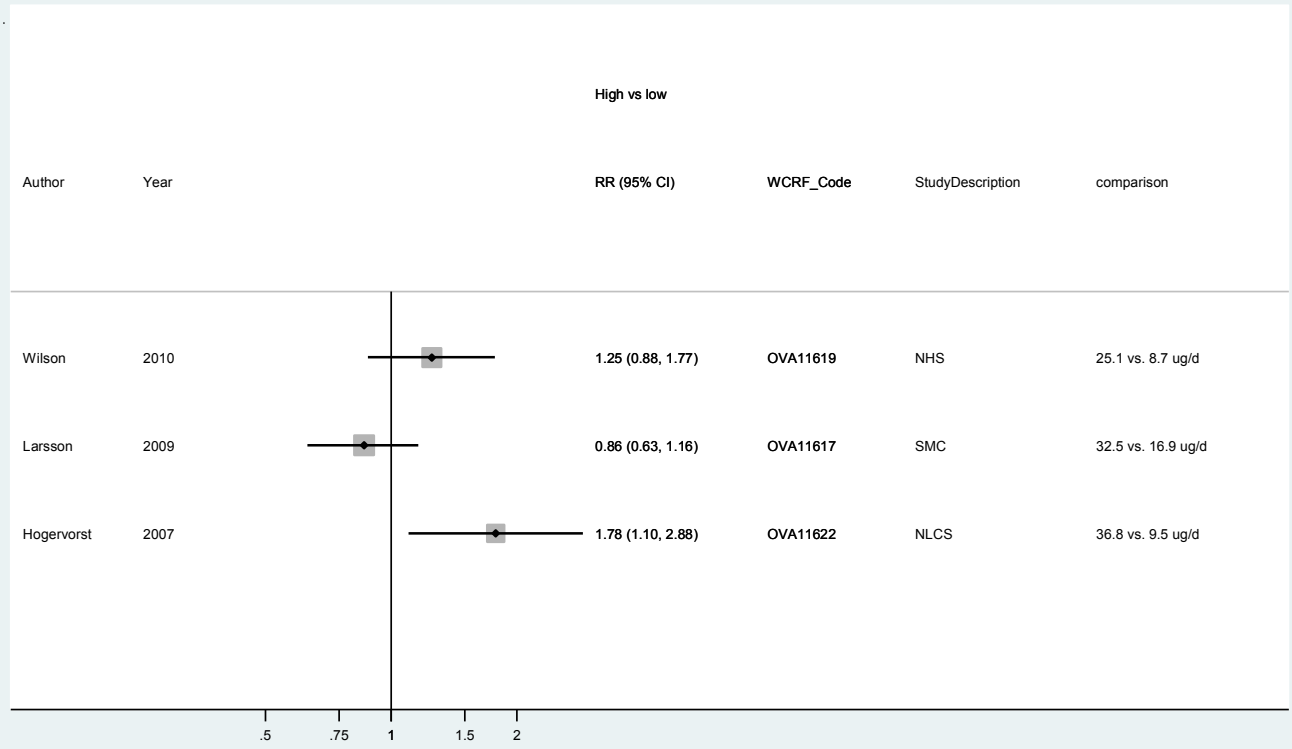


Figure 70 Dose-response meta-analysis of dietary acrylamide and ovarian cancer, per 10 µg/d

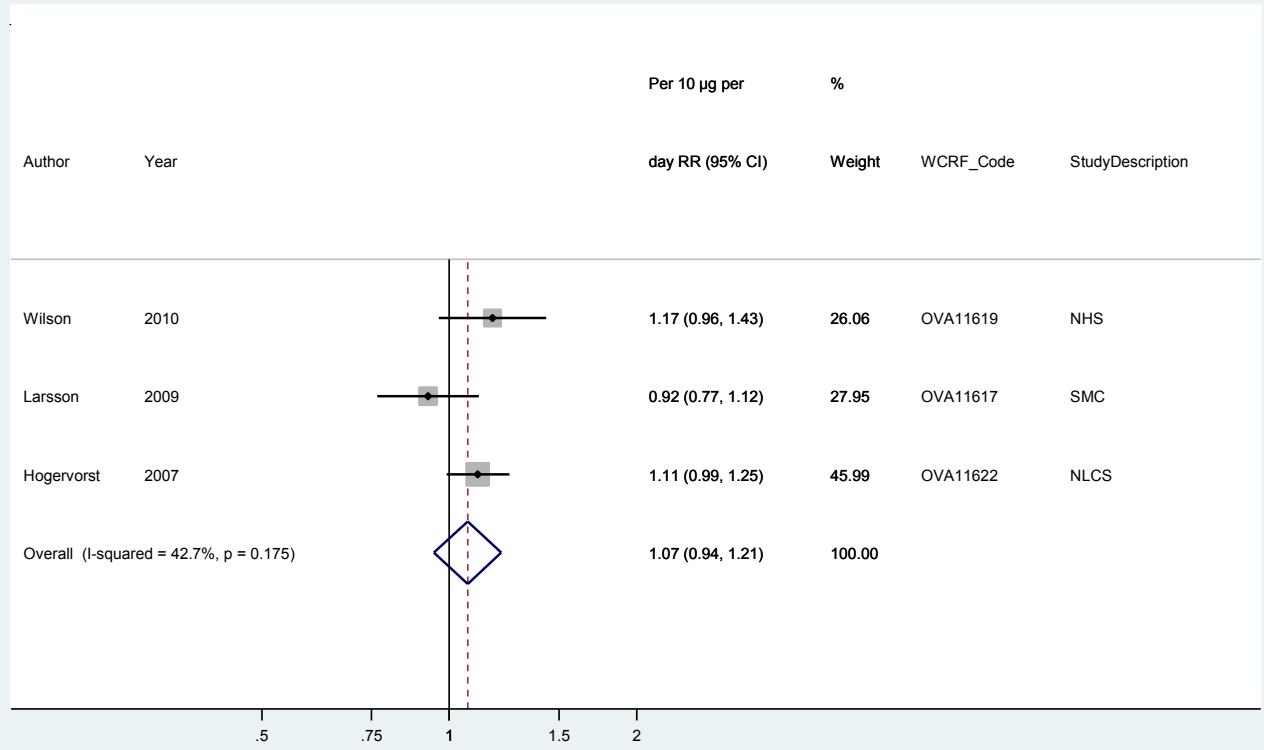


Figure 71 Dose-response graph of acrylamide and ovarian cancer

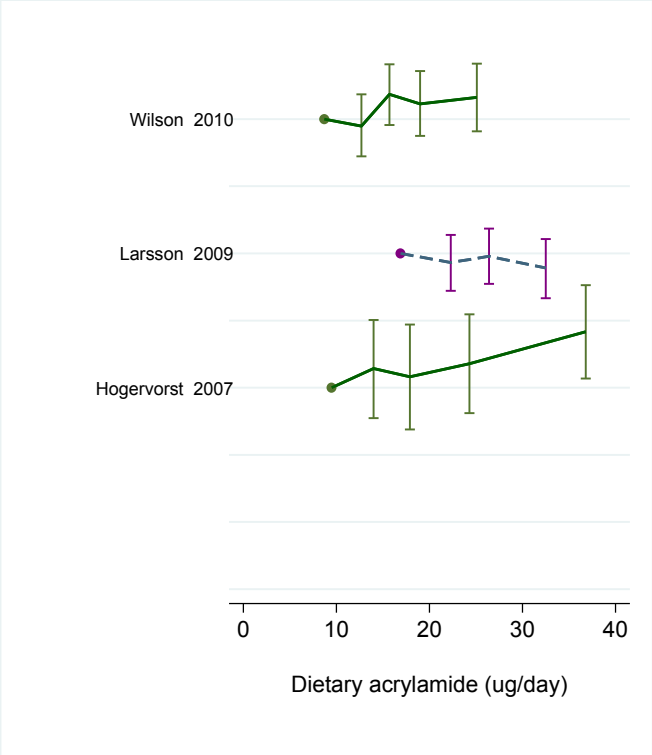
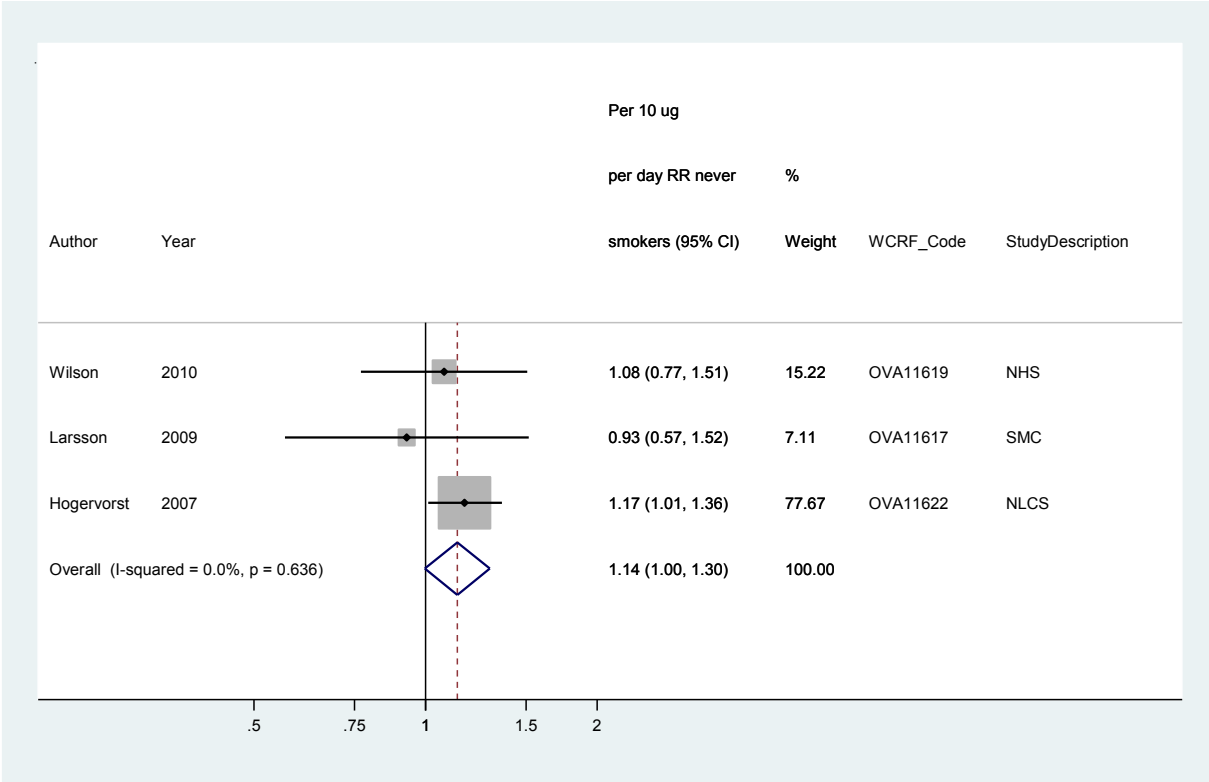


Figure 72 Dose-response meta-analysis of dietary acrylamide and ovarian cancer in never smokers, per 10 µg/d



5 Dietary constituents

5.1.2 Dietary fibre

Methods

Up to December 2012, four cohort studies were identified, three of which were identified during the Continuous Update Project. One study had no intake level data and was only used for high versus low analysis. In Hedelin et al, 2010 study fibre intake was converted from g/day/MJ to g/day using the energy intake provided in the study. Dose-response analyses were conducted per 5 gram/day increase.

Main results

The summary RR per 5 grams/day was 0.94 (95% CI: 0.84 - 1.05, $I^2 = 0$ %, $P_{heterogeneity} = 0.81$) for all studies combined. In influence analysis, the RR did not change significantly when any of the three studies were excluded.

Heterogeneity

There was no heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.81$). Egger's tests suggested no evidence of publication bias (p = 0.94).

Table 78 Studies on dietary fibre identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Hedelin, 2010	Sweden	Women's Lifestyle and Health Study	163	16	0.82	0.50	1.35	69.3 vs. 0 g/day
Chang, 2007	USA	California Teachers Study 1995	280	8.1	1.24	0.84	1.84	Q5 vs. Q1
Silvera, 2007	Canada	Canadian National Breast Screening Study	264	16.4	0.77	0.52	1.14	>24 vs. <15.6 g/day

Table 79 Overall evidence on dietary fibre and ovarian cancer

	Summary of evidence
SLR	One study which was identified during the SLR and found no association with ovarian cancer.
Continuous Update Project	Three cohort studies were identified; none of them reported any association. Two studies could be included in the meta-analysis. Overall, three studies were included in the meta-analysis.

Table 80 Summary of results of the dose response meta-analysis of dietary fibre intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	566
Increment unit used	-	Per 5g/day
Overall RR (95%CI)	-	0.94 (0.84 - 1.05)
Heterogeneity (I^2,p-value)	-	0 %, p=0.81

*No meta-analysis was conducted in the 2nd report

Table 81 Inclusion/exclusion table for meta-analysis of dietary fibre intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11620	Hedelin	2010	Prospective Cohort study	Women's Lifestyle and Health Study	Incidence	No	Yes	Yes	Mean intake in g/d/MJ rescaled to g/d, mid-exposure values	-
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study, 1995	Incidence	No	No	Yes	-	Only high vs. low data
OVA11640	Silvera	2007	Prospective Cohort study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	-

Figure 73 Highest versus lowest forest plot dietary fibre intake and ovarian cancer

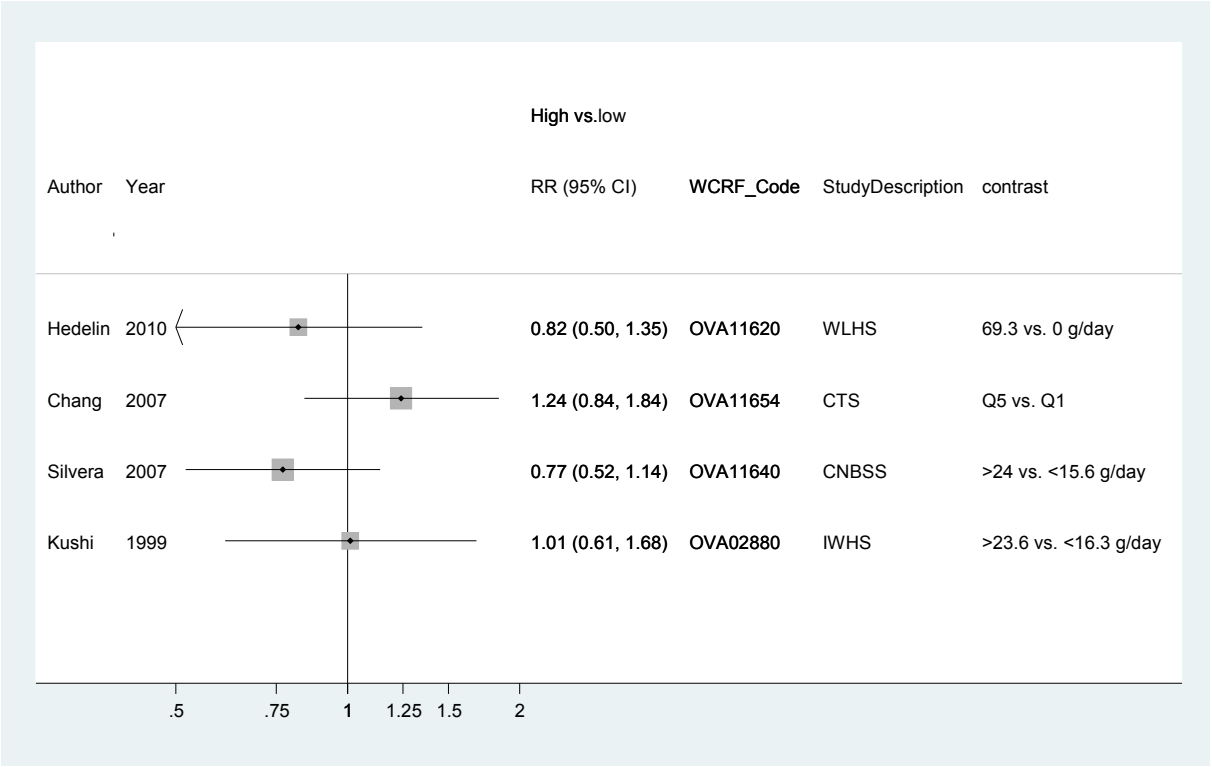


Figure 74 Dose-response meta-analysis of dietary fibre intake and ovarian cancer - per 5 grams/day

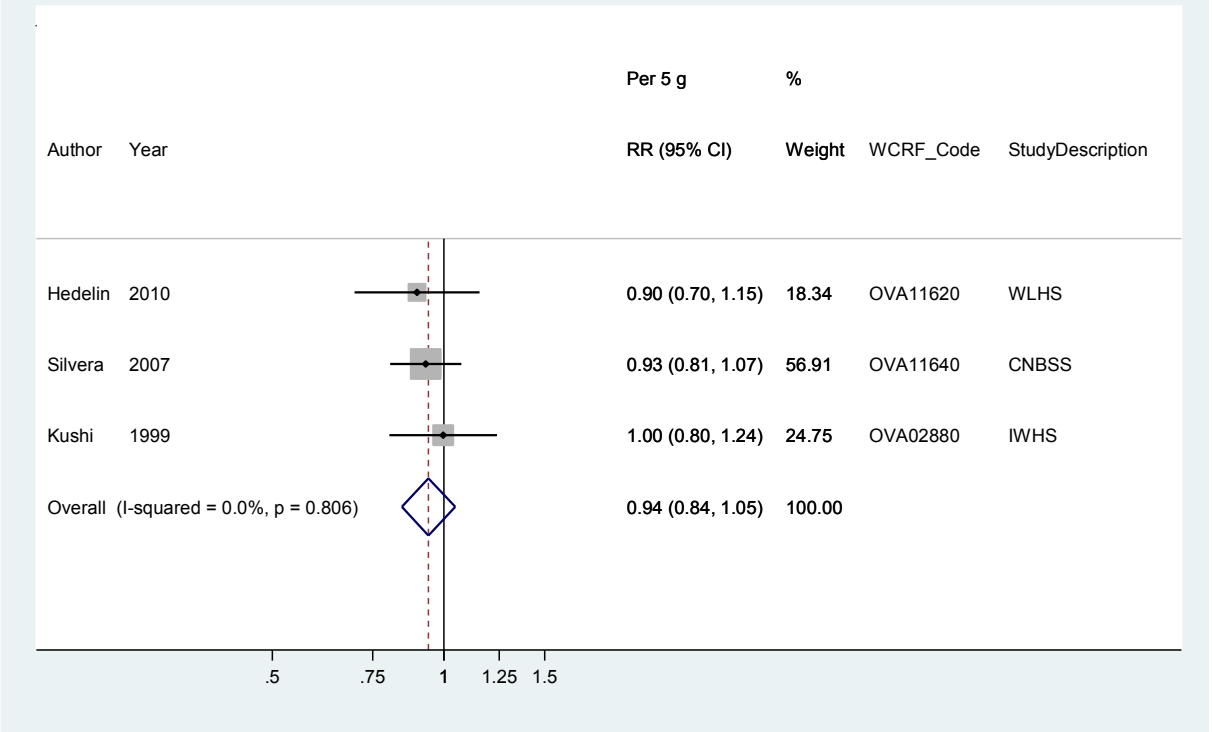


Figure 75 Funnel plot of dietary fibre intake and ovarian cancer

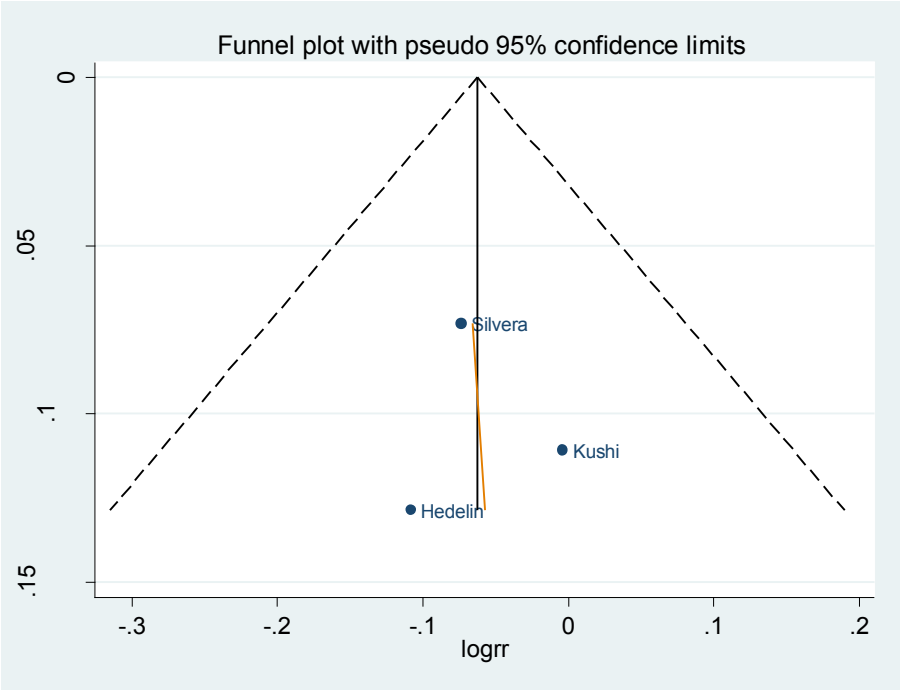
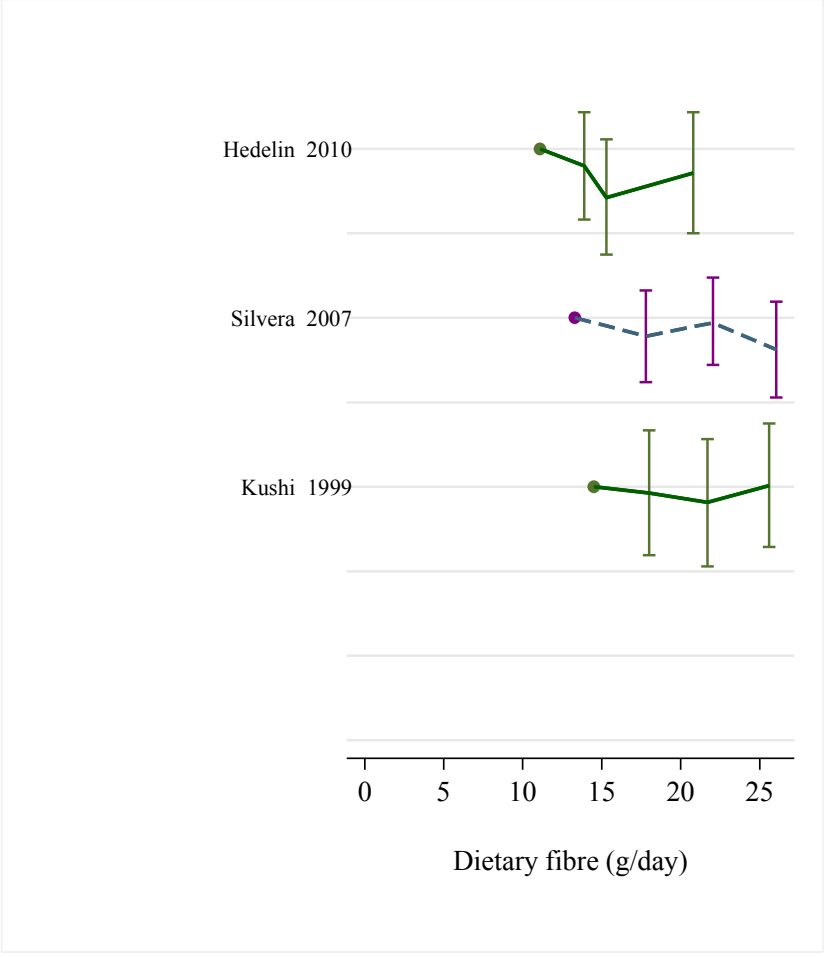


Figure 76 Dose-response graph of dietary fibre intake and ovarian cancer



5.1.4 Lactose

Summary

A total of 6 cohort studies have been published on lactose and ovarian cancer risk up to 2012, two of which were identified in the CUP. Dose-response analyses were conducted per 10 g/d.

Main results

The summary RR per 10 g/d of lactose was 1.03 (95% CI: 0.94-1.13, I^2=40.0%, $p_{heterogeneity}$=0.14). There was no evidence of publication bias with Egger's test, p=0.40.

Heterogeneity

There was moderate heterogeneity, I^2=40.0%, $p_{heterogeneity}$=0.14.

Published pooled analysis and meta-analyses

A meta-analysis of nine case-control studies and one cohort study found a summary RR of 0.94 (95% CI: 0.72-1.24) for high vs. low lactose intake and ovarian cancer risk (Qin et al, 2005).

A meta-analysis of nine case-control studies and three cohort studies found no association between lactose intake and ovarian cancer risk in the overall analysis, summary RR = 1.01 (95% CI: 0.85-1.21, I^2=54.6%, $p_{heterogeneity}$=0.01), however, there was a positive association among the three cohort studies, summary RR=1.47 (95% CI: 1.17-1.84, I^2=0%, $p_{heterogeneity}$=0.92) (Larsson et al, 2006).

A pooled analysis of 12 cohort studies found a pooled RR=1.19 (95% CI: 1.01-1.40, $p_{heterogeneity}$=0.58) for ≥30 vs. <10 g/d of lactose (Genkinger et al, 2006). The RR for an increment of 10 g was 1.04 (95% CI: 0.99-1.08). All the studies in the CUP meta-analysis were included in the pooled analysis.

Table 82 Table of results of new studies

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Kiani, 2006	USA	Adventist Health Study	71	~16 years	0.78	0.61	1.04	Per 83.7 g/wk
Koralek, 2006	USA	Breast Cancer Detection Demonstration Project	146	8.3 years	0.88	0.47	1.65	22.5 vs. 4.4 g/d

Table 83 Table of the overall evidence

SLR	Summary of evidence
2005 SLR	Four cohort studies reported on lactose and ovarian cancer and found no significant associations between lactose intake and ovarian cancer risk (two of these showed non-significantly increased risks).
Continuous Update Project	Two additional studies reported on lactose and ovarian cancer risk and found no significant association. In a pooled analysis of 12 cohort studies the RR for 10 g increase of lactose intake was 1.04 (95% CI: 0.99-1.08).

Table 84 Summary of results of the dose-response meta-analysis of lactose intake and ovarian cancer in the 2nd Report and in the Continuous Update Project.

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	6
Cases (n)	-	1175
RR (95% CI)	-	1.03 (0.94-1.13)
Quantity	-	Per 10 g/d
Heterogeneity (I^2, p-value)	-	40.0%, p=0.14

*No meta-analysis was conducted in the 2nd report

Table 85 Inclusion/exclusion table of lactose and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11647	Kiani	2006	Prospective study	Adventist Health Study	Incidence	No	Yes	No	-	Only continuous estimates
OVA11662	Koralek	2006	Prospective study	Breast Cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Distribution of person-years	
OVA09788	Mommers	2006	Prospective study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	-	
OVA11491	Fairfield	2004	Prospective study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	
OVA10870	Larsson	2004	Prospective study	Swedish Mammography Cohort	Incidence	Yes	Yes	No	-	Continuous estimates, high vs. low comparison only for serous ovarian cancer (not total ovarian cancer)
OVA02880	Kushi	1999	Prospective study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Distribution of person-years, midpoints	

Figure 77 Lactose and ovarian cancer, cancer, highest vs. lowest

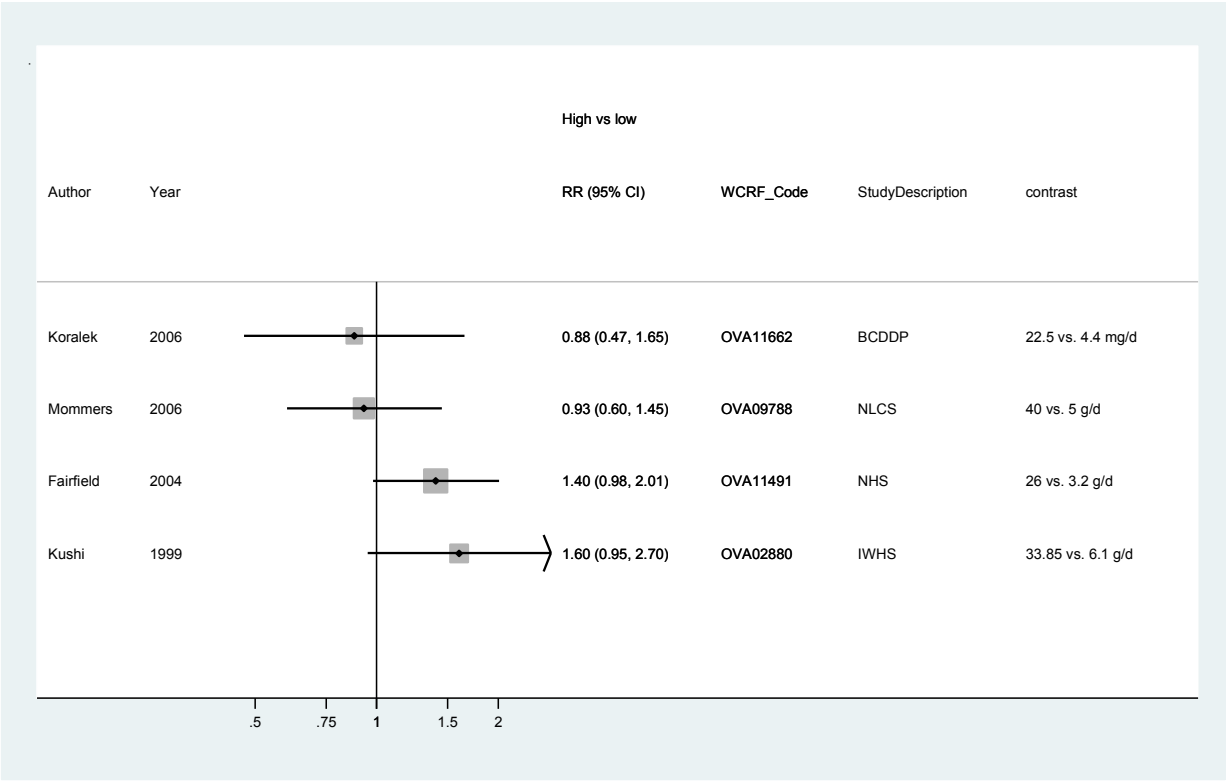


Figure 78 Lactose and ovarian cancer, dose-response per 10 g/d

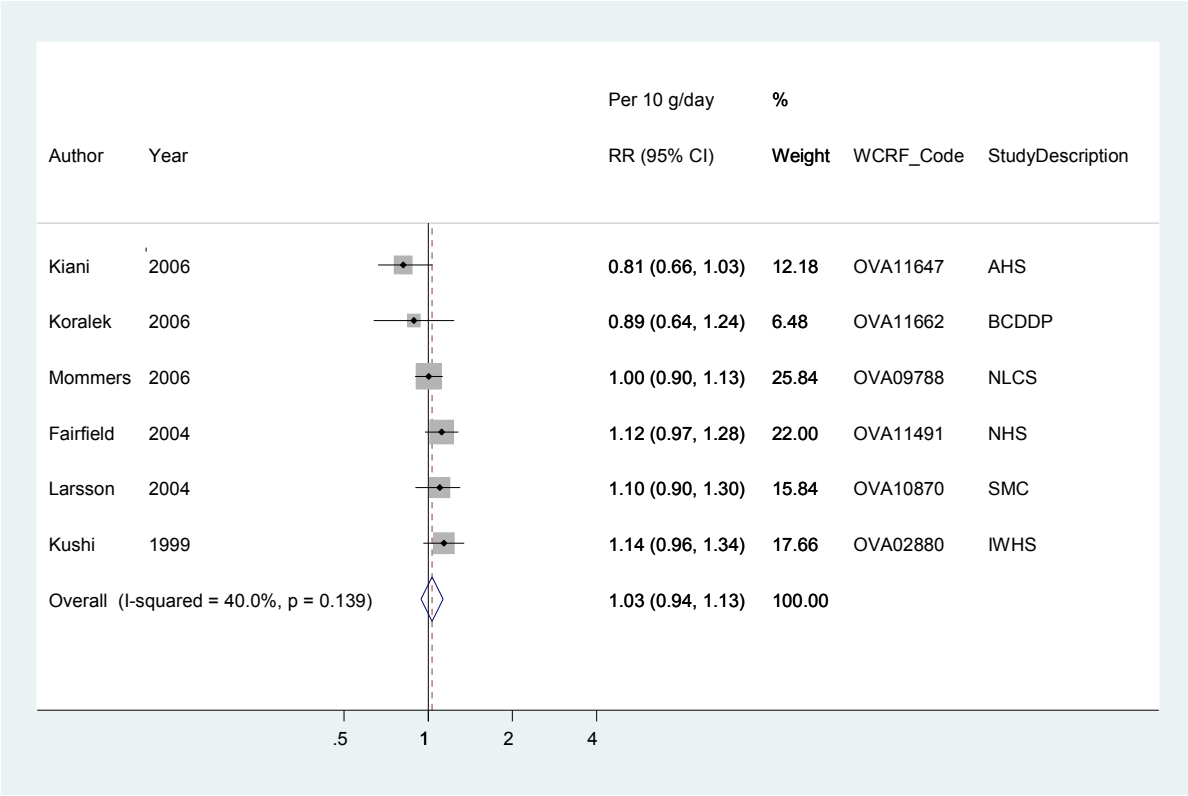


Figure 79 Dose-response graph of lactose and ovarian cancer

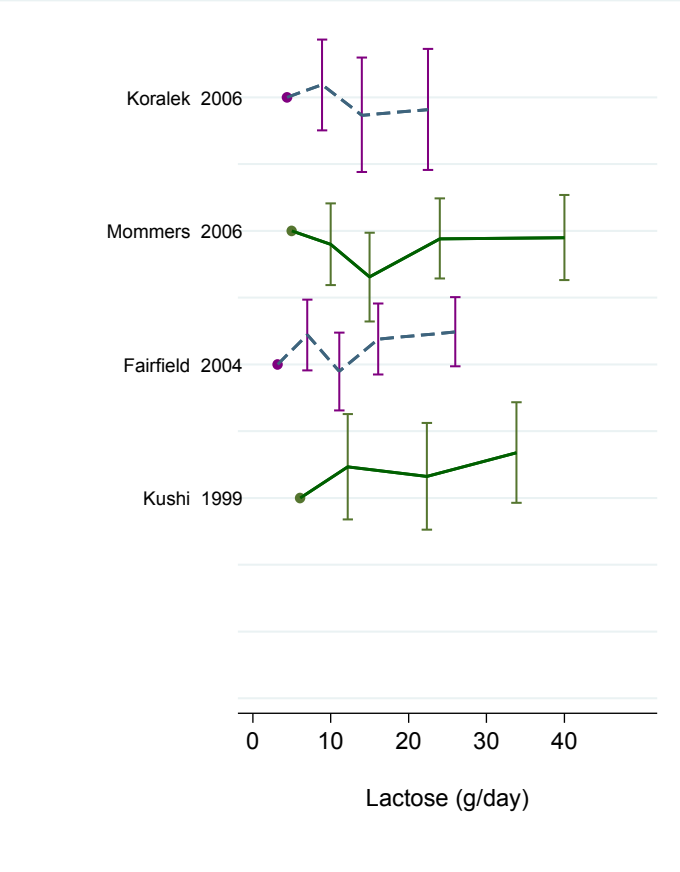
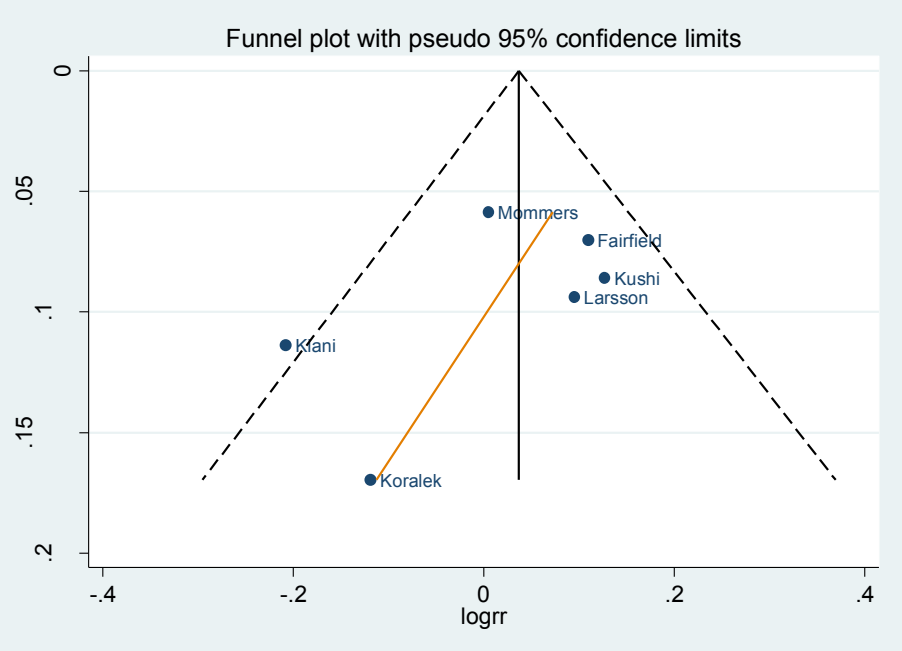


Figure 80 Funnel plot of lactose and ovarian cancer



5.2.1 Total fat

Methods

Up to December 2012, five cohort studies were identified, three of which were identified during the Continuous Update Project. One study had no data intake levels and was only used for high versus low analysis. In one study (Blank et al, 2012) the percentage of kcal from fat by intake category was rescaled to g/day using calorie intake per category reported in the paper. Dose-response analyses were conducted per 10 gram/day increase. Four studies were included in the dose-response meta-analysis.
The dose-response RR estimate of one study identified in the CUP (NIH-AARP) was combined with the overall estimate of a pooled analysis of 12 cohorts (Genkinger et al, 2006).

Main results

The summary RR per 10 grams/day was 1.03 (95% CI: 0.99 - 1.07, $I^2 = 0\%$, $P_{heterogeneity} = 0.44$) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.93 – 1.06) when excluding the NIH-AARP Diet and Health Study to 1.04 (95% CI: 0.99-1.09) when excluding the Nurses' Health Study (NHS) Cohort 1976-1996.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.44$). Egger's test detected some evidence for small study bias ($p = 0.04$).

Published pooled analysis

A published pooled analysis of 12 prospective cohort studies reported a pooled multivariate RR = 1.08 (95% CI: 0.86-1.34) when comparing total fat intakes of >45% to 30-<35% of calories from fat. The age-, energy- adjusted and measurement error corrected RR for an increment of 5% of energy from total fat was 1.01 (95% CI: 0.93-1.09) (Genkinger et al, 2006).

When the results of the NIH-AARP (Blank et al, 2012) were combined with the pooled analysis by Genkinger et al, 2006, the overall RR for 5% increase of energy from fat was 1.03 (95% CI: 0.99-1.07). The other study identified in the CUP did not provide the data needed to be included in this analysis.

Table 86 Studies on total fat identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Chang, 2007	USA	California Teachers Study 1995	280	8.1	0.85	0.58	1.24	Q5 vs. Q1
Gilsing, 2011	The Netherlands	The Netherlands Cohort study	340	16.3	1.06 1.01	0.73 0.9	1.49 1.13	86.5g/day vs. <61.0 g/day Per 10.3g/day intake
Blank, 2012	USA	NIH- AARP Diet and Health Study	695	9	1.28	1.01	1.63	75.7 g/day vs. 32.4g/day

Table 87 Overall evidence on total fat and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR. Both studies found no association between total fat intake and ovarian cancer risk.
Continuous Update Project	Three cohort studies were identified, two of which could be included in the meta-analysis. Two studies reported no association. Only the NIH-AARP study (Blank et al, 2012) reported a positive significant association. Overall, four studies were included in the meta-analysis. No association with % of energy from fat was observed in a pooled analysis of 12 prospective cohort studies.

Table 88 Summary of results of the dose response meta-analysis of total fat intake and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1475
Increment unit used	-	Per 10g/day
Overall RR (95%CI)	-	1.03 (0.99 - 1.07)
Heterogeneity (I^2,p-value)	-	0 %, p=0.44
NIH-AARP and pooled analysis		12 cohorts
Studies (n)		13
Cases (n)		2827
Increment unit used		Per 5 % energy
Overall RR (95%CI)		1.01 (0.93-1.09)

*No meta-analysis was conducted in the 2nd report

Table 89 Inclusion/exclusion table for meta-analysis of total fat intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11675	Blank	2012	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Percentage of kcal from fat rescaled to g/day using calorie intake per category; mid-exposure values	
OVA11616	Gilsing	2011	Case-Cohort	The Netherlands Cohort study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study 1995	Incidence Invasive or borderline ovarian cancer	No	No	Yes	-	No intake amounts per category
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	Yes	Yes	Person/ years per category	
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	

Figure 81 Highest versus lowest forest plot of total fat intake and ovarian cancer

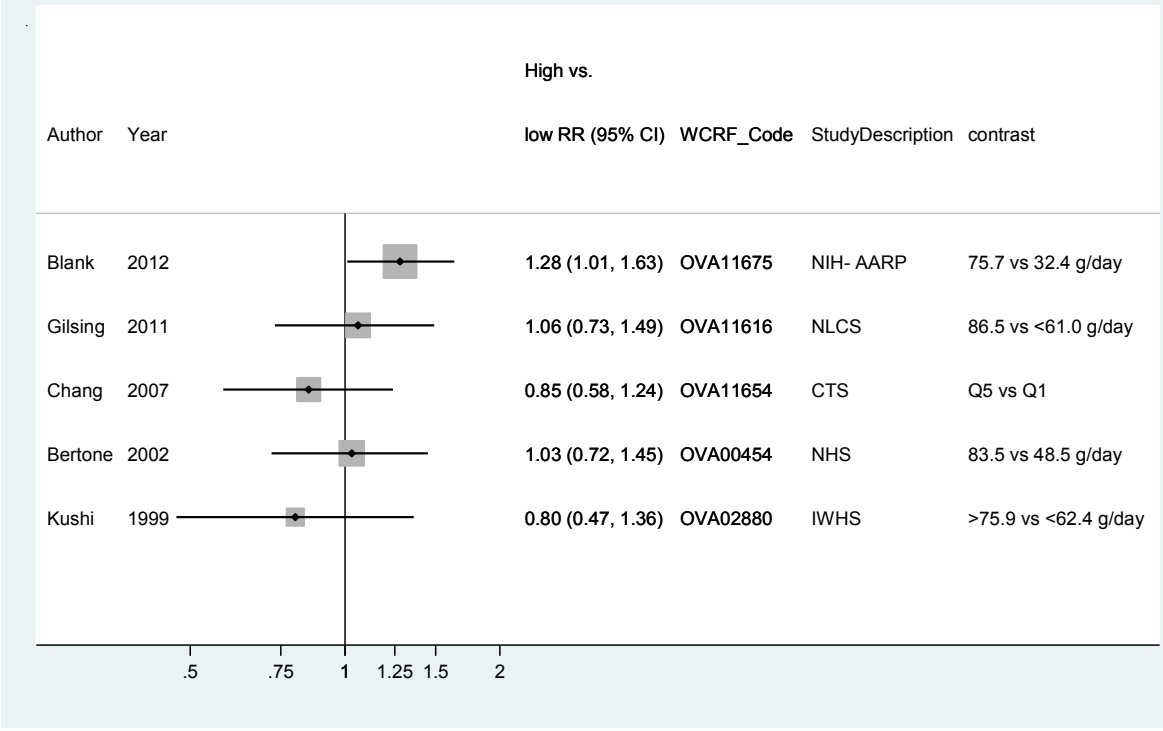


Figure 82 Dose-response meta-analysis of total fat intake and ovarian cancer - per 10 grams/day

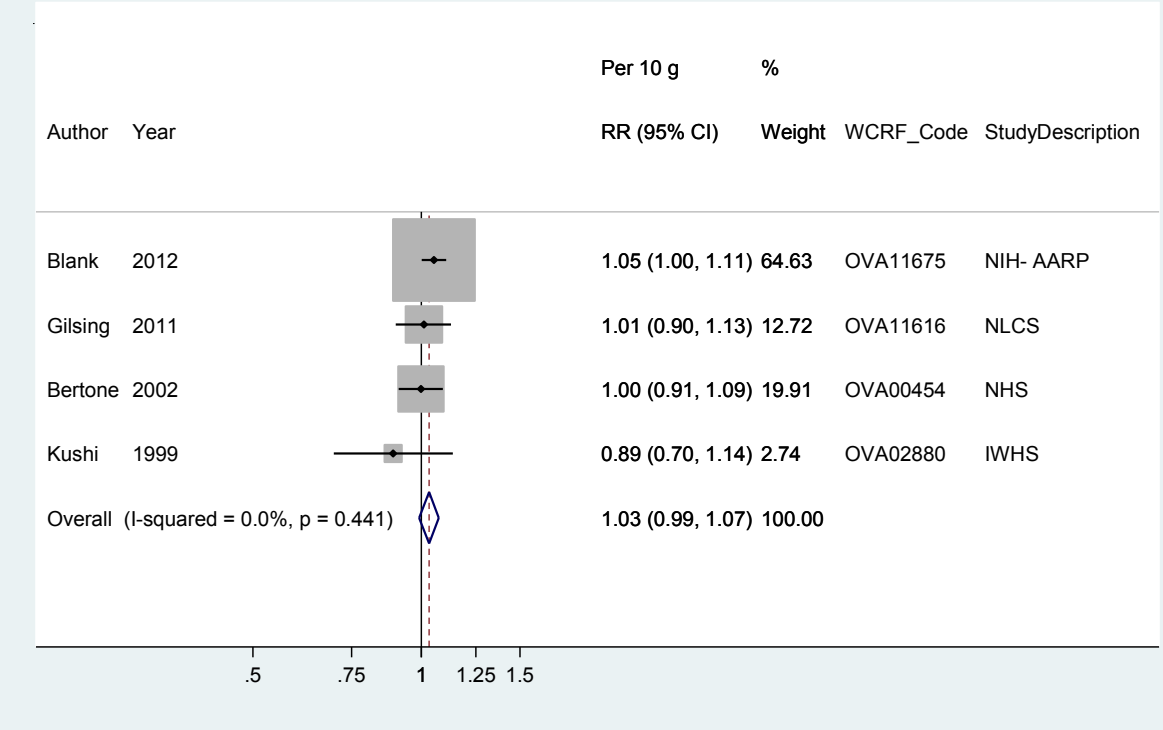


Figure 83 Funnel plot of total fat intake and ovarian cancer

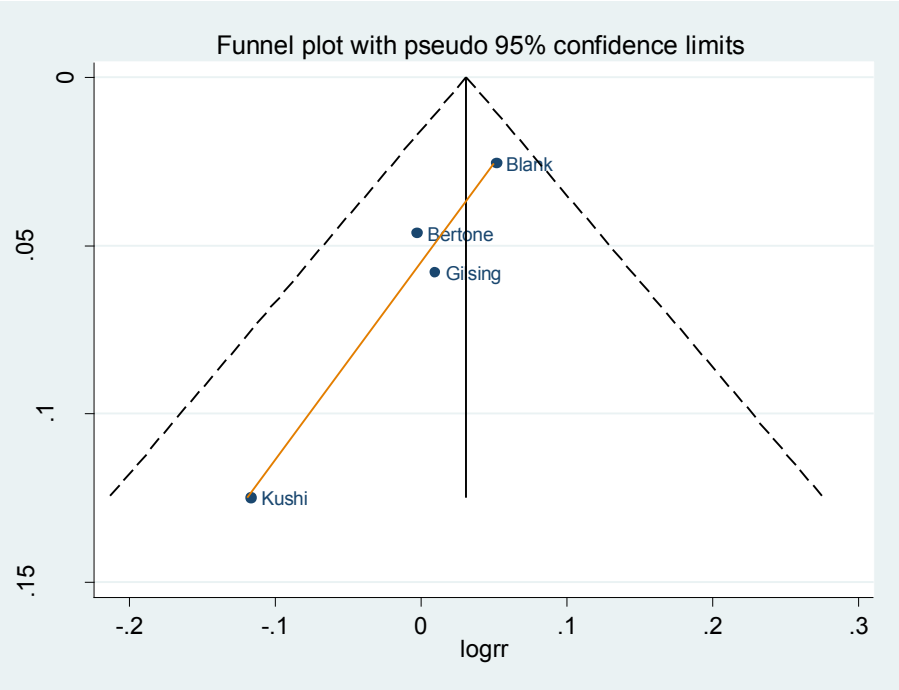
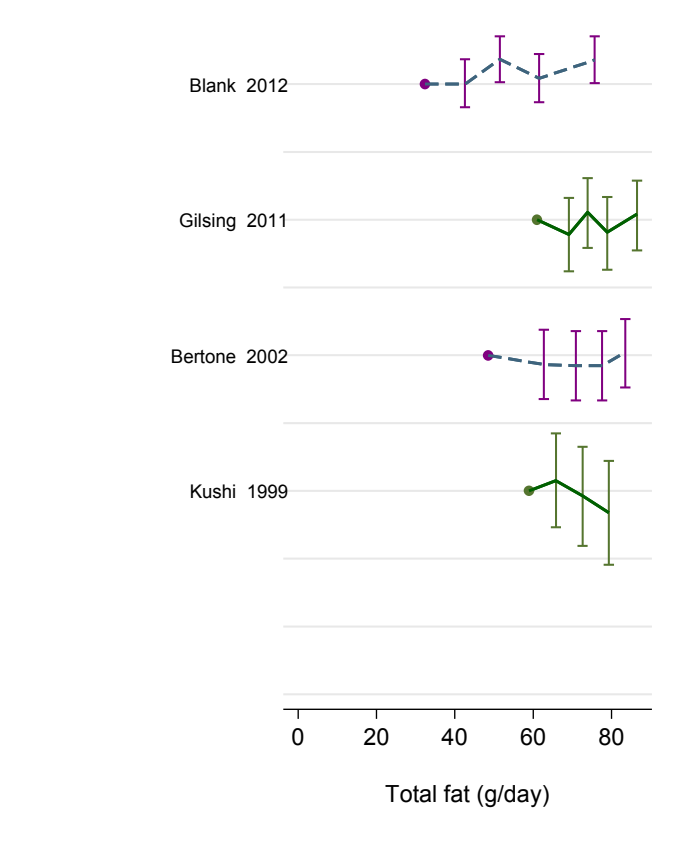


Figure 84 Dose-response graph of total fat intake and ovarian cancer



5.2.2 Saturated fat

Methods

Up to December 2012, five cohort studies were identified, three of which were identified during the Continuous Update Project. Two studies had no intake level data and were only used for high vs. low analysis. Dose-response analyses were conducted per 5 gram/day increase. The dose-response RR estimate of one study identified in the CUP (NIH-AARP) was combined with the overall estimate of a pooled analysis of 12 cohorts (Genkinger et al, 2006).

Main results

The summary RR per 5 grams/day was 1.07 (95% CI: 0.95 - 1.20, $I^2 = 41.7$ %, $P_{heterogeneity} = 0.18$) for all studies combined. In influence analysis, the RR ranged from 1.01 (95% CI: 0.91 – 1.12) when excluding the Netherlands Cohort study to 1.14 (95% CI: 1.01-1.29) when excluding the NIH- AARP Diet and Health Study.

Heterogeneity

There was moderate heterogeneity across the limited number of published studies ($I^2 = 41.7\%$, $P_{heterogeneity} = 0.18$). Egger's tests suggested no evidence of publication bias ($p = 0.99$).

Published pooled analysis

In a published pooled analysis of 12 prospective studies the summary pooled multivariate RR of ovarian cancer for highest versus lowest decile was 1.29 (95% CI: 1.01-1.66) and 1.14 (95% CI: 0.97-1.34) for highest versus lowest quintile. Pooled age, energy adjusted, and measurement error corrected RR was 1.14 (95% CI: 0.94-1.38) for an increment of 5% in energy intake from saturated fat and there was no significant evidence of heterogeneity (test for heterogeneity = 0.26) (Genkinger et al, 2006).

When the CUP added the results of the NIH-AARP (Blank et al, 2012) to the pooled analysis by Genkinger et al, 2006, the overall RR for 5% increase in energy intake from saturated fat was 1.07 (95% CI: 0.99-1.15). The other study identified in the CUP did not provide data to be included in this analysis.

Table 90 Studies on saturated fat identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Chang, 2007	USA	California Teachers Study 1995	280	8.1	0.72	0.48	1.08	Q5 vs. Q1
Gilsing, 2011	The Netherlands	The Netherlands Cohort study	340	16.3	1.48	0.94	2.34	37.5g/day vs. 23.1 g/day
Blank, 2012	USA	NIH- AARP Diet and Health Study	695	9	1.03	0.71	1.5	25 g/day vs. 9.3 g/day

Table 91 Overall evidence on saturated fat and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR; both studies found no association between saturated fat intake and ovarian cancer.
Continuous Update Project	Three cohort studies were identified; none of them reported any association in categorical analysis. In one of these studies, a significant risk increase was observed when the dose-response was expressed for an increment on 1 standard deviation (Gilsing et al, 2011). Overall, three studies were included in the meta-analysis. The pooled analysis of 13 cohort studies did not provide evidence of association

Table 92 Summary of results of the dose response meta-analysis of saturated fat intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1174
Increment unit used	-	Per 5g/day
Overall RR (95%CI)	-	1.07 (0.95 - 1.20)
Heterogeneity (I^2,p-value)	-	41.7 %, p=0.180
NIH-AARP and pooled analysis		12 cohorts
Studies (n)		13
Cases (n)		2827
Increment unit used		Per 5 % energy
Overall RR (95%CI)		1.07 (0.99-1.15).

*No meta-analysis was conducted in the 2nd report

Table 93 Inclusion/exclusion table for meta-analysis of saturated fat intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11675	Blank	2012	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Percentage of kcal from fat rescaled to g/day using calorie intake per category; mid-exposure values	
OVA11616	Gilsing	2011	Case-Cohort	The Netherlands Cohort study	Incidence	No	Yes	Yes	-	
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study, 1995	Incidence	No	No	Yes	-	Only high vs. low data
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	No	Yes	-	Only high vs. low data
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	

Figure 85 Highest versus lowest forest plot saturated fat intake and ovarian cancer

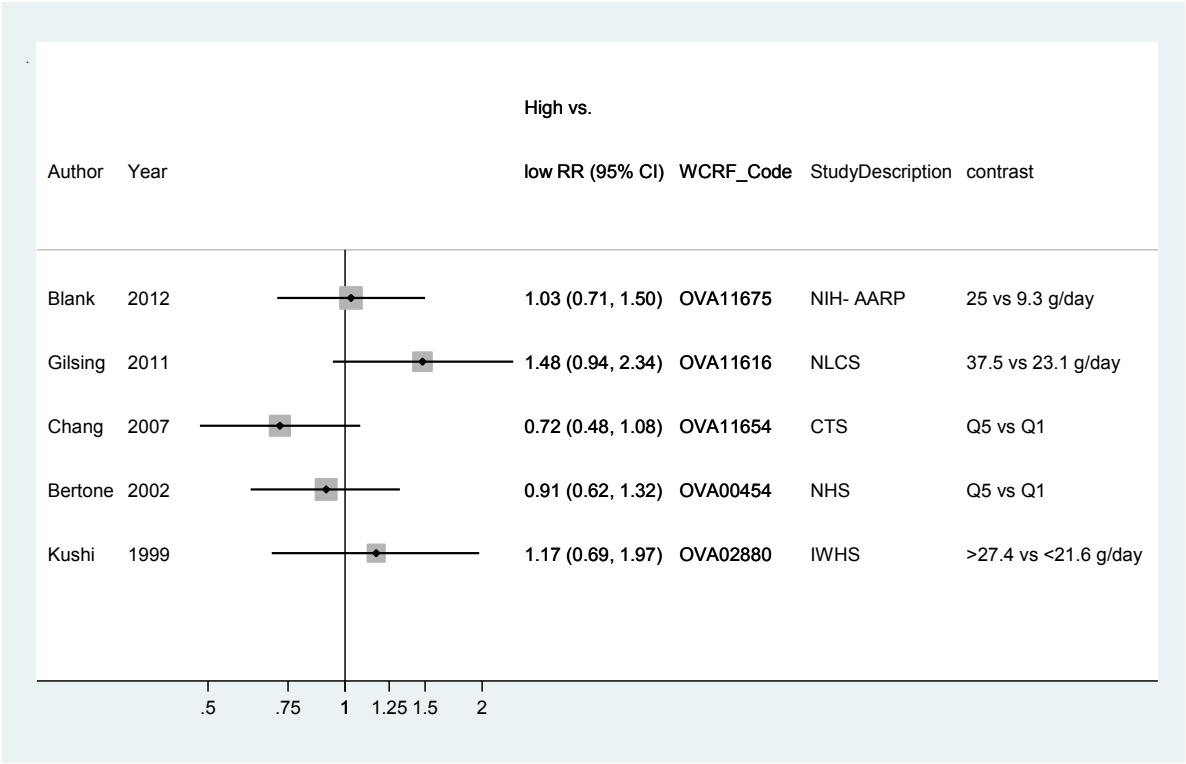


Figure 86 Dose-response meta-analysis of saturated fat intake and ovarian cancer - per 5 grams/day

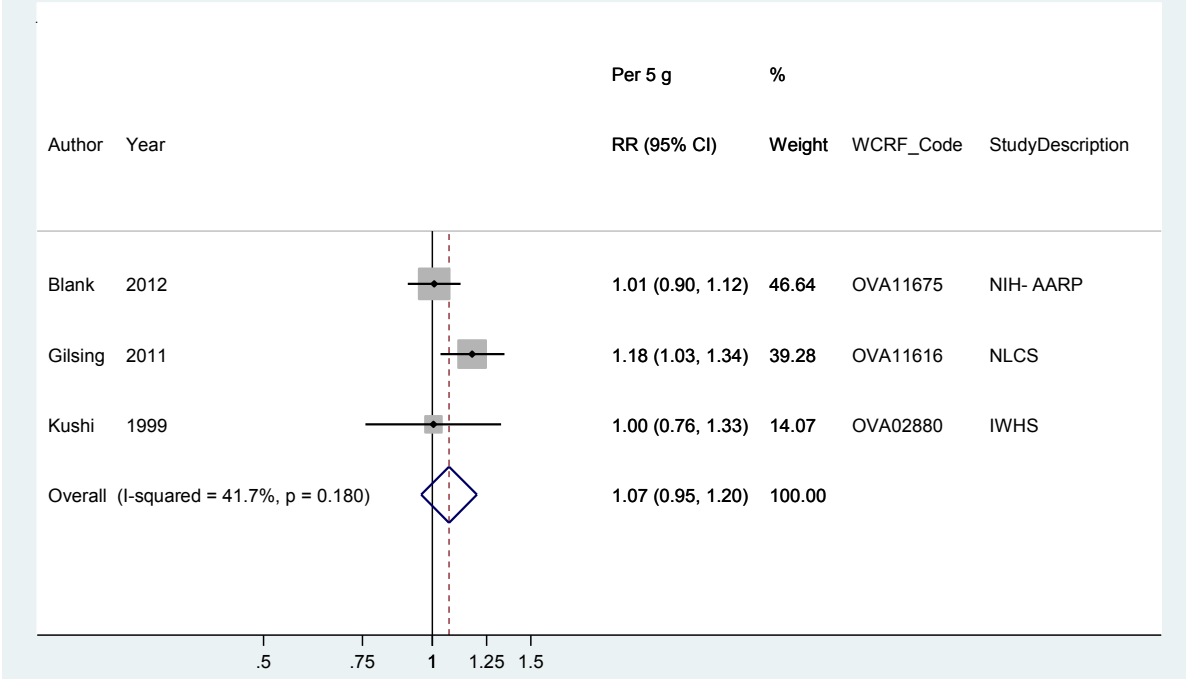


Figure 87 Funnel plot of saturated fat intake and ovarian cancer

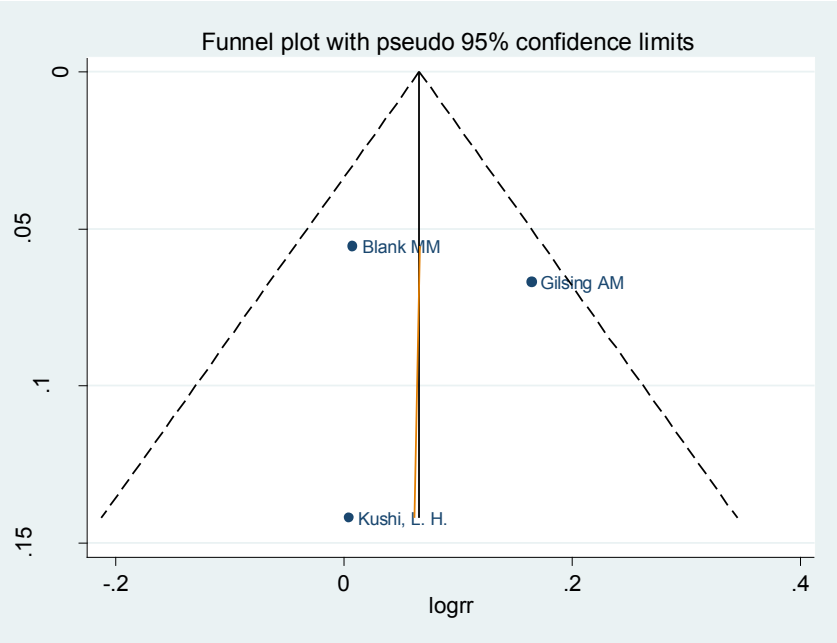
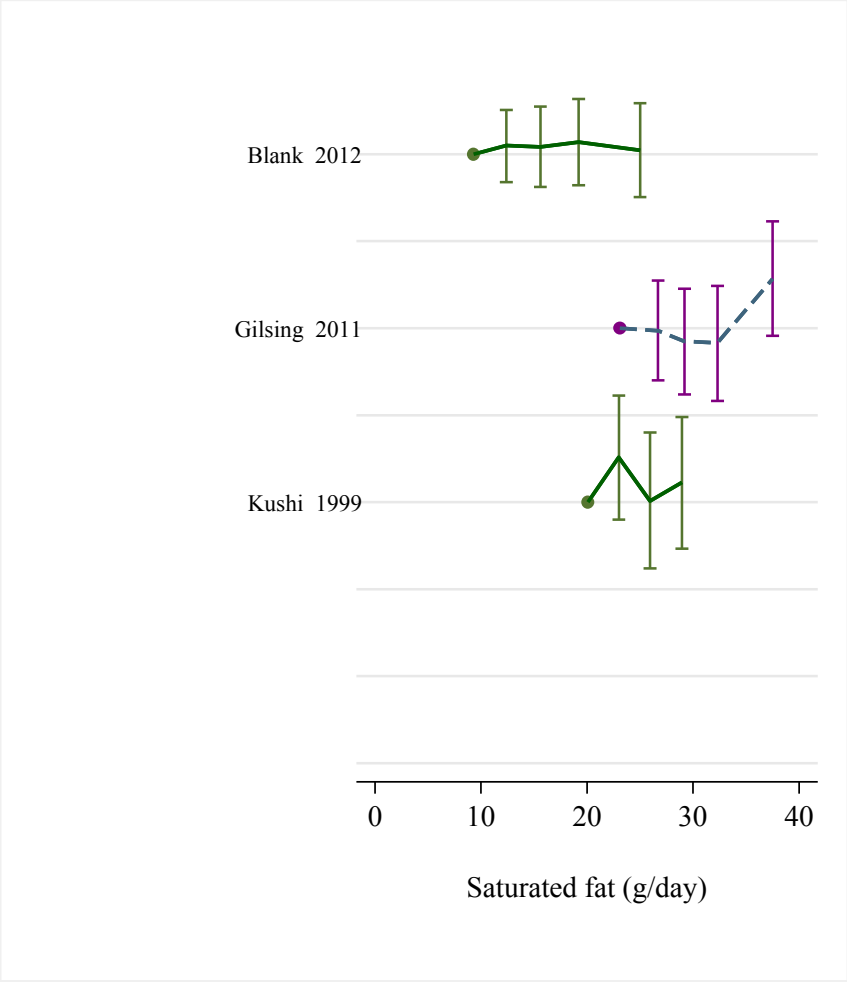


Figure 88 Dose-response graph of saturated fat intake and ovarian cancer



5.2.3 Monounsaturated fat

Methods

Up to December 2012, four cohort studies were identified, two of which were identified during the Continuous Update Project. One study had no exposure data and was only used for high versus low analysis. Dose-response analyses were conducted per 5 gram/day increase. The dose-response RR estimate of one study identified in the CUP (NIH-AARP) was combined with the overall estimate of a pooled analysis of 12 cohorts (Genkinger et al, 2006).
The dose-response RR estimate of one study identified in the CUP (NIH-AARP) was combined with the overall estimate of a pooled analysis of 12 cohorts (Genkinger et al, 2006).

Main results

The summary RR per 5 grams/day was 0.97 (95% CI: 0.88 - 1.06, $I^2 = 0$ %, $P_{heterogeneity} = 0.69$) for all studies combined. In influence analysis, the RR ranged from 0.86 (95% CI: 0.74 – 0.99) when excluding the NIH- AARP Diet and Health Study to 0.98 (95% CI: 0.87-1.10) when excluding the Netherlands Cohort study.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.69$). Egger's tests suggested no evidence of publication bias ($p = 0.57$).

Published pooled analysis

In a published pooled analysis of 12 prospective studies the summary pooled multivariate RR of ovarian cancer for highest versus lowest quintile of monounsaturated fat intake was 0.98 (95% CI: 0.86-1.12). Pooled age, energy adjusted, and measurement error corrected RR was 1.02 (95% CI: 0.82-1.28) for an increment of 5% intake of energy from monounsaturated fat and there was no evidence of heterogeneity (test for heterogeneity = 0.68) (Genkinger et al, 2006).

When the CUP added the results of the NIH-AARP (Blank et al, 2012) to the pooled analysis by Genkinger et al, 2006, the overall RR for 5% increase of energy from monounsaturated fat was 1.00 (95% CI: 0.91-1.10).

Table 94 Studies on monounsaturated fat identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Gilsing, 2011	The Netherlands	The Netherlands Cohort study	340	16.3	0.90 0.85	0.55 0.80	1.46 1.12	33.5 vs. 21.7 g/day Per 1 SD increase
Blank, 2012	USA	NIH- AARP Diet and Health Study	695	9	1.01	0.63	1.6	28.6 vs. 11.6 g/day

Table 95 Overall evidence on monounsaturated fat and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR; Kushi et al, 1999 reported a not significant protective association between monounsaturated fat intake and ovarian cancer.
Continuous Update Project	Two cohort studies were identified. No significant associations were reported. Overall, three studies were included in the meta-analysis. The pooled analysis of 12 cohorts did not find evidence of association.

Table 96 Summary of results of the dose response meta-analysis of monounsaturated fat intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1174
Increment unit used	-	Per 5g/day
Overall RR (95%CI)	-	0.97 (0.88 - 1.06)
Heterogeneity (I^2,p-value)	-	0 %, p=0.69
NIH-AARP and pooled analysis		12 cohorts
Studies (n)		13
Cases (n)		2827
Increment unit used		Per 5 % energy
Overall RR (95%CI)		1.00 (0.91-1.10)

*No meta-analysis was conducted in the 2nd report

Table 97 Inclusion/exclusion table for meta-analysis of monounsaturated fat intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11675	Blank	2012	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Percentage of kcal from fat rescaled to g/day using calorie intake per category; mid-exposure values	
OVA11616	Gilsing	2011	Case-Cohort	The Netherlands Cohort study	Incidence	No	Yes	Yes	-	
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	No	Yes	-	No intake amounts per category
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	

Figure 89 Highest versus lowest forest plot monounsaturated fat intake and ovarian cancer

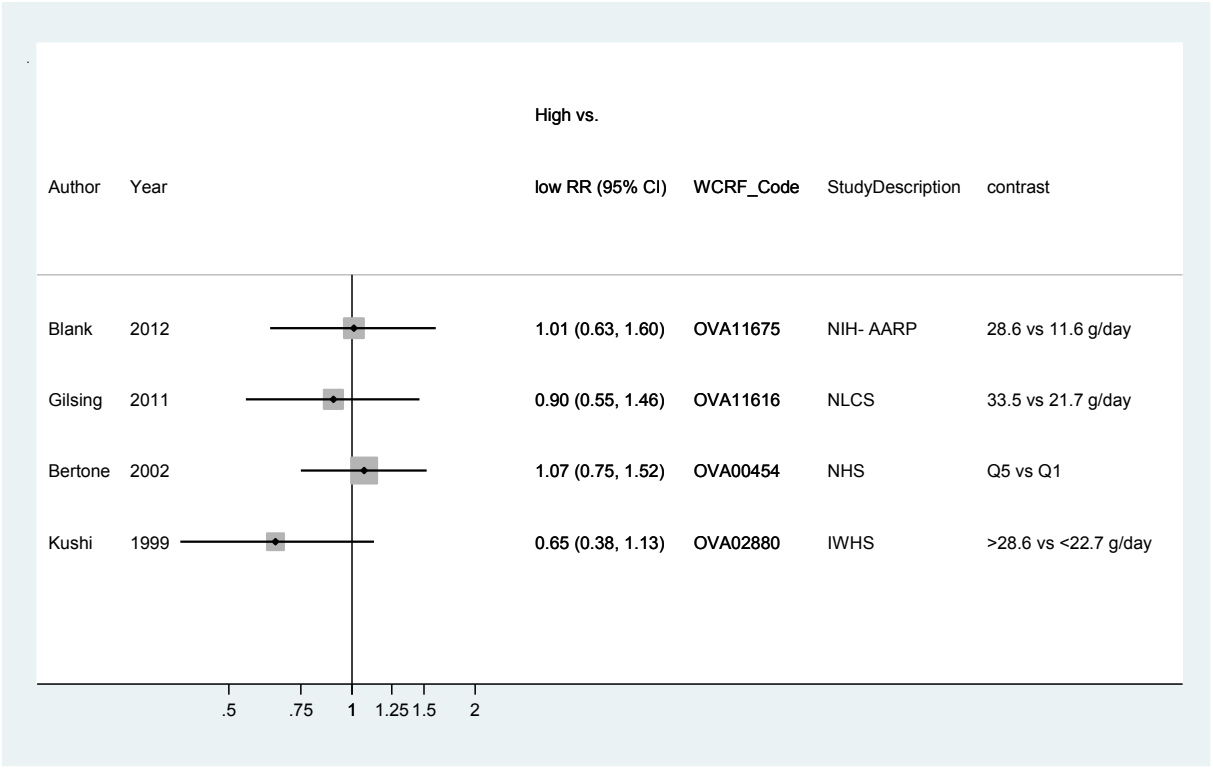


Figure 90 Dose-response meta-analysis of monounsaturated fat intake and ovarian cancer - per 5 grams/day

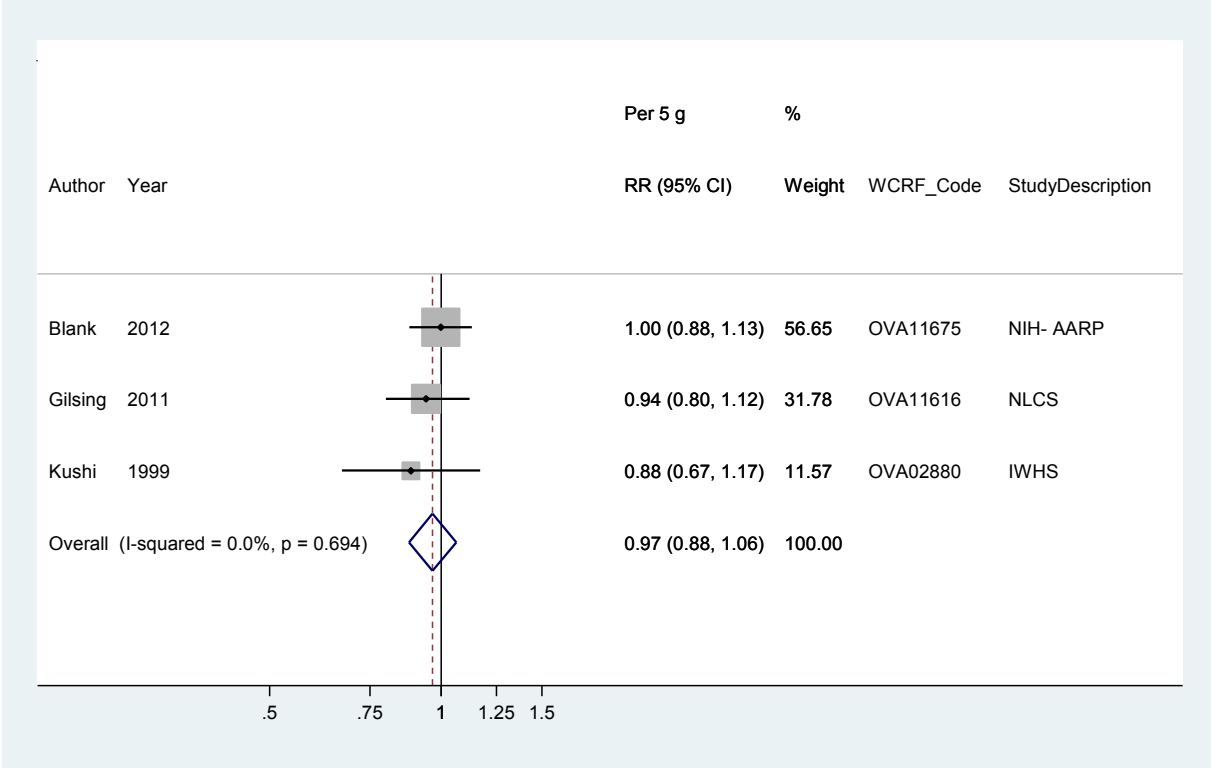


Figure 91 Funnel plot of monounsaturated fat intake and ovarian cancer

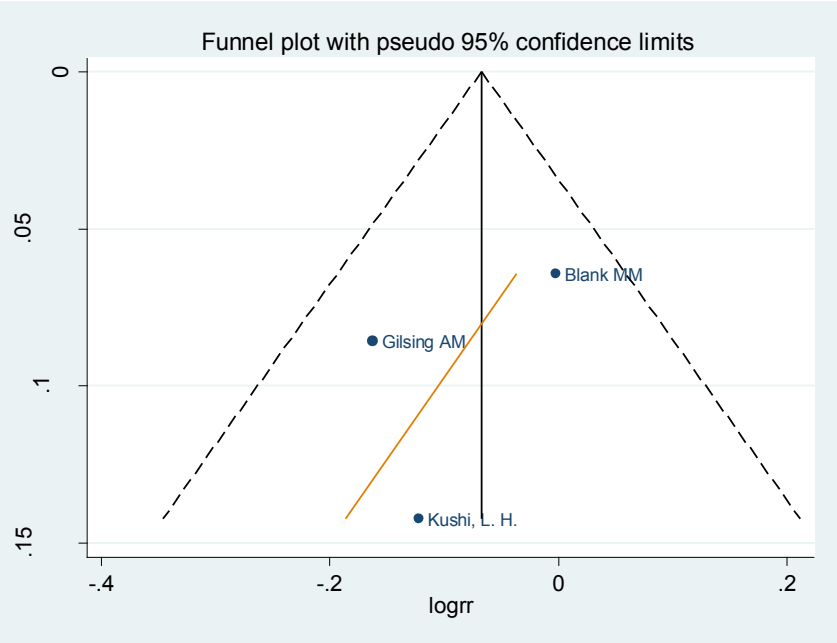
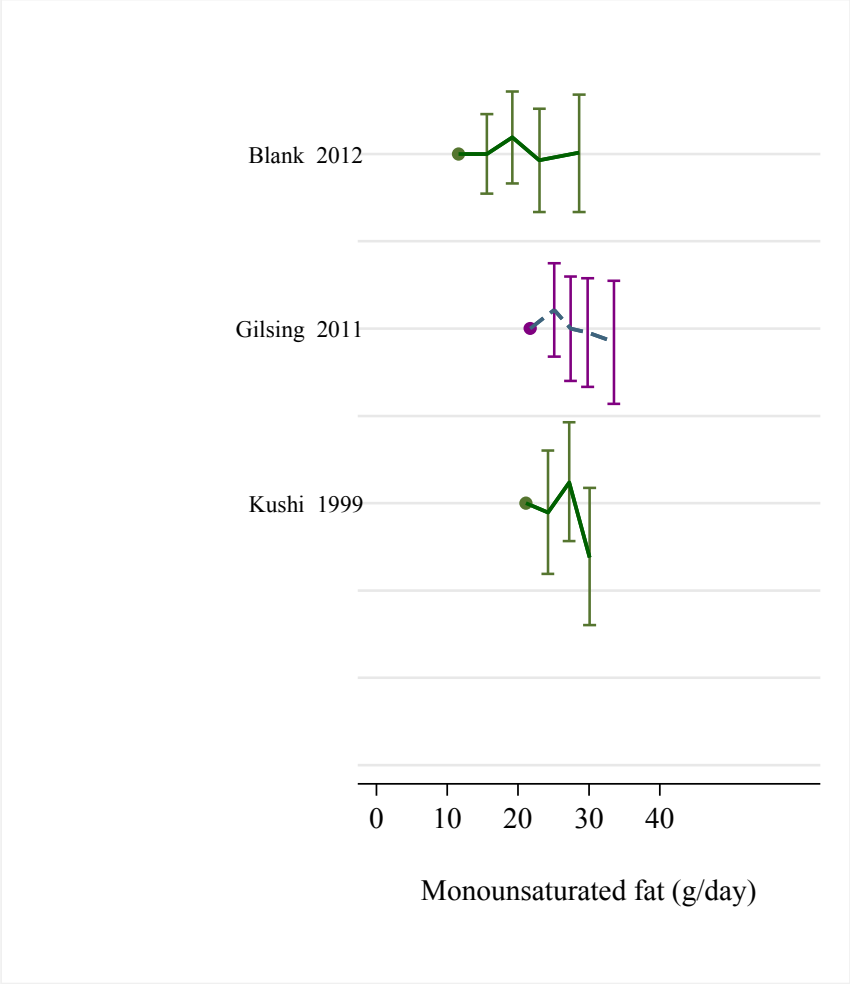


Figure 92 Dose-response graph of monounsaturated fat intake and ovarian cancer



5.2.4 Polyunsaturated fat

Methods

Up to December 2012, four cohort studies were identified, two of which were identified during the Continuous Update Project. One study had no intake data and was only used for high versus low analysis. Dose-response analyses were conducted per 5 grams/day increase. In one study (Blank et al, 2012) the percentages of kcal from fat by intake category were rescaled to g/day using calorie intake per category reported in the paper.

The dose-response RR estimate of one study identified in the CUP (NIH-AARP) was combined with the overall estimate of a pooled analysis of 12 cohorts (Genkinger et al, 2006).

Main results

The summary RR per 5 grams/day was 0.96 (95% CI: 0.80 - 1.16, $I^2 = 73.2$ %, $P_{heterogeneity} = 0.02$) for all studies combined. In influence analysis, the RR ranged from 0.89 (95% CI: 0.78 – 1.03) when excluding the NIH- AARP Diet and Health Study to 1.00 (95% CI: 0.83-1.22) when excluding Iowa Women's Health Study.

Heterogeneity

There was high heterogeneity across the limited number of published studies ($I^2 = 73.2\%$, $P_{heterogeneity} = 0.02$). Egger's tests suggested no evidence of publication bias (p = 0.73).

Published pooled analysis

In a published pooled analysis of 12 prospective studies the summary pooled multivariate RR of ovarian cancer for highest versus lowest quintile of polyunsaturated fat intake was 0.94 (95% CI: 0.80-1.09). Pooled age, energy adjusted, and measurement error corrected RR was 0.82 (95% CI: 0.62-1.10) for an increment of 5% intake of energy from polyunsaturated fat and there was no evidence of heterogeneity (test for heterogeneity = 0.97) (Genkinger et al, 2006).

When the CUP added the results of the NIH-AARP (Blank et al, 2012) to the pooled analysis by Genkinger et al, 2006, the overall RR for 5% increase in energy intake from polyunsaturated fat was 1.08 (95% CI: 0.80-1.45). There was significant heterogeneity in the combined analysis (I^2: 82.7%; p=0.016).

Table 98 Studies on polyunsaturated fat identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Gilsing, 2011	The Netherlands	The Netherlands Cohort study	340	16.3	0.89 0.9	0.47 0.79	1.01 1.03	23.2g/day vs. 8 g/day Per 6.1g/day intake
Blank, 2012	USA	NIH- AARP Diet and Health Study	695	9	1.28	0.92	1.77	19.3 g/day vs. 7.3 g/day

Table 99 Overall evidence on polyunsaturated fat and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR; none of them reported significant associations
Continuous Update Project	Two cohort studies were identified. No study reported significant associations. Overall, three studies were included in the meta-analysis.

Table 100 Summary of results of the dose response meta-analysis of polyunsaturated fat intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1174
Increment unit used	-	Per 5g/day
Overall RR (95%CI)	-	0.96 (0.80 - 1.16)
Heterogeneity (I^2,p-value)	-	73.2 %, p=0.02
NIH-AARP and pooled analysis		12 cohorts
Studies (n)		13
Cases (n)		2827
Increment unit used		Per 5 % energy
Overall RR (95%CI)		1.08 (0.80-1.45)

*No meta-analysis was conducted in the 2nd report

Table 101 Inclusion/exclusion table for meta-analysis of polyunsaturated fat intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11675	Blank	2012	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Percentage of kcal from fat rescaled to g/day using calorie intake per category; mid-exposure values	
OVA11616	Gilsing	2011	Case-Cohort	The Netherlands Cohort study	Incidence	No	Yes	Yes	-	
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	No	Yes	-	No intake amounts per category
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	

Figure 93 Highest versus lowest forest plot polyunsaturated fat intake and ovarian cancer

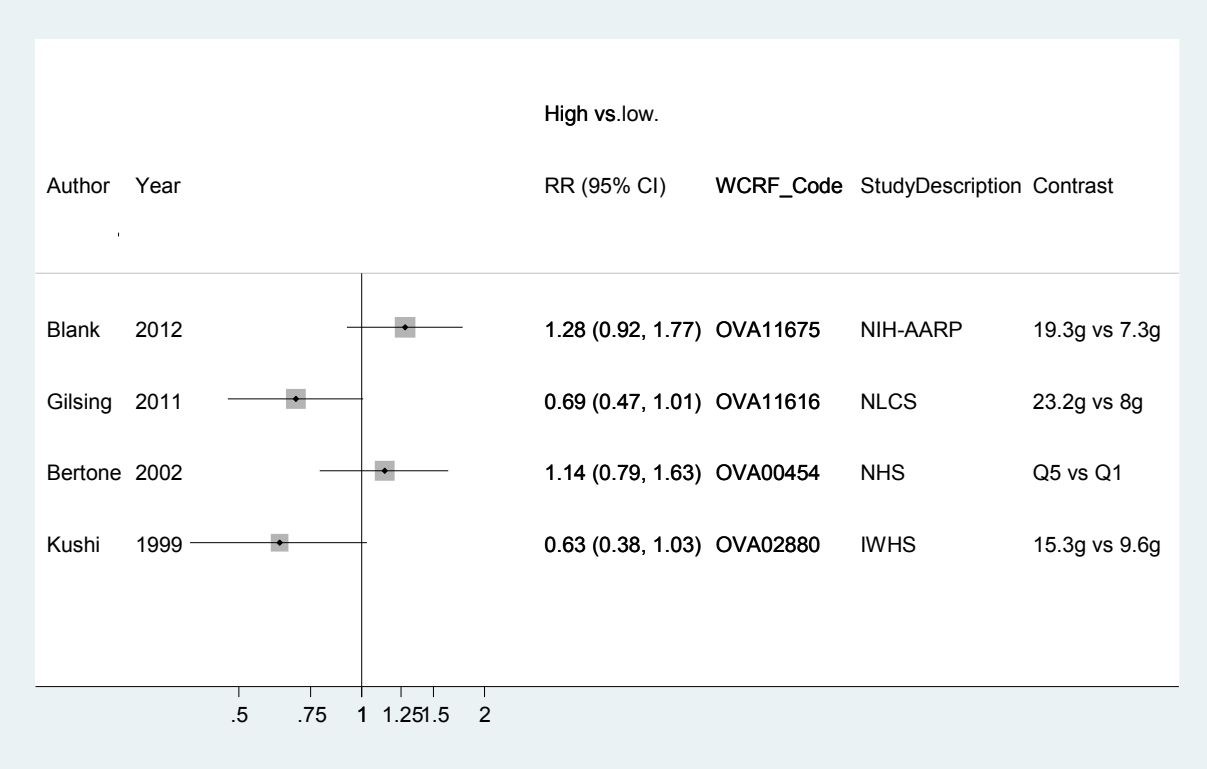


Figure 94 Dose-response meta-analysis of polyunsaturated fat intake and ovarian cancer - per 5 grams/day

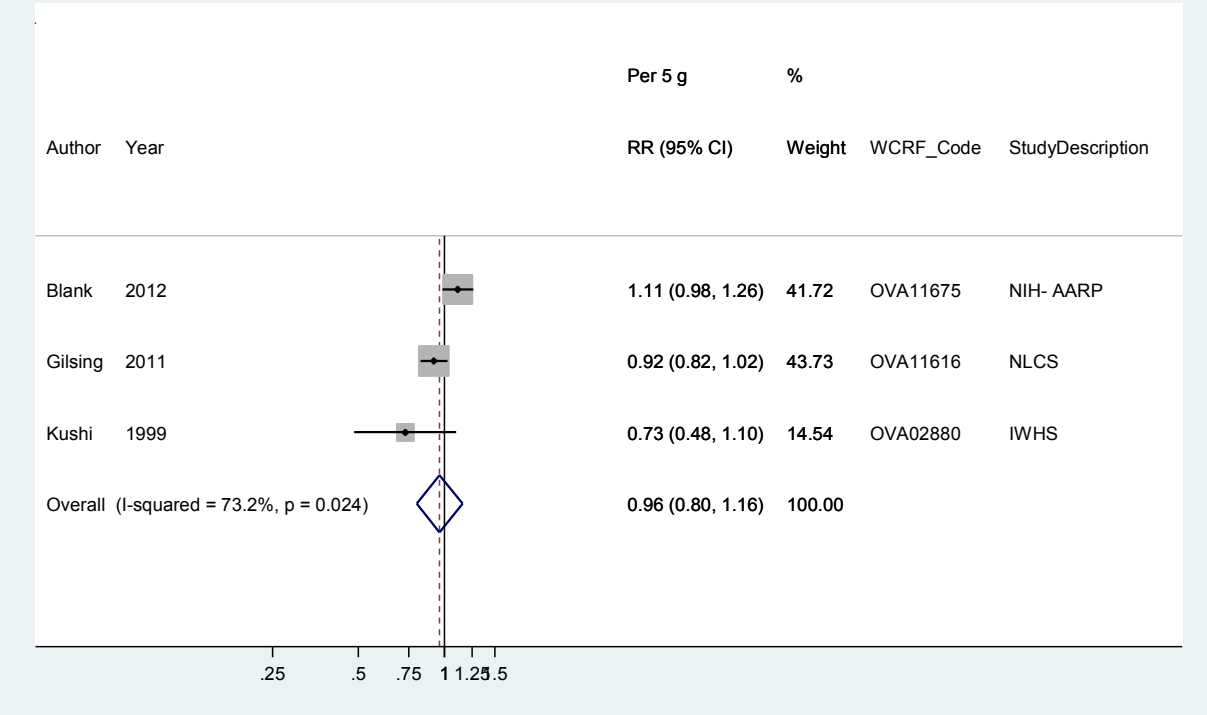


Figure 95 Funnel plot of polyunsaturated fat intake and ovarian cancer

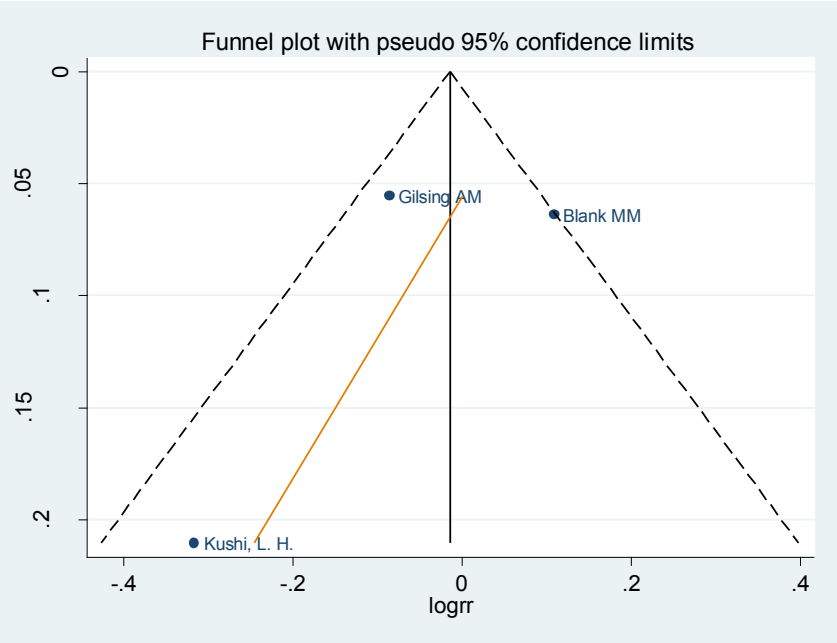
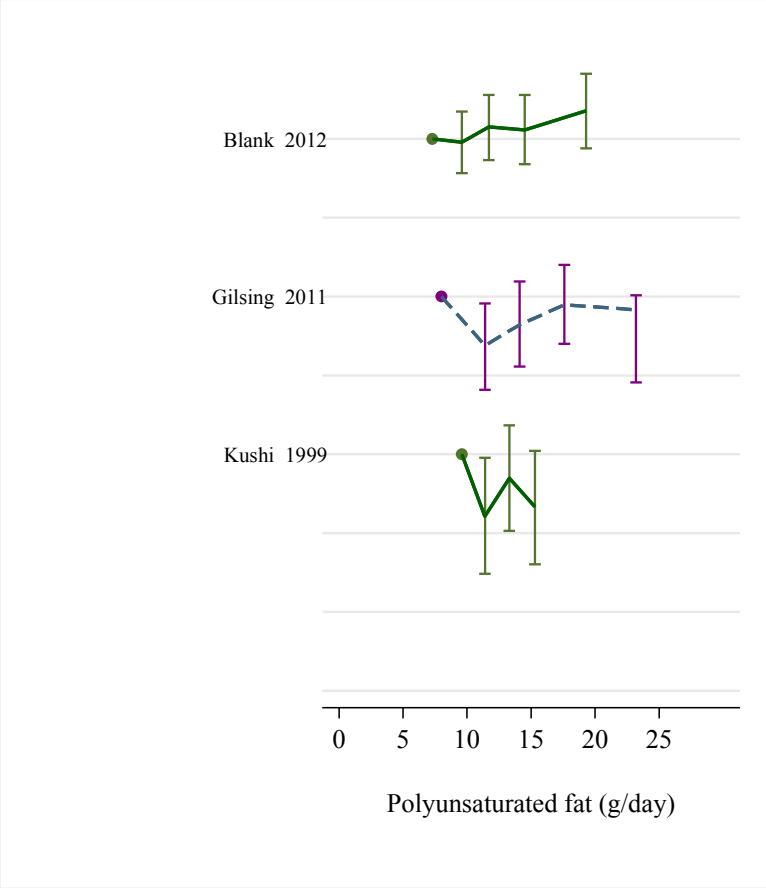


Figure 96 Dose-response graph of polyunsaturated fat intake and ovarian cancer



5.2.5 Trans fatty acids

Methods

Up to December 2012, three cohort studies were identified, two of which were identified during the Continuous Update Project. Two studies had no exposure data and dose-response meta-analysis was not possible.
The highest vs lowest RR estimates of two studies identified in the CUP (NLCS -Gilsing et al, 2011- and NIH-AARP- Blank et al, 2011) were combined with the results of a pooled analysis of 4 cohorts (Genkinger at al, 2006). This highest vs lowest meta-analysis was conducted to complement the evidence of other fatty acids in the report. The data of the studies identified and the results of the pooled analysis of 4 cohort studies are shown in a forest plot (Figure 96).

Main results

No dose-response meta-analysis was possible.
The highest vs lowest meta-analysis of the two studies identified in the CUP (Gising et al, 2011 and Blank et al, 2012) and the overall pooled estimate of 4 cohorts from a pooled analysis (Genkinger et al, 2006) was 1.18 (95% CI: 0.98- 1.41).

Published pooled analysis

In a published pooled analysis of 12 prospective studies (eight studies excluded from the analysis) (Genkinger et al, 2006) the summary pooled multivariate RR of 4 studies for highest versus lowest quartile of % of energy from trans-unsaturated fatty acids was 1.04 (95% CI: 0.84-1.28).

Table 102 Studies on trans-unsaturated fatty acids identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Blank, 2012	USA	NIH-AARP Diet and Health Study	695	9	1.19	0.94	1.50	Q4 vs Q1 (% kcal from total energy)
Gilsing, 2011	The Netherlands	The Netherlands Cohort study	340	16.3	1.51 1.14	1.04 1.03	2.20 1.28	3.5 vs 1.5 g/day Per 0.1 g/day intake

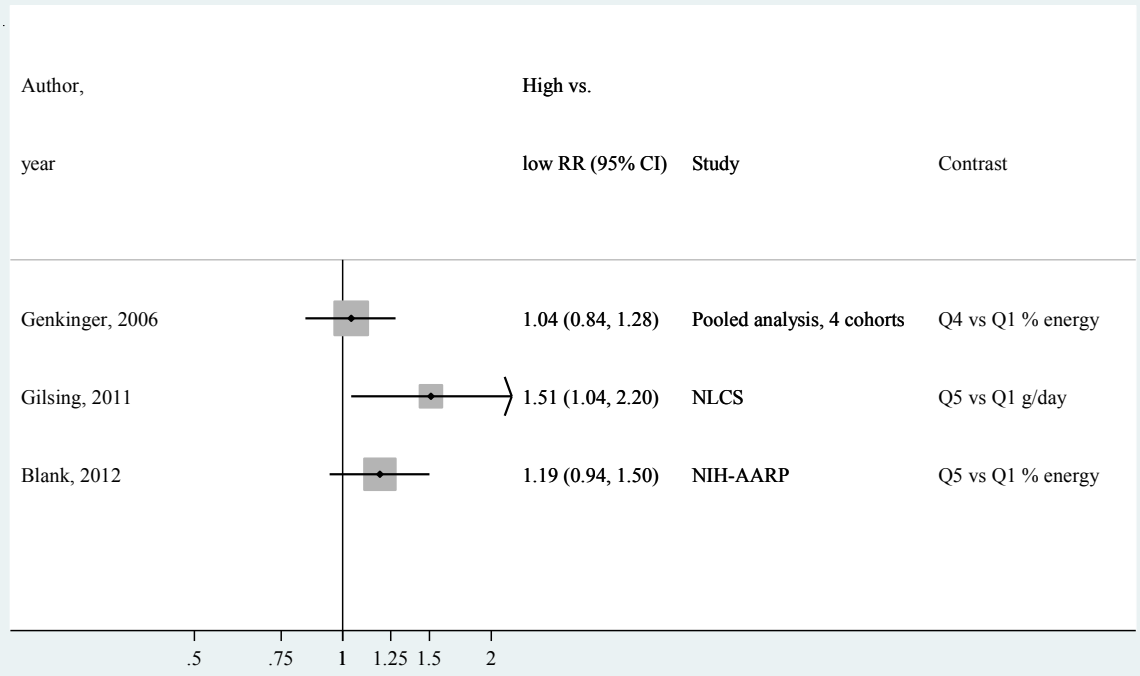
Table 103 Overall evidence on trans-unsaturated fatty acids and ovarian cancer

	Summary of evidence
SLR	One cohort study reported no association.
Continuous Update Project	Two cohort studies were identified. One reported a significant positive dose-response association and the other reported no association. The pooled analysis of 4 cohorts did not find a significant association.

Table 104 Inclusion/exclusion table for meta-analysis of trans-unsaturated fatty acids and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11675	Blank	2012	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	No	Yes		Only highest vs lowest comparison
OVA11616	Gilsing	2011	Case-Cohort	The Netherlands Cohort study	Incidence	No	No	Yes	-	
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	No	No	-	No exposure level reported

Figure 97 Highest versus lowest forest plot of trans-unsaturated fatty acids intake and ovarian cancer



5.2.6 Animal fat

Methods

Up to December 2012, four cohort studies were identified, two of which were identified during the Continuous Update Project. One study had no data intake levels and was only used for high versus low analysis. In one study (Blank et al, 2012) the percentages of energy from animal fat by intake category were rescaled to g/day using calorie intake per category reported in the paper. Three studies were included in the dose-response meta-analysis. Dose-response analyses were conducted per 5 grams/day increase of energy from animal fats.
The dose-response RR estimate of one study identified in the CUP (NIH-AARP) was combined with the overall estimate of a published pooled analysis of 9 cohorts (Genkinger et al, 2006).

Main results

The summary RR per 5 grams/day increase was 1.03 (95% CI: 1.01 - 1.05, $I^2 = 0\%$, $P_{heterogeneity} = 0.88$) for all studies combined. There was no evidence of study influence when repeating the analysis excluding one study each time.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.88$). Egger's test did not provide evidence for publication bias (p = 0.96).

Published pooled analysis

A published pooled analysis of 9 prospective cohort studies reported a pooled multivariate RR = 1.15 (95% CI: 0.99-1.33) when comparing the highest vs. the lowest quartile of energy from animal fat and a RR of 1.04 (95% CI= 0.99-1.08) for an increment of 5% of energy from animal fat (Genkinger et al, 2006).

When we added the results of the NIH-AARP (Blank et al, 2012) to the pooled analysis by Genkinger et al, 2006, the overall RR for a 5% increase in energy from animal fat was 1.04 (95% CI: 1.03-1.06).

Table 105 Studies on animal fat identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Gilsing, 2011	The Netherlands	The Netherlands Cohort study	340	16.3	1.30 1.01	0.93 0.9	1.83 1.13	56.6/day vs. <23.9 g/day Per 10.3g/day intake
Blank, 2012	USA	NIH-AARP Diet and Health Study	695	9	1.30	1.02	1.66	22 vs. 7.9 % of energy from fat

Table 106 Overall evidence on animal fat and ovarian cancer

	Summary of evidence
SLR	Two large US Cohort studies (Bertone et al, 2002 –NHS-, Kushi et al, 1999 –IOWA-) did not find any association
Continuous Update Project	Two cohort studies were identified and included in the dose-response meta-analysis. The NIH-AARP study (Blank et al, 2012) reported a positive significant association. The Netherlands cohort report did not find a significant association. Overall, three studies were included in the meta-analysis. The published pooled analysis of 9 cohorts did not find significant evidence of association

Table 107 Summary of results of the dose response meta-analysis of animal fat intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1174
Increment unit used	-	Per 5 g/day
Overall RR (95%CI)	-	1.03 (1.01 - 1.05)
Heterogeneity (I^2,p-value)	-	0 %, p=0.69
NIH-AARP and published pooled analysis		
Studies (n)		10
Cases (n)		2120
Increment unit used		Per 5 % energy
Overall RR (95%CI)		1.04 (1.03-1.06)

*No meta-analysis was conducted in the 2nd report

Table 108 Inclusion/exclusion table for meta-analysis of animal fat intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11675	Blank	2012	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Percentage of kcal from animal fat rescaled to g/day using calorie intake per category; mid-exposure values	
OVA11616	Gilsing	2011	Case-Cohort	The Netherlands Cohort study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	No	Yes	-	No intake levels
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	

Figure 98 Highest versus lowest forest plot of animal fat intake and ovarian cancer

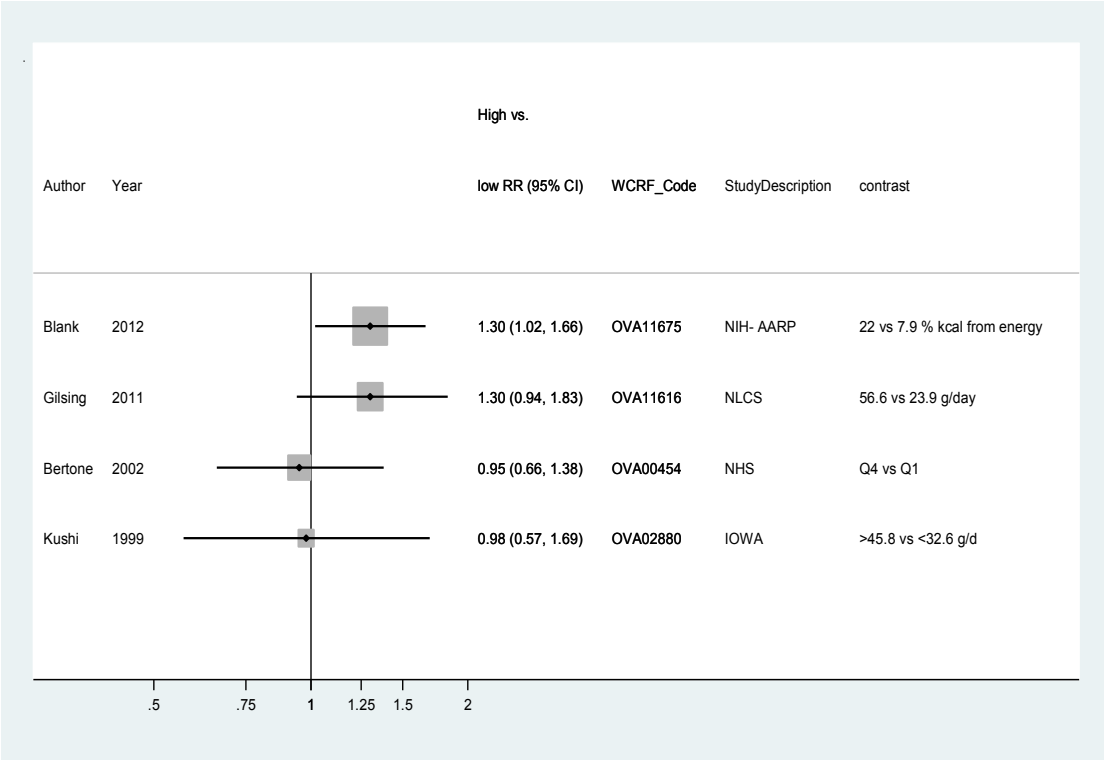


Figure 99 Dose-response meta-analysis of animal fat intake and ovarian cancer - per 5 grams/day

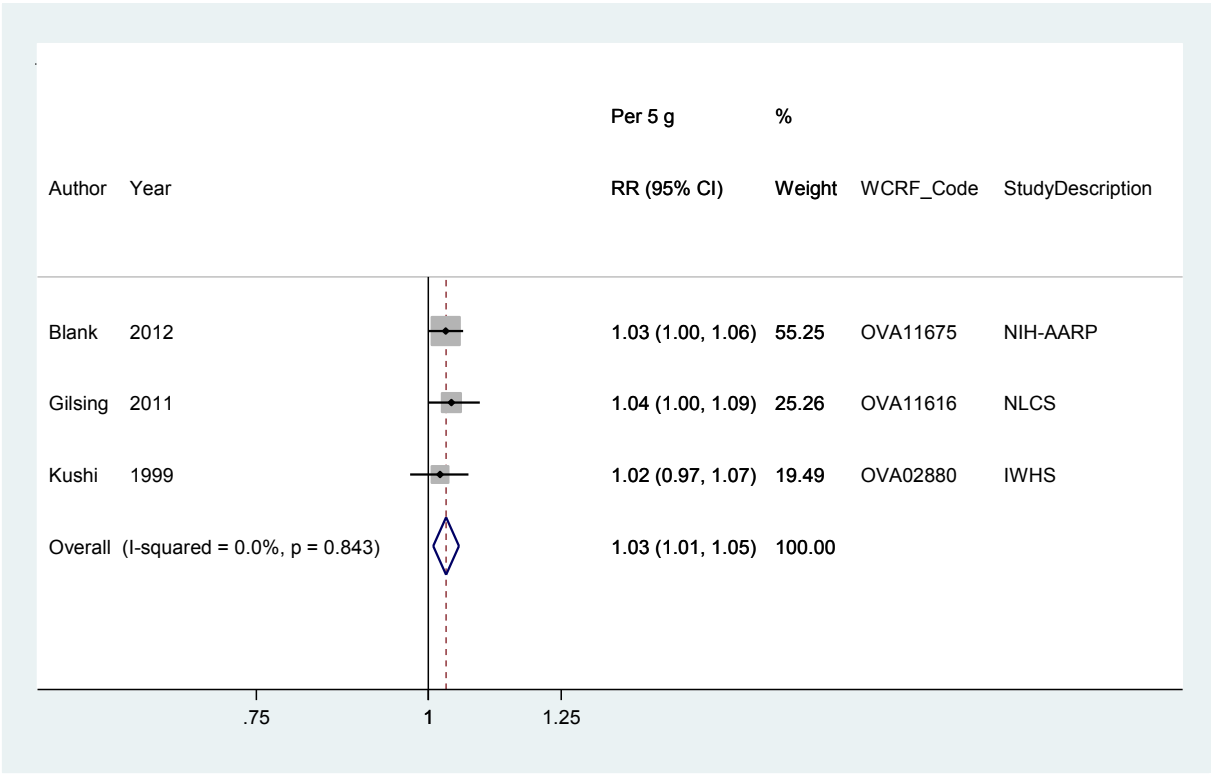


Figure 100 Funnel plot of animal fat intake and ovarian cancer

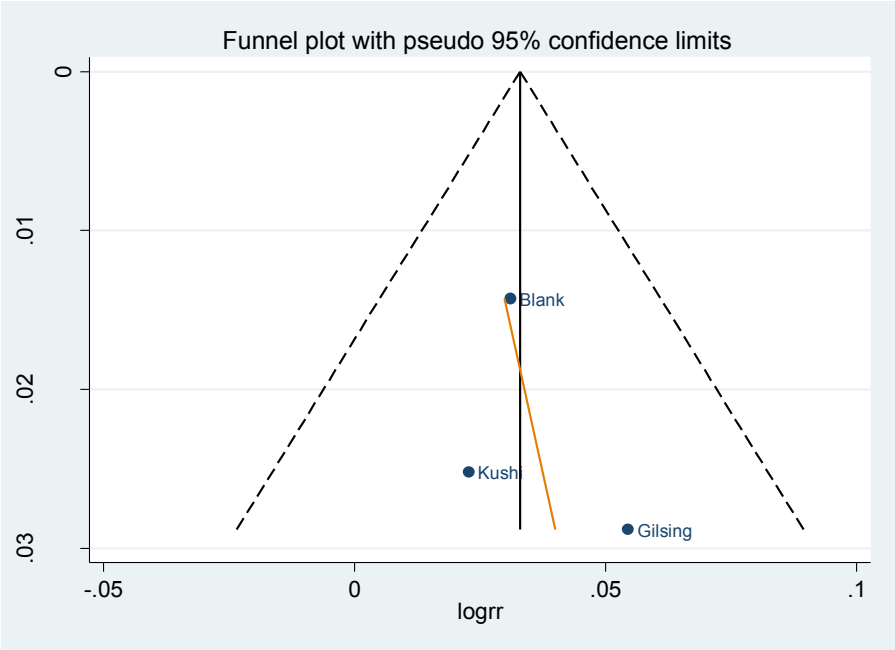
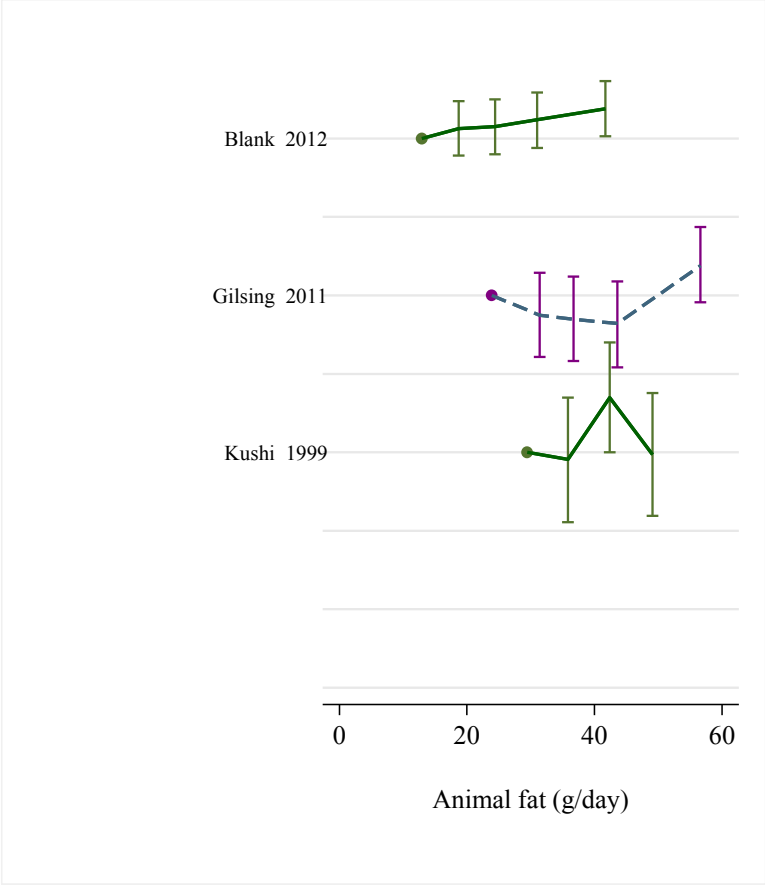


Figure 101 Dose-response graph of animal fat intake and ovarian cancer



5.2.7 Vegetable fat

Methods

Up to December 2012, four cohort studies were identified, two of which were identified during the Continuous Update Project. One study had no data intake levels and was only used for high versus low analysis (Bertone et al., 2002). In one study (Blank et al, 2012) the percentages of energy from vegetable fat by intake category were rescaled to g/day using calorie intake per category reported in the paper. Three studies were included in the dose-response meta-analysis. Dose-response analyses were conducted for an increase of 5 g/day of energy from vegetable fats.
The dose-response RR estimate of one study identified in the CUP (NIH-AARP) was combined with the overall estimate of a published pooled analysis of 9 cohorts (Genkinger et al, 2006). The dose-response for this analysis is reported as increase for 5% increase of energy intake from vegetable fats.

Main results

The summary RR per 5 g/day was 1.00 (95% CI: 0.97 - 1.02, I^2 = 0%, $P_{heterogeneity}$ = 0. 49) for all studies combined. There was no evidence of study influence when repeating the analysis excluding one study each time.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies (I^2 = 0%, $P_{heterogeneity}$ = 0.51). Egger's test provided strong evidence for publication bias (p = 0. 004).

Published pooled analysis

A published pooled analysis of 9 prospective cohort studies reported a pooled multivariate RR = 1.01 (95% CI: 0.87-1.18) when comparing the highest vs. the lowest quartile of energy from vegetable fat and a RR of 0.98 (95% CI: 0.93-1.04) for an increment of 5% of energy from vegetable fat (Genkinger et al, 2006).
When we added the results of the NIH-AARP (Blank et al, 2012) to the pooled analysis by Genkinger et al, 2006, the overall RR for a 5% increase of energy from vegetable fats was 0.99 (95% CI: 0.95-1.04).

Table 109 Studies on vegetable fat identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Gilsing, 2011	The Netherlands	The Netherlands Cohort study	340	16.3	0.64 0.93	0.45 0.81	0.91 1.07	15.9/day vs. <2.8 g/day Per 6.8 g/day intake
Blank, 2012	USA	NIH- AARP Diet and Health Study	695	9	1.00 1.02	0.79 0.95	1.27 1.10	>19.4 vs. <6.4 of energy from fat Per 5% energy increase

Table 110 Overall evidence on vegetable fat and ovarian cancer

	Summary of evidence
SLR	None of the two large US cohort studies identified (Bertone et al, 2002 –NHS-, Kushi et al, 1999 –IOWA-) found any association
Continuous Update Project	Two cohort studies were identified and included in the dose-response meta-analysis. The Netherlands cohort (Gilsing et al. 2011) found a significant inverse association when comparing the highest vs. the lowest quintile. The NIH-AARP study (Blank et al, 2012) did not find significant association. The published pooling project did not find a significant association with energy from vegetable fats. Overall, three studies were included in the dose-response meta-analysis.

Table 111 Summary of results of the dose response meta-analysis of vegetable fat intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1174
Increment unit used	-	Per 5 g/day
Overall RR (95%CI)	-	1.00 (0.97 - 1.02)
Heterogeneity (I^2,p-value)	-	0 %, p=0.49
NIH-AARP and published pooled analysis		
Studies (n)		10
Cases (n)		2120
Increment unit used		Per 5 % energy
Overall RR (95%CI)		0.99 (0.95-1.04)

*No meta-analysis was conducted in the 2nd report

Table 112 Inclusion/exclusion table for meta-analysis of vegetable fat intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11675	Blank	2012	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Percentage of kcal from vegetable fat rescaled to g/day using calorie intake per category; mid-exposure values	-
OVA11616	Gilsing	2011	Case-Cohort	The Netherlands Cohort study	Incidence	No	Yes	Yes	Rescale of RR for continuous increase	
OVA00454	Bertone	2002	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	No	Yes	-	No intake levels
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	-

Figure 102 Highest versus lowest forest plot of vegetable fat intake and ovarian cancer

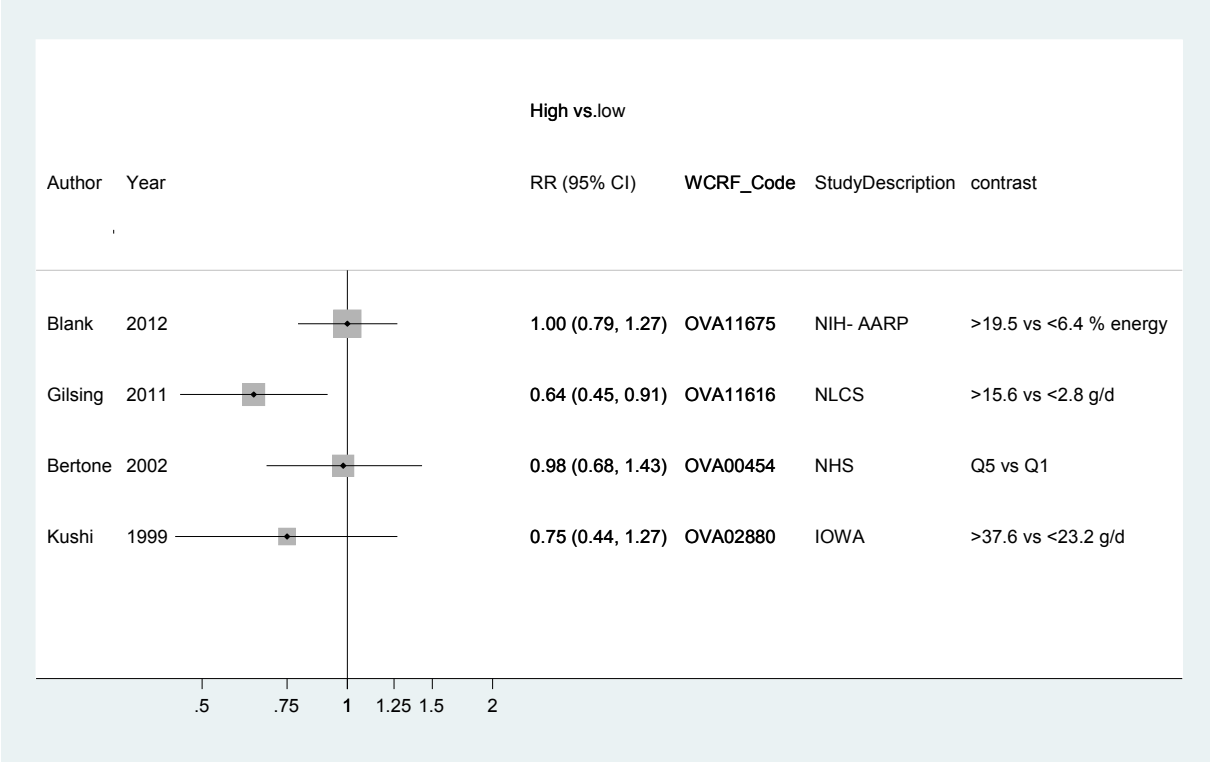


Figure 103 Dose-response meta-analysis of vegetable fat intake and ovarian cancer - per 5 grams/day

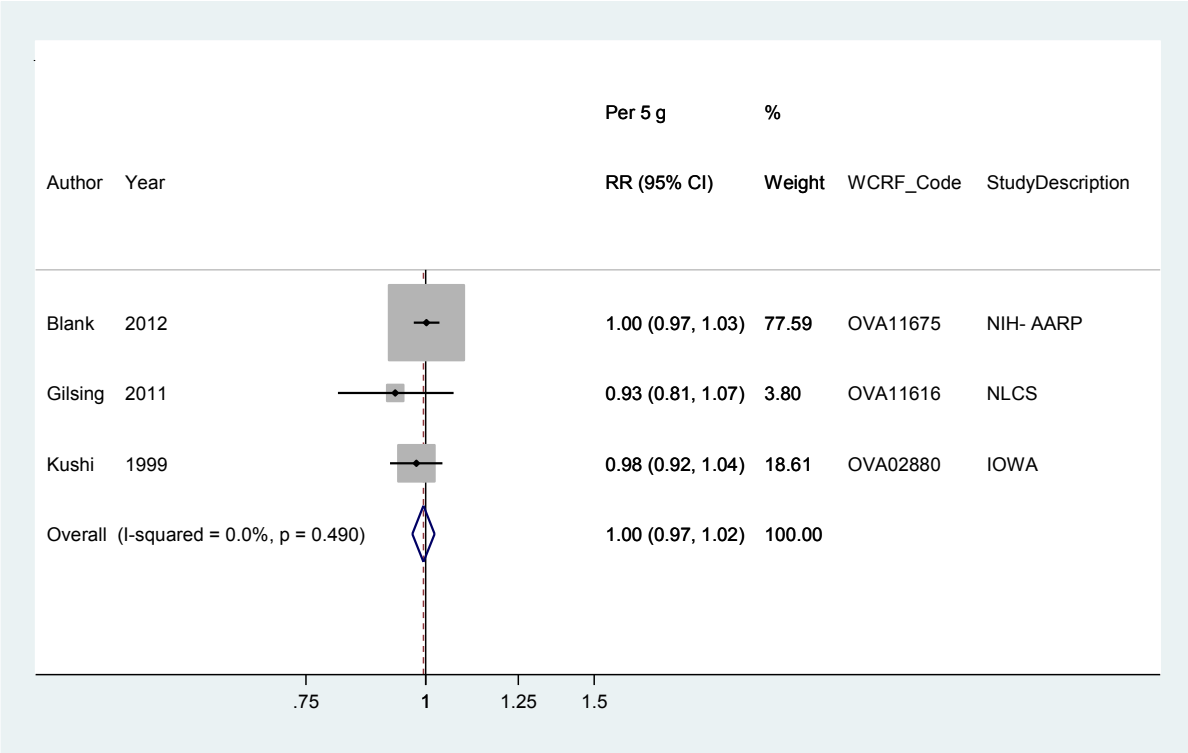


Figure 104 Funnel plot of vegetable fat intake and ovarian cancer

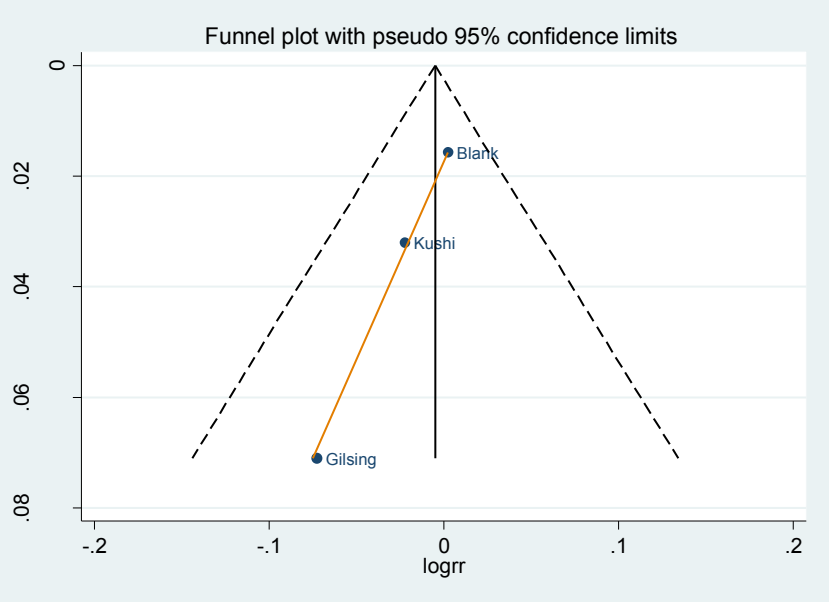
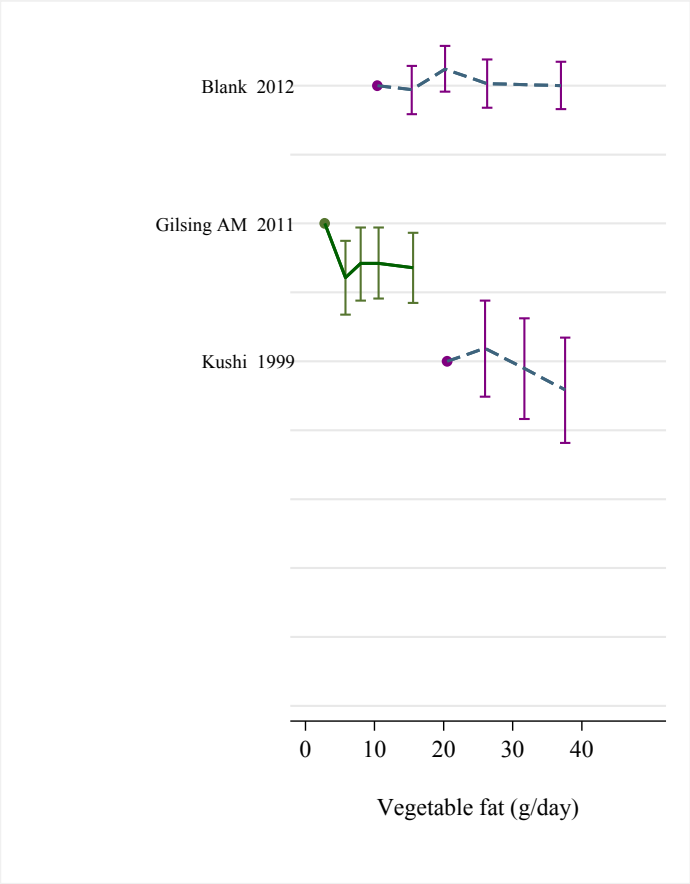


Figure 105 Dose-response graph of vegetable fat intake and ovarian cancer



5.4.1 Alcohol (as ethanol)

Methods

Up to December 2012, reports from 10 cohort studies on ovarian cancer incidence and 12 publications were identified. Eight publications from seven studies were identified during the CUP. The CUP meta-analysis included eight studies (five studies identified during the CUP and three studies identified during the 2007 SLR). The dose-response results are presented for an increment of 10 g/day.

The results of a published pooled analysis of cohort studies was combined with those of the non-overlapping studies identified in the SLR. The summary result is shown in a forest plot.

Main results

The summary RR per 10 g/day was 1.01 (95% CI: 0.96-1.06; I^2= 7.0%, $P_{heterogeneity}$=0.37) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.95-1.04) when excluding the California Teachers Study (Chang et al, 2007) to 1.02 (95% CI: 0.95-1.10) when excluding the Million Women Study (Allen et al, 2009).

Heterogeneity

Low heterogeneity was observed (I^2= 7.0%, p=0.37). Egger's tests did not show evidence of publication bias (p= 0.66).

Comparison with the Second Expert Report

No significant association was observed in the SLR. The CUP results found no evidence of association of alcohol intake with ovarian cancer risk.

Meta-analysis and Pooled studies

In a pooled analysis of 10 prospective studies (Genkinger et al, 2006) including 2001 incident epithelial ovarian cancer cases, no association was alcohol intake was observed (multivariate adjusted RR for an increase of 30g/day 1.01 (95% CI: 0.93-1.11)

In a more recent meta-analysis including 27 studies (23 case-controls, 3 cohort studies and the results of the pooling project published by Genginker et al, 2006). The RR for any alcohol drinking compared with non/occasional drinking in cohort studies was 1.03 (CI 95%: 0.97-1.09). The RR was 0.97 (95% CI, 0.92–1.02) for light (≤1 drink/day), 1.03 (95% CI, 0.96–1.11) for moderate (>1 to <3 drinks) and 1.09 (95% CI, 0.80–1.50) for heavy drinking (≥3 drinks/day) (Rota et al, 2012).

When the studies identified in the CUP were pooled with the studies included in the Pooling Project of Cohort Studies, the pooled RR estimate for an increase of 10g/d of alcohol was 1.01 (95% CI: 0.97, 1.05).

Table 113 Studies on alcohol consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Weiderpass, 2011	Japan	Japan Public Health Center-based Prospective Study	86	7.6	1.0 1.0	0.50 0.99	1.80 1.00	Yes vs. No Per grams per week
Yang, 2011	United States	National Health Institute-American Association of Retired Persons	849	9.8	0.93	0.67	1.30	>=24 g/d vs 0 g/d
Allen, 2009	United Kingdon	Million Women Study	846	7.2	0.94	0.81	1.09	>=15 drinks/week vs. never and former drinkers
Kabat, 2008	Canada	Canadian National Breast Cancer Screening Study	264	16.4	1.23	0.74	2.04	>=30 g/d vs. 0 g/d
Tworoger, 2008	United States	Nurses' Health Study	507	24	0.99	0.72	1.36	>=15 g/d vs. <0.1 g/d
Chang, 2007	United States	California Teacher Study	253	8.1	1.15	0.71	1.84	>=20 g/d vs. 0 g/d
Sakauchi, 2007	Japan	Japan Collaborative Cohort (JACC) Study	77 deaths	~14	0.65	0.35	1.23	Yes vs. No
Navarro-Silvera 2006	Canada	Canadian National Breast Cancer Screening Study	264	16.4	1.10	0.74	1.65	>10 g/day versus non-drinkers

Table 114 Overall evidence on alcohol consumption and ovarian cancer

	Summary of evidence
SLR	Three cohort studies evaluated the association between alcohol consumption and ovarian cancer risk. None of the studies reported a significant association. The pooled RR per 30 g/day of two studies was 0.95 (95% CI: 0.87-1.03).
Continuous Update Project	Seven cohort studies and eight publications were identified; of which five could be included in the final meta-analysis. Overall, eight studies were included in the CUP meta-analysis.

Table 115 Summary of results of the dose response meta-analysis of alcohol consumption and ovarian cancer

Ovarian cancer incidence		
	SLR	Continuous Update Project
Studies (n)	2	8
Cases (n)	413	2954
Increment unit used	Per 30 g/day	Per 10g/day
Overall RR (95%CI)	0.95 (0.87-1.03)	1.01 (0.96-1.06)
Heterogeneity (I^2,p-value)	45.9%	7.0%, p=0.37
Pooling project and 4 cohorts		
Studies (n)		14
Cases (n)		4053
Increment unit used		Per 10 g/day
Overall RR (95%CI)		1.01 (0.97- 1.05).

Table 116 Inclusion/exclusion table for meta-analysis of alcohol consumption and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11669	Weiderpass	2011	Prospective Cohort Study	Japan Public Health Center-based Prospective Study	Incidence	No	Yes	Yes	Rescale of reported RR for continuous increase	
OVA11672	Yang	2011	Prospective Cohort Study	National Health Institute- American Association of Retired Persons	Incidence	No	Yes	Yes	Person/ years per category mid-exposure values	
OVA11667	Allen	2009	Prospective Cohort Study	Million Women Study	Incidence	No	Yes	Yes	-	
OVA11681	Kabat	2008	Prospective Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	No	No	Yes	-	Cases and person-years per category not reported
OVA11633	Tworoger	2008	Prospective Cohort Study	Nurses' Health Study	Incidence	No	Yes	Yes	Mid-exposure values	
OVA11626	Chang	2007	Prospective Cohort Study	California Teacher Study	Incidence	No	Yes	Yes	Person/ years per category	
OVA11661	Sakauchi	2007	Prospective Cohort Study	Japan Collective Cohort Study	Mortality	No	No	Yes	-	Only two categories (yes versus no)
OVA11624	Navarro-Silvera	2006	Prospective Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	No	No	No	-	Superseded by Kabat, et al, 2008. Reported only high vs low
OVA10451	Kelemen	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
OVA09696	Larsson	2004	Prospective Cohort Study	Swedish Mammography Study	Incidence	Yes	Yes	Yes	Mid-exposure values cases and person/years per category	
OVA09692	Schouten	2004	Case-Cohort Study	Netherland Cohort Study	Incidence	Yes	Yes	Yes	-	
OVA02880	Kushi	1999	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Superseded by Kelemen et al, 2004

Figure 106 Highest versus lowest forest plot of alcohol consumption and ovarian cancer

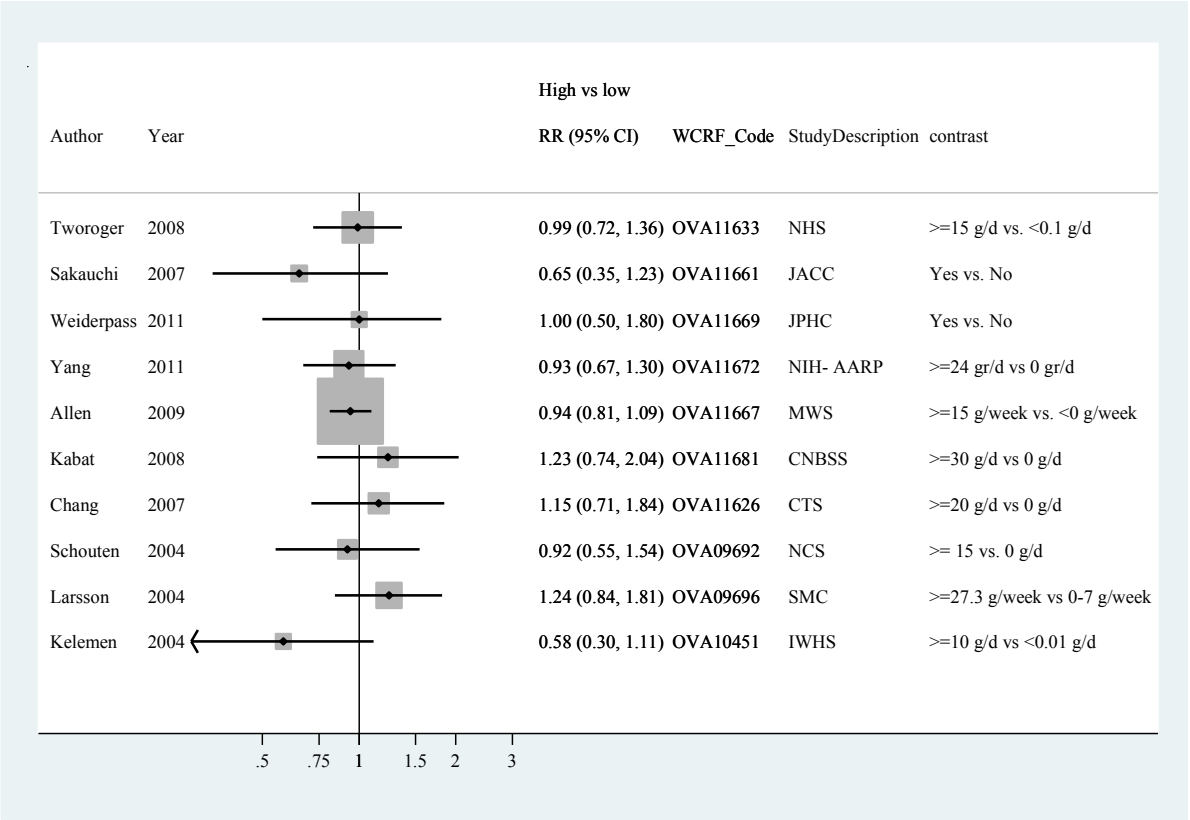


Figure 107 Dose-response meta-analysis of alcohol and ovarian cancer - per 10 g/d

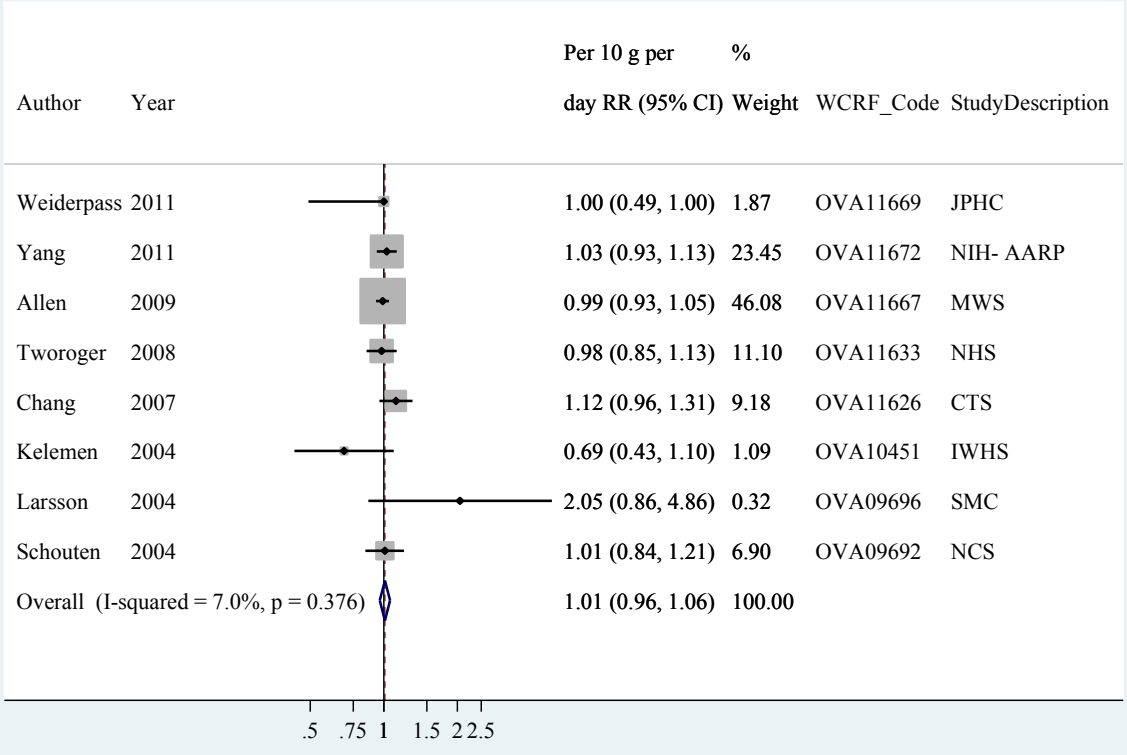


Figure 108 Funnel plot of alcohol consumption and ovarian cancer

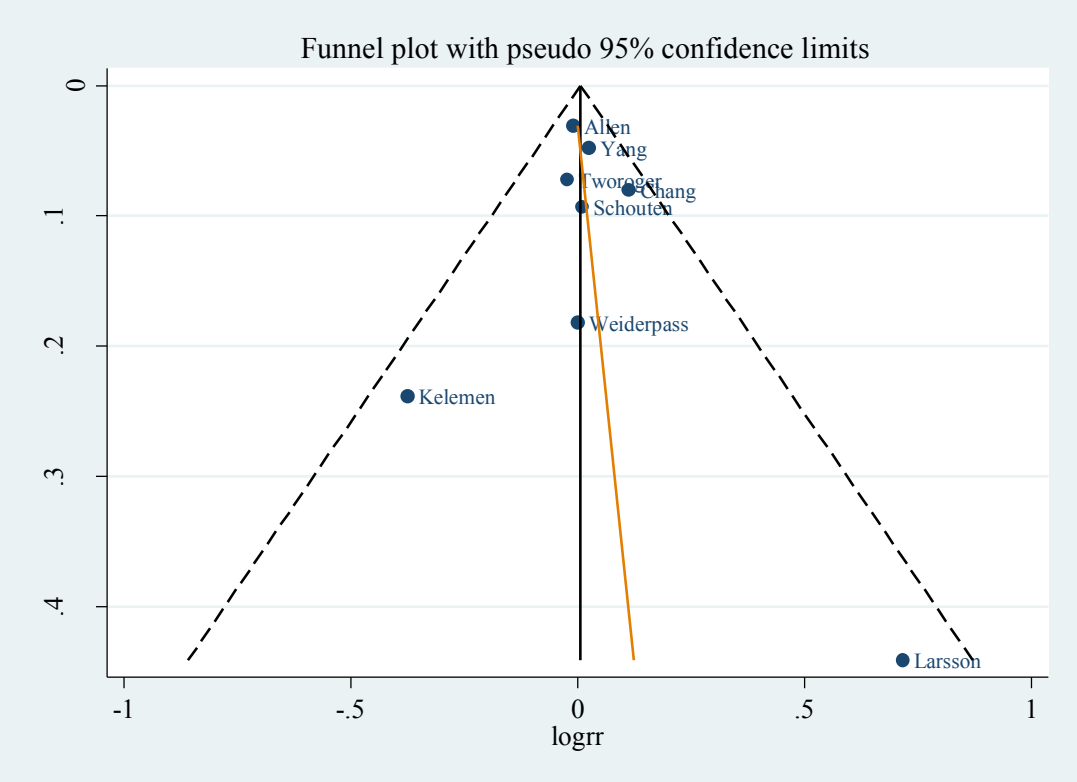


Figure 109 Dose-response graph of alcohol and ovarian cancer

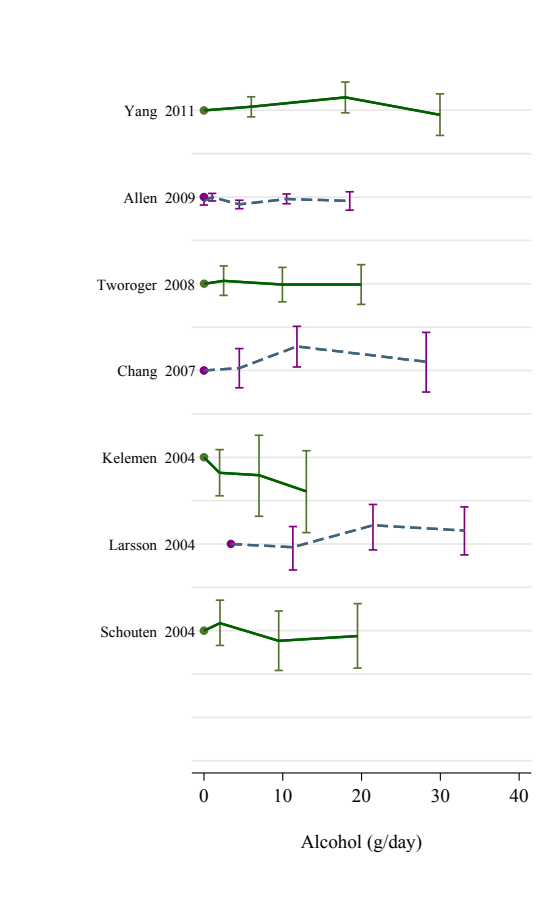
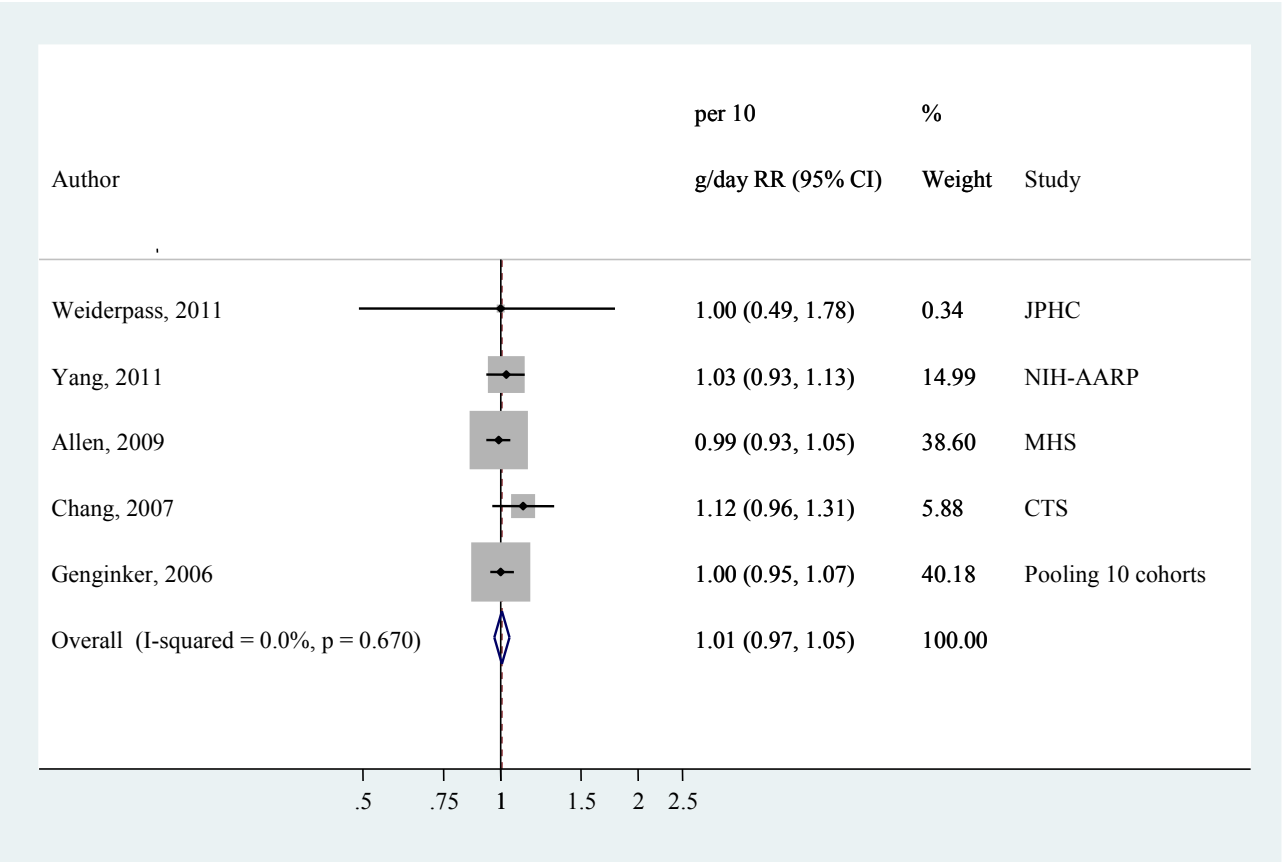


Figure 110 Sensitivity analysis: Pooling project of 10 cohort studies and studies identified in the CUP



5.4.1.1 Beer (as ethanol)

Methods

Up to December 2012, reports from four cohort studies were identified, two of which were identified during the CUP. The CUP meta-analysis included three studies (two studies identified during the CUP and one study identified during the 2007 SLR). For the dose-response analyses all results were converted to a common scale of exposure level of 13.2 grams per bottle or can of beer that was used as an average serving size (Tworoger et al, 2008). The dose-response results are presented for an increment of 10 g/day of beer as ethanol.

Main results

The summary RR per 10 g/day was 1.06 (95% CI: 0.60-1.88; I^2= 63.0%, $P_{heterogeneity}$=0.06) for all studies combined. In influence analysis, the RR ranged from 0.90 (95% CI: 0.90-1.17) when excluding the Swedish Mammography Study (Larsson et al, 2004) to 1.49(95% CI: 0.51-4.34) when excluding the California Teacher's Study (Chang et al, 2007).

Heterogeneity

High heterogeneity was observed (I^2= 63.3%, p=0.06). Egger's tests did not show evidence of publication bias (p= 0.68).

Comparison with the Second Expert Report

No analysis was done during the SLR on ovarian cancer and beer consumption. The CUP results found no evidence of association of beer intake with ovarian cancer risk.

Meta-analysis and Pooled studies

In a pooled analysis of 10 prospective studies (Genkinger et al, 2006), including 1924 incident epithelial ovarian cancer cases, no association with beer intake was observed (multivariate adjusted RR for an increase of 15 g/day 1.02 (95% CI: 0.84-1.24). Risk estimates for total alcohol intake were similar for endometrioid (N=260, RR=1.05, 95% CI: 0.87–1.26), mucinous (N=121, RR=1.06, 95% CI: 0.84–1.34) and serous (N=981, RR=1.07, 95% CI: 0.98–1.17) ovarian cancers (P-value for difference by histological type=0.98).

When the study by Chang et al, 2007 (CTS) identified in the CUP was combined with the studies included in the Pooling Project of Cohort Studies, the pooled RR estimate for an increase of 10g/d of ethanol from beer was 0.95 (95% CI: 0.71-1.25).

Table 117 Studies on beer consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Tworoger, 2008	United States	Nurses' Health Study	507	24	0.86	0.44	1.68	>=1 drink/d vs. non drinkers
Chang, 2007	United States	California Teacher Study	253	8.1	0.54	0.17	1.70	>=13.1 g/d vs. non drinkers

Table 118 Overall evidence on beer consumption and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR. A Swedish prospective cohort study (Larsson et al., 2004) showed a significant increased risk of epithelial ovarian cancer. No association was observed in the other study
Continuous Update Project	Two additional cohort studies were identified and included in the meta-analysis. None of the studies found an association between beer consumption and ovarian cancer. Overall, three cohorts were included in the CUP meta-analysis. No association was observed in the published pooling project of cohort studies

Table 119 Summary of results of the dose response meta-analysis of beer consumption and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1026
Increment unit used	-	Per 10 g/day
Overall RR (95%CI)	-	1.06 (0.60-1.88)
Heterogeneity (I^2,p-value)	-	63.3%, p=0.06
Pooling project and CTS		
Studies (n)		10
Cases (n)		2177
Increment unit used		Per 10g/day
Overall RR (95%CI)		0.95 (0.71-1.25)

*No meta-analysis was conducted in the 2nd report

Table 120 Inclusion/exclusion table for meta-analysis of beer consumption and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11633	Tworoger	2008	Prospective Cohort Study	Nurses' Health Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA11626	Chang	2007	Prospective Cohort Study	California Teacher Study	Incidence	No	Yes	Yes	Person/ years per category	-
OVA010867	Larsson	2004	Prospective Cohort Study	Swedish Mammography Study	Incidence	Yes	Yes	Yes	Cases per category estimation mid-exposure values and person/years per category	-
OVA09692	Schouten	2004	Prospective Cohort Study	Netherland Cohort Study	Incidence	Yes	No	Yes	-	Only two categories

Figure 111 Highest versus lowest forest plot of beer consumption and ovarian cancer

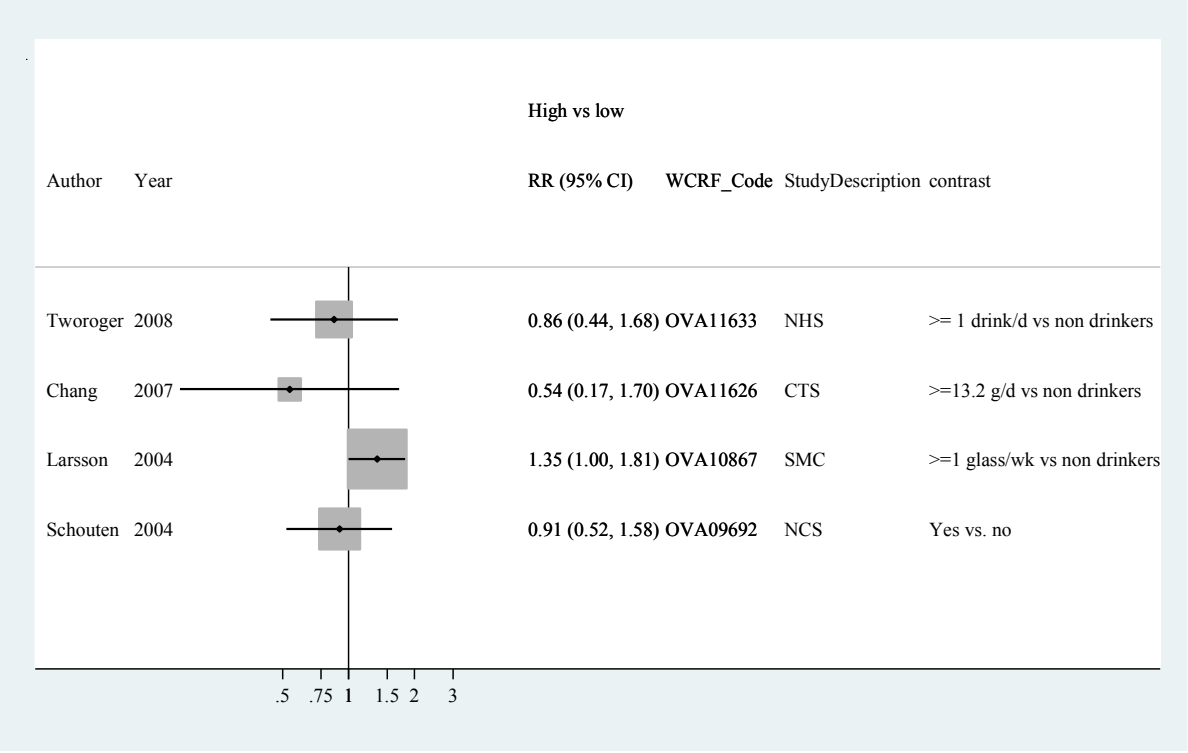


Figure 112 Dose-response meta-analysis of beer and ovarian cancer - per 10 g/d

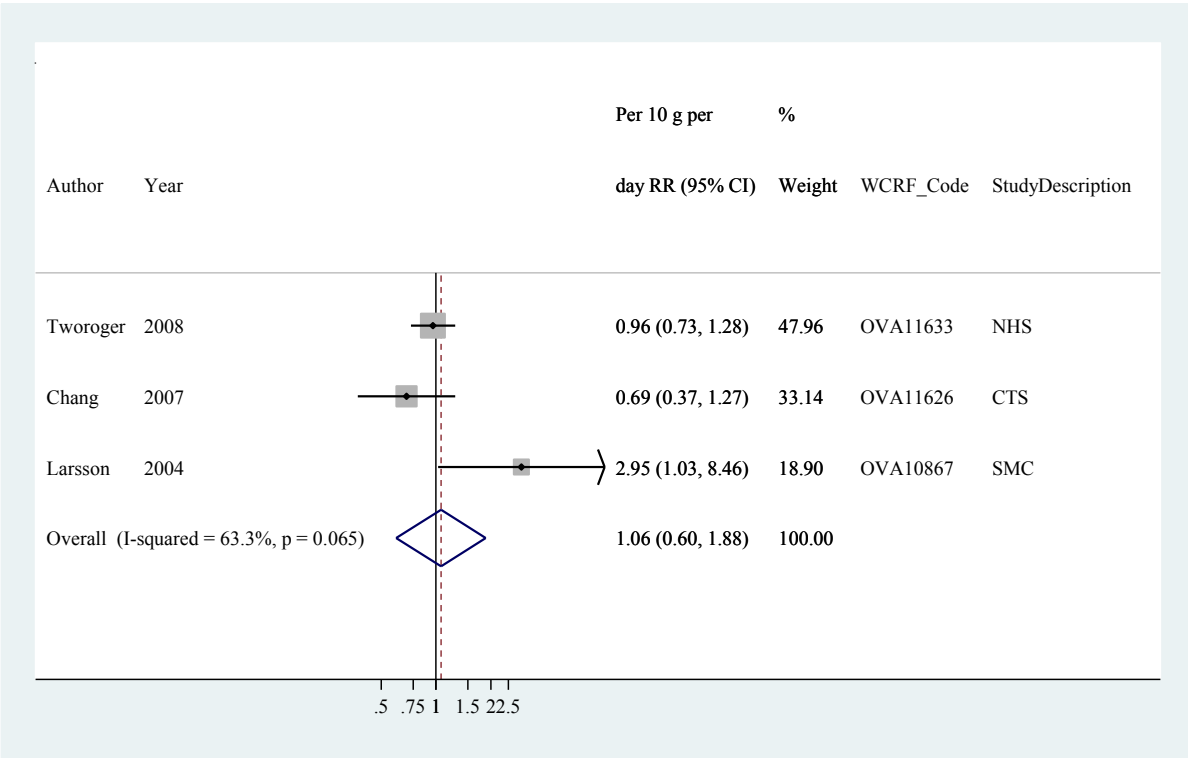


Figure 113 Funnel plot of beer consumption and ovarian cancer

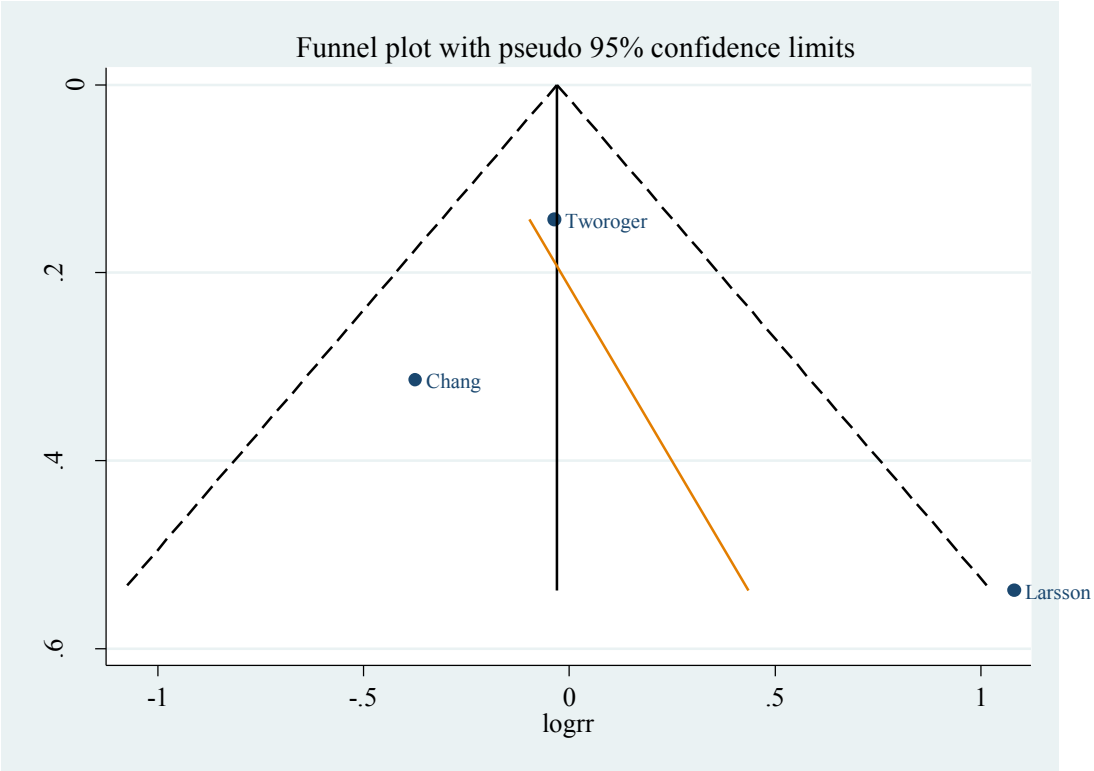
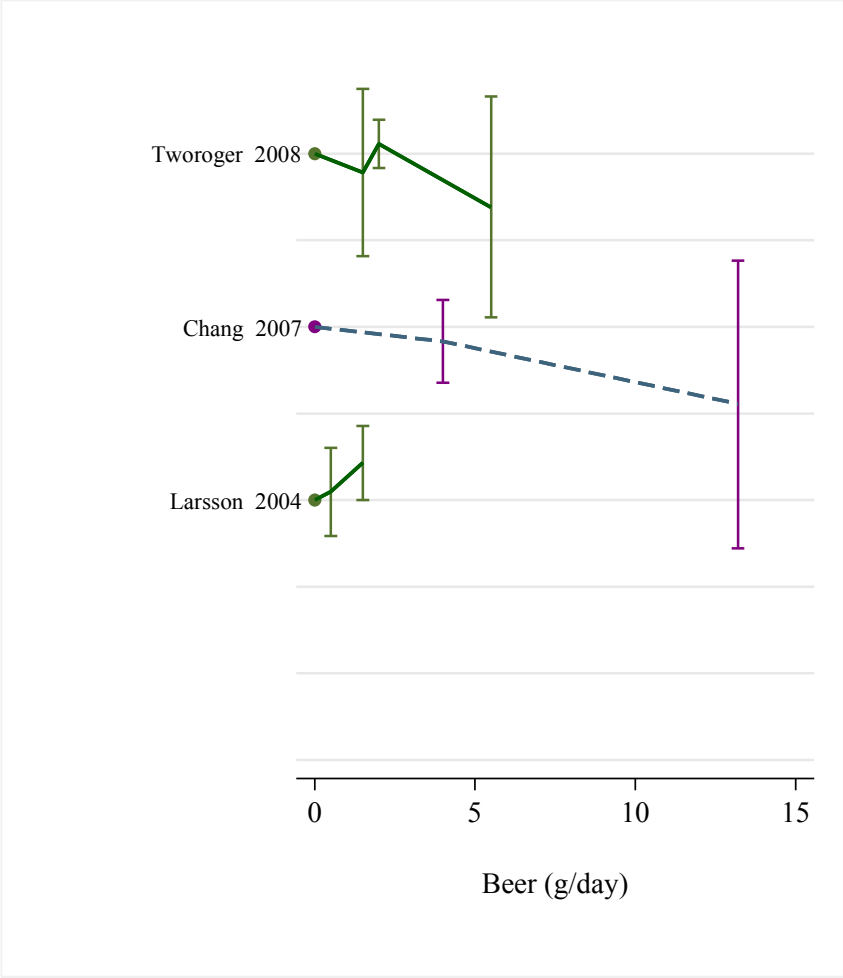


Figure 114 Dose-response graph of beer and ovarian cancer



5.4.1.2 Wine (as ethanol)

Methods

Up to December 2012, reports from four cohort studies were identified; two of them were identified during the CUP. The CUP meta-analysis included four studies (two of them identified during the SLR and two during the CUP). For the dose-response analyses all results were converted to a common scale of exposure level of 10.8 (Tworoger et al, 2008) per glass of wine that was used as an average serving size. The dose-response results are presented for an increment of 10 g/day of wine as ethanol.

Main results

The summary RR per 10 g/day was 1.07 (95% CI: 0.88-1.1.29; I^2= 59.1%, $P_{heterogeneity}$=0.06) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.97-1.02) when excluding the California Teacher's Study (Chang et al, 2007) to 1.17 (95% CI: 0.82-68) when excluding the Nurses' Health Study (Tworoger et al, 2008).

Heterogeneity

High heterogeneity was observed (I^2= 59.1%, p=0.06). Egger's tests did not show evidence of publication bias (p= 0.60).

Comparison with the Second Expert Report

No significant association was observed in the SLR. The CUP results found no evidence of association of wine intake with ovarian cancer risk.

Published meta-analysis

In a published meta-analysis of cohort and case-control studies (Kim HS et al, 2010), the summary RR of ovarian cancer for highest vs. lowest wine intake was 1.14 (95% CI: 0.91-1.43; I^2=88%), based on 10 studies (three cohort and seven case-control studies). When a re-analysis according to the study design was performed, the cohort studies demonstrated that there was also no significant difference in ovarian cancer risk between wine intake and never drinkers, with a RR=1.44 (95% CI: 0.74-2.82; I^2=95%) and 1.04 (95% CI, 0.88 to 1.22; I^2=76%) for the case-control studies.

In a pooled analysis of 10 prospective studies (Genkinger et al, 2006), including 1924 incident epithelial ovarian cancer cases (9 studies included in the analysis), no association with wine intake was observed (multivariate adjusted RR for an increase of 15 g/day 1.07 (95% CI: 0.95-1.21).

When the Pooling Project of Cohort Studies was combined with the non-overlapping study identified in the CUP (Chang et al, 2007, CTS) the pooled RR estimate for an increase of 10g/d of wine as ethanol was 1.23 (95% CI: 0.88-1.72).

Table 121 Studies on wine consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Tworoger, 2008	United States	Nurses' Health Study	507	24	0.85	0.56	1.26	>=1 drink/d vs. non drinkers
Chang, 2007	United States	California Teacher Study	253	8.1	1.57	1.11	1.22	>=11.1 g/d vs. non drinkers

Table 122 Overall evidence on wine consumption and ovarian cancer

	Summary of evidence
SLR	Two cohorts identified during the SLR Showed no association. In the Sweden cohort (Larsson et al, 2004) a significant decreased risk of epithelial ovarian cancer was observed in drinker women with high folate intake.
Continuous Update Project	Two additional cohort studies were identified and included in the meta-analysis from which only one study found a significant and positive association and the other found no association Overall, the CUP meta-analysis included four studies. No association with ethanol from wine was observed in a published pooled analysis of 10 cohort studies.

Table 123 Summary of results of the dose response meta-analysis of wine consumption and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1240
Increment unit used	-	Per 10g/day
Overall RR (95%CI)	-	1.07 (0.88-1.29)
Heterogeneity (I^2,p-value)	-	59.1%, p=0.06
Pooling project and CTS		
Studies (n)		10
Cases (n)		2177
Increment unit used		Per 10g/day
Overall RR (95%CI)		1.23 (0.88-1.72)

*No meta-analysis was conducted in the 2nd report

Table 124 Inclusion/exclusion table for meta-analysis of wine consumption and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11633	Tworoger	2008	Prospective Cohort Study	Nurses' Health Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA11626	Chang	2007	Prospective Cohort Study	California Teacher Study	Incidence	No	Yes	Yes	Person/ years per category	-
OVA010867	Larsson	2004	Prospective Cohort Study	Swedish Mammography Study	Incidence	Yes	Yes	Yes	Cases per category estimation mid-exposure values person/years per category	-
OVA09692	Schouten	2004	Case-Cohort Study	Netherland Cohort Study	Incidence	Yes	Yes	Yes	Rescale of RR for continuous increase	-

Figure 115 Highest versus lowest forest plot of wine consumption and ovarian cancer

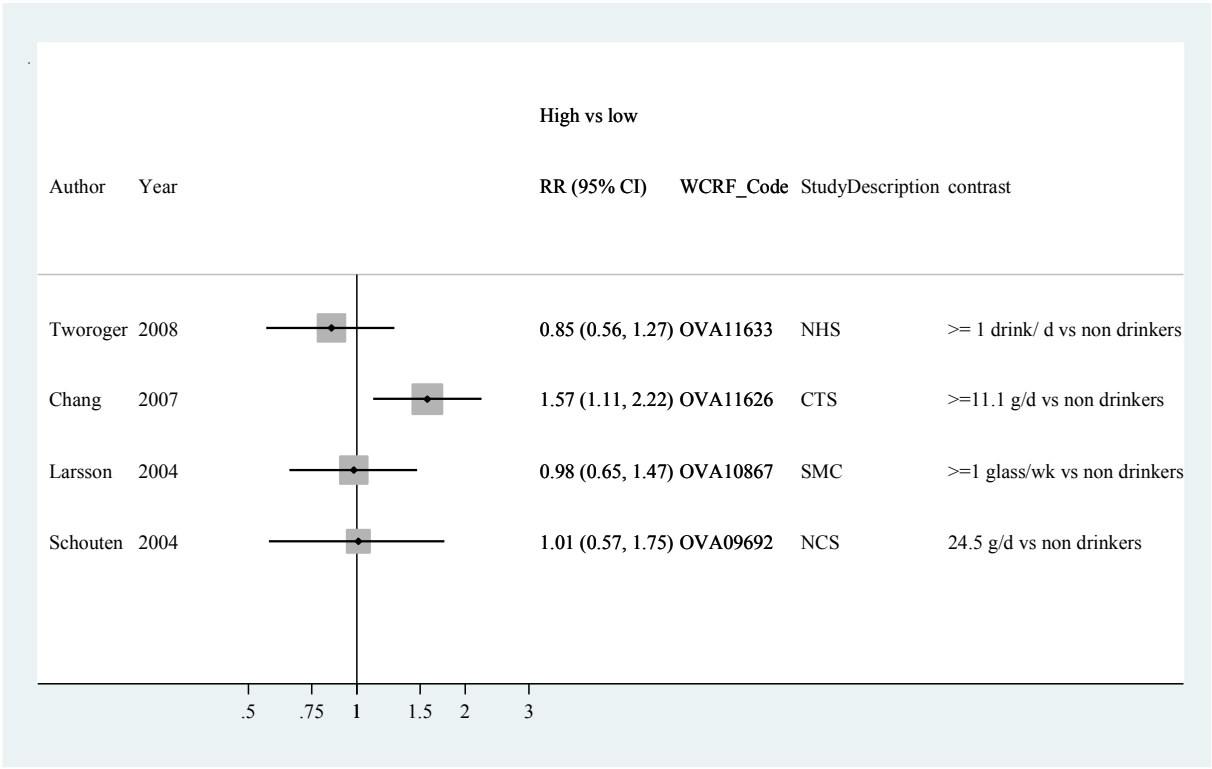


Figure 116 Dose-response meta-analysis of wine and ovarian cancer - per 10 g/d

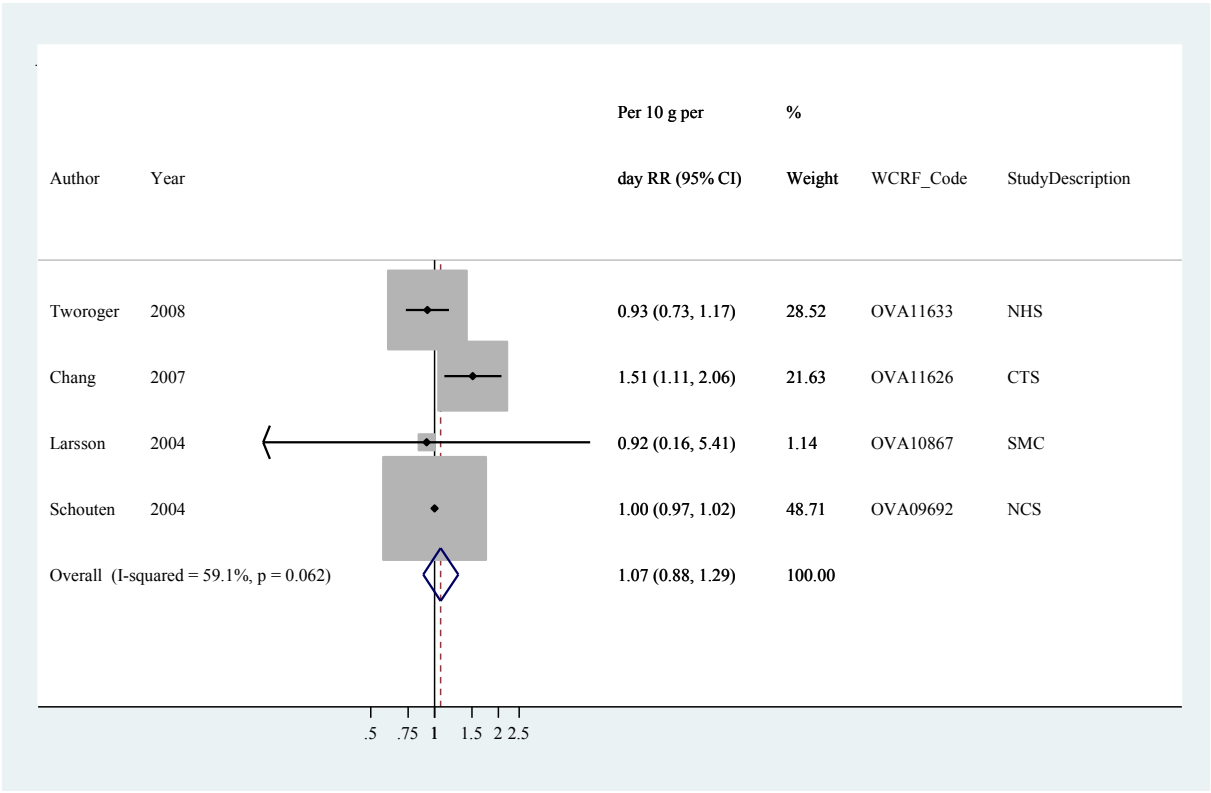


Figure 117 Funnel plot of wine consumption and ovarian cancer

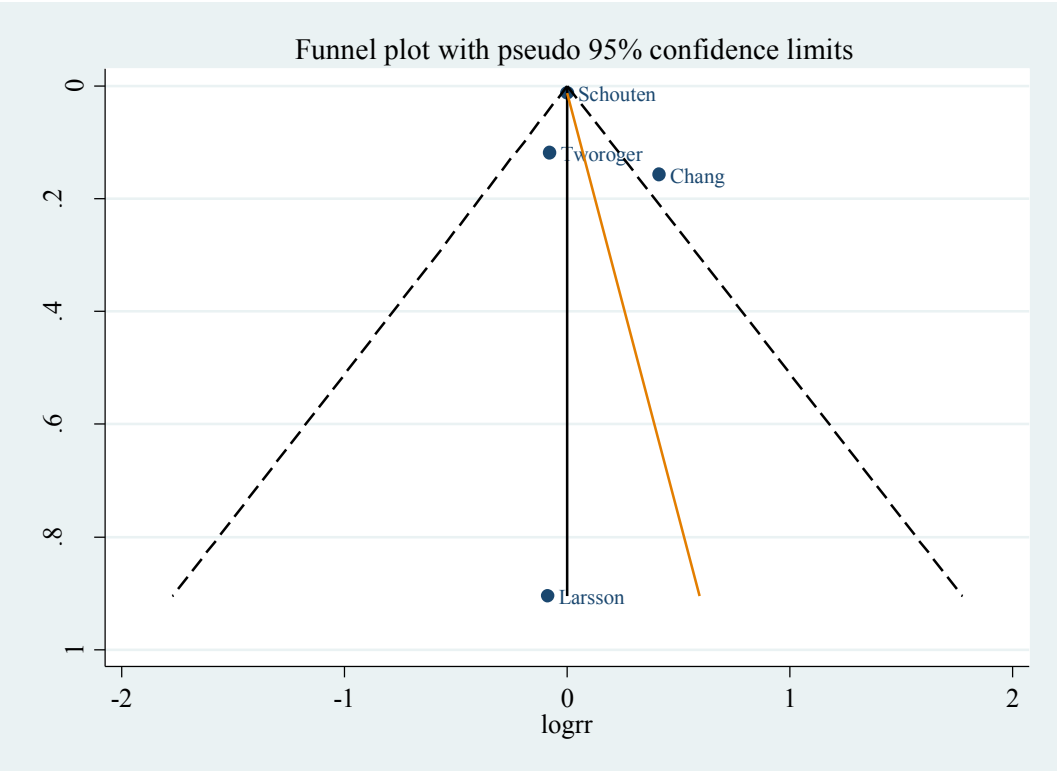
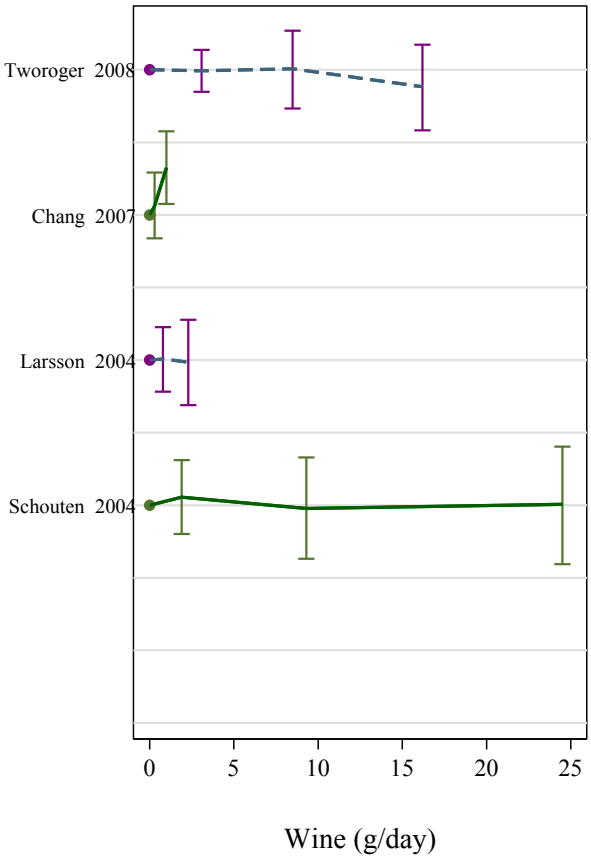


Figure 118 Dose-response graph of wine and ovarian cancer



5.5.1 Dietary vitamin A

Methods

Up to December 2012, four cohort studies were identified, two of which were identified during the Continuous Update Project. One study had amount of intake expressed in µg RAE/day instead of IU and was excluded from meta-analysis. Dose-response analyses were conducted per 2000 IU/day increase.

Main results

The summary RR per 2000 IU/day was 0.99 (95% CI: 0.95 - 1.03, $I^2 = 0\%$, $P_{heterogeneity} = 0.50$) for all studies combined. In influence analysis, the RR did not change significantly excluding any of the three studies.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.50$). Egger's tests suggested no evidence of publication bias (p = 0.83).

Table 125 Studies on dietary vitamin A identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Silvera, 2006	Canada	Canadian National Breast Screening Study	264	16.4	0.77	0.52	1.14	>11534 vs. <6589 IU/day
Thomson, 2008	USA	Women's Health Initiative	352	8.3	0.91	0.62	1.32	>=926 vs. <486 µg RAE/day

Table 126 Overall evidence on dietary vitamin A and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR; both studies found no association between dietary vitamin A intake and ovarian cancer.
Continuous Update Project	Two studies were identified, one of which could be included in the meta-analysis. Both studies reported no association between dietary vitamin A intake and ovarian cancer. Overall, three studies were included in the meta-analysis.

Table 127 Summary of results of the dose response meta-analysis of dietary vitamin A intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	704
Increment unit used	-	Per 2000 IU/day
Overall RR (95%CI)	-	0.99 (0.95 - 1.03)
Heterogeneity (I^2,p-value)	-	0 %, p=0.5

*No meta-analysis was conducted in the 2nd report

Table 128 Inclusion/exclusion table for meta-analysis of dietary vitamin A intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence	No	No	Yes	-	Different units
OVA11645	Silvera	2006	Prospective Cohort study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2001	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	Yes	Yes	Person/ years per category, 95% confidence intervals	-
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category, mid-exposure values	-

Figure 119 Highest versus lowest forest plot of dietary vitamin A intake and ovarian cancer

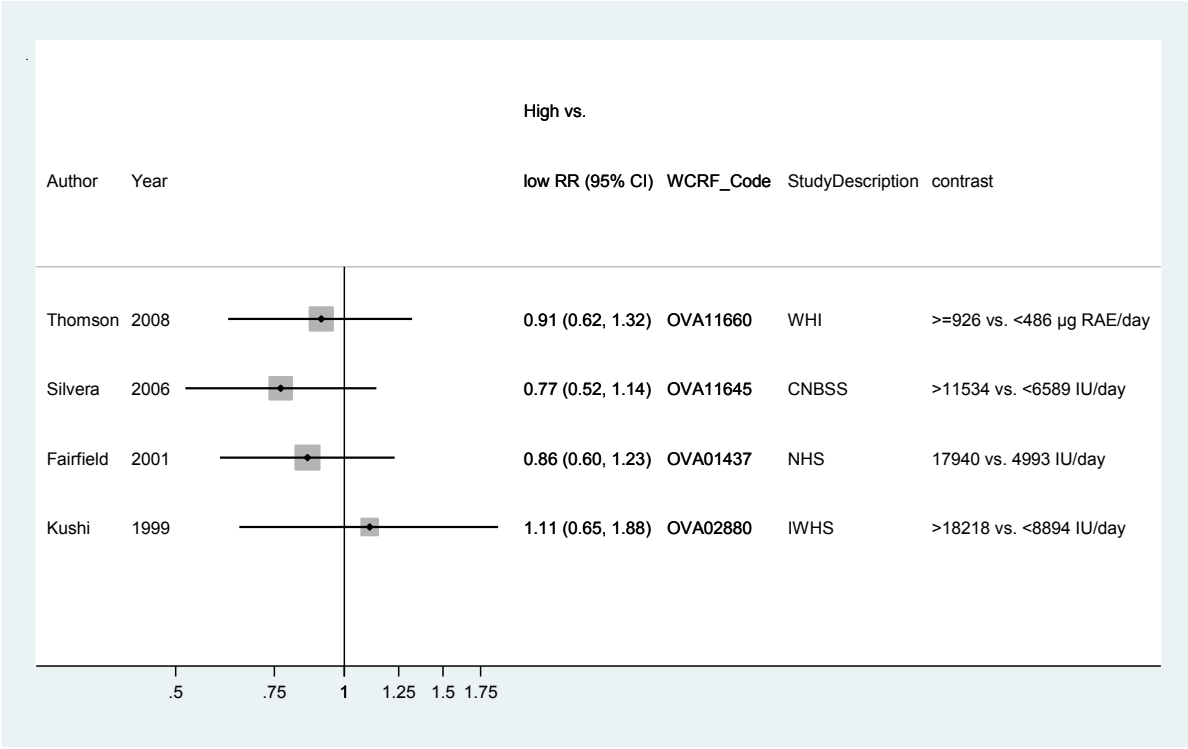


Figure 120 Dose-response meta-analysis of dietary vitamin A intake and ovarian cancer - per 2000 IU/day

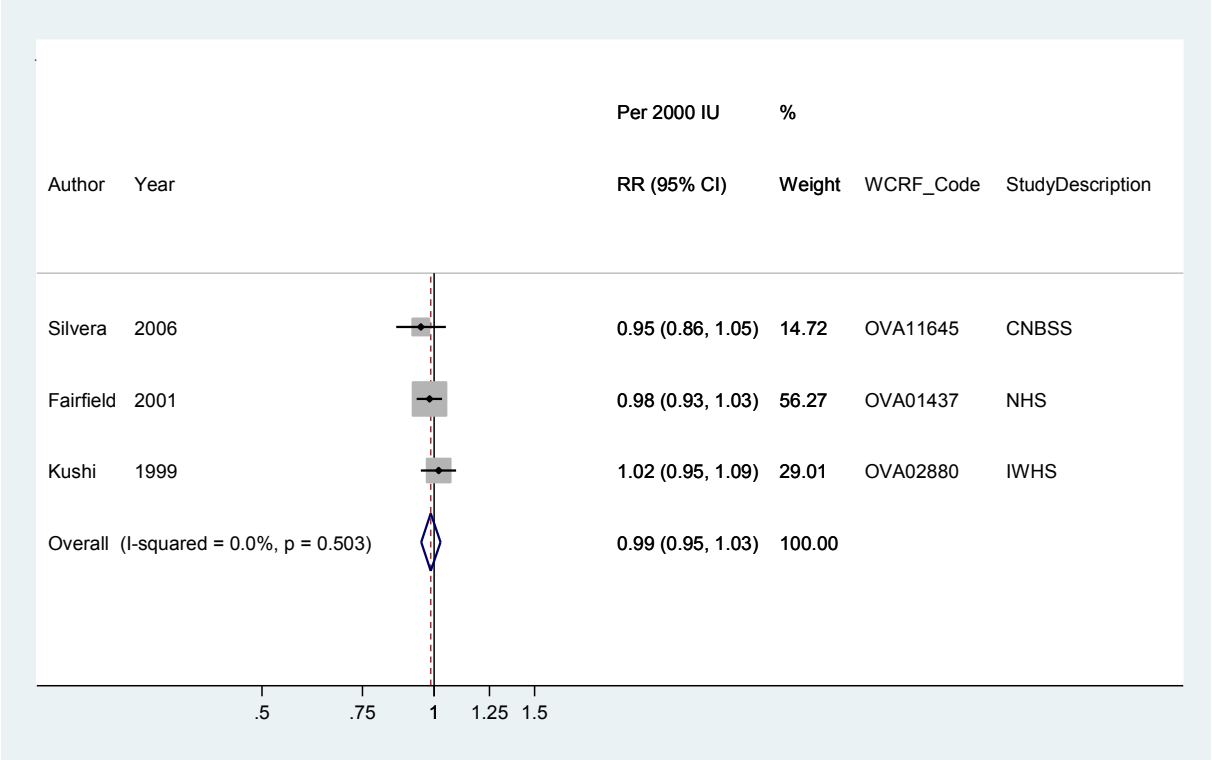


Figure 121 Funnel plot of dietary vitamin A intake and ovarian cancer

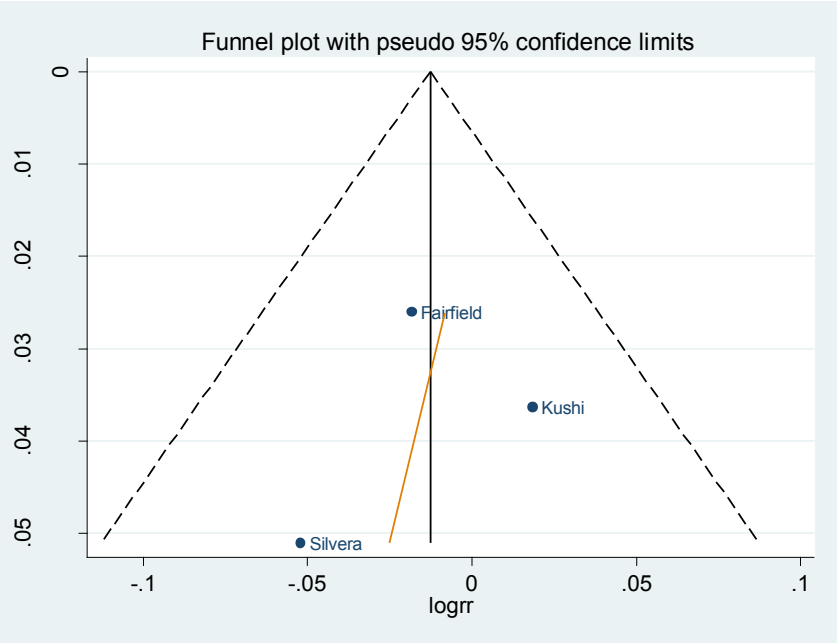
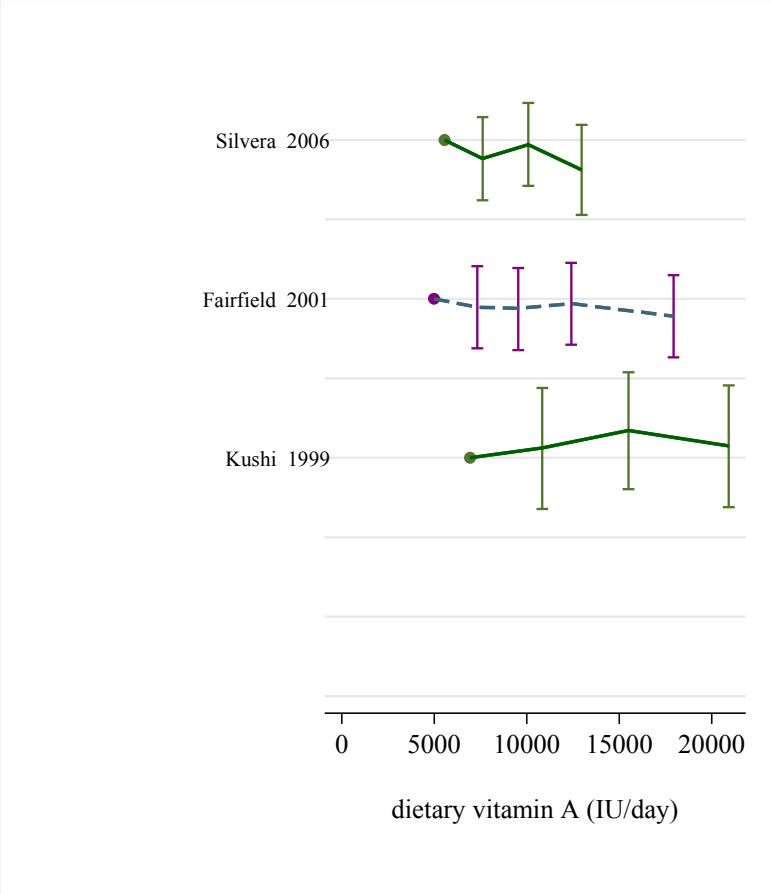


Figure 122 Dose-response graph of dietary vitamin A intake and ovarian cancer



5.5.1.2 Dietary alpha-carotene

Methods

Up to December 2012, three cohort studies were identified, two of which were identified during the Continuous Update Project. Dose-response analyses were conducted per 600 µg/day increase.

Main results

The summary RR per 600 µg/day was 1.00 (95% CI: 0.98 - 1.01, $I^2 = 0\%$, $P_{heterogeneity} = 0.94$) for all studies combined. In influence analysis, the RR was 1.01 (95% CI: 0.89 - 1.14) when excluding the Canadian National Breast Screening Study in which the reported intakes were approximately 20 times higher than in the other two studies and the study weight was 98.7%.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.94$). Egger's tests suggested no evidence of publication bias (p = 0.59).

Published pooled analysis

In a published pooled analysis of 10 prospective studies the summary pooled multivariate RR of ovarian cancer per 600 µg/day alpha-carotene intake was 1.00 (95% CI: 0.95-1.05). Multivariate RR for highest versus lowest quintile of alpha-carotene was 1.00 (0.85-1.18) and there was no evidence of heterogeneity between the studies ($P_{heterogeneity} = 0.23$) (Koushik et al, 2006). The association was not modified by histogical type (p-value test for differences by serous,endometrioid and mucinous cancers =0.35)

When the results of the WHI (Thomson et al, 2008) identified in the CUP were combined with the published pooled analysis (Koushik et al, 2006), the overall RR for a 600 µg/day increase in dietary alpha-carotene was 1.00 (95% CI: 0.95-1.05).

Table 129 Studies on dietary alpha-carotene identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	USA	Women's Health Initiative	352	8.3	1.06	0.77	1.48	>=885 vs. <335µg/day
Silvera, 2006	Canada	Canadian National Breast Screening Study	264	16.4	0.94	0.64	1.38	>15500 vs. 0 µg/day

Table 130 Overall evidence on dietary alpha-carotene and ovarian cancer

	Summary of evidence
SLR	One study was identified during the SLR; no association was reported between dietary α-carotene intake and ovarian cancer.
Continuous Update Project	Two cohort studies were identified. No associations were reported between α-carotene intake and ovarian cancer. Overall, three studies were included in the meta-analysis. A published pooled analysis of 10 cohort studies did not report any association.

Table 131 Summary of results of the dose response meta-analysis of dietary alpha-carotene intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	917
Increment unit used	-	Per 600μg/day
Overall RR (95%CI)	-	1.00 (0.98 - 1.01)
Heterogeneity (I^2,p-value)	-	0 %, p=0.94
Pooling project and WHI study		
Studies (n)		11
Cases (n)		2364
Increment unit used		Per 600μg/day
Overall RR (95%CI)		1.00 (0.95-1.05)

*No meta-analysis was conducted in the 2nd report

Table 132 Inclusion/exclusion table for meta-analysis of dietary alpha-carotene intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence	No	Yes	Yes	Person/ years per category	-
OVA11645	Silvera	2006	Prospective Cohort study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2001	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	Yes	Yes	Person/ years per category, 95% confidence intervals	-

Figure 123 Highest versus lowest forest plot of dietary alpha-carotene intake and ovarian cancer

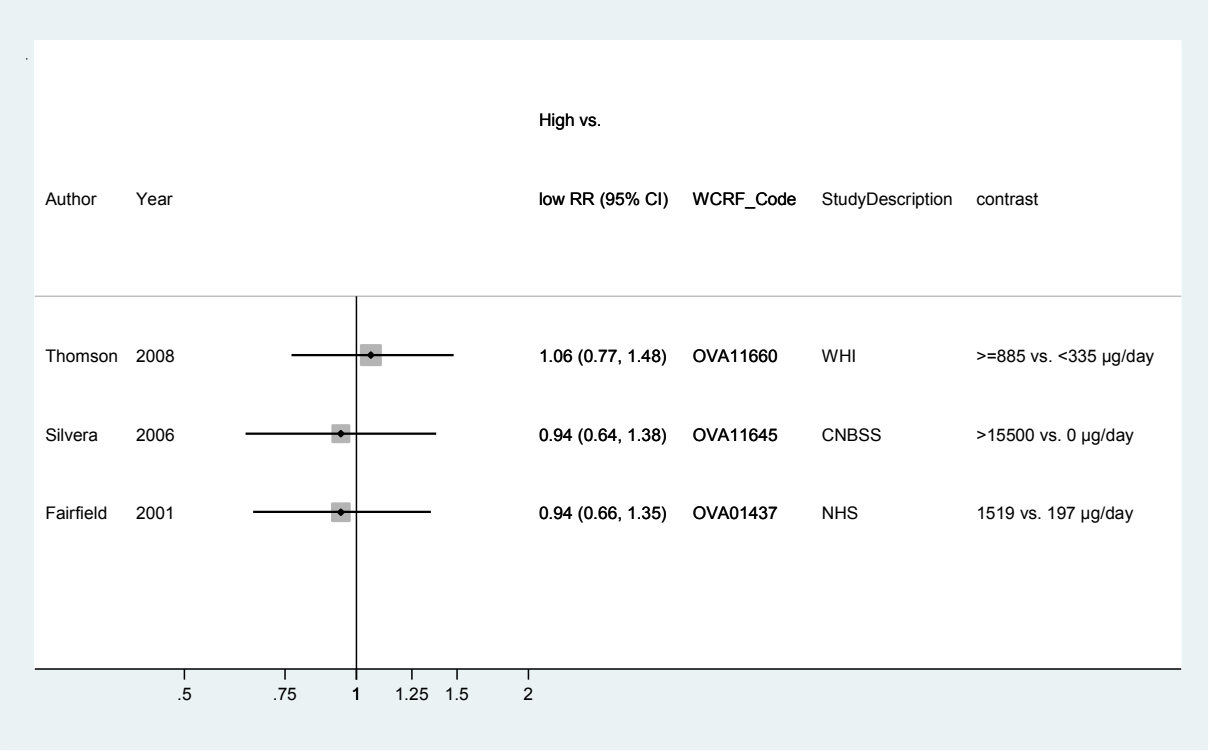


Figure 124 Dose-response meta-analysis of dietary alpha-carotene intake and ovarian cancer - per 600 µg/day

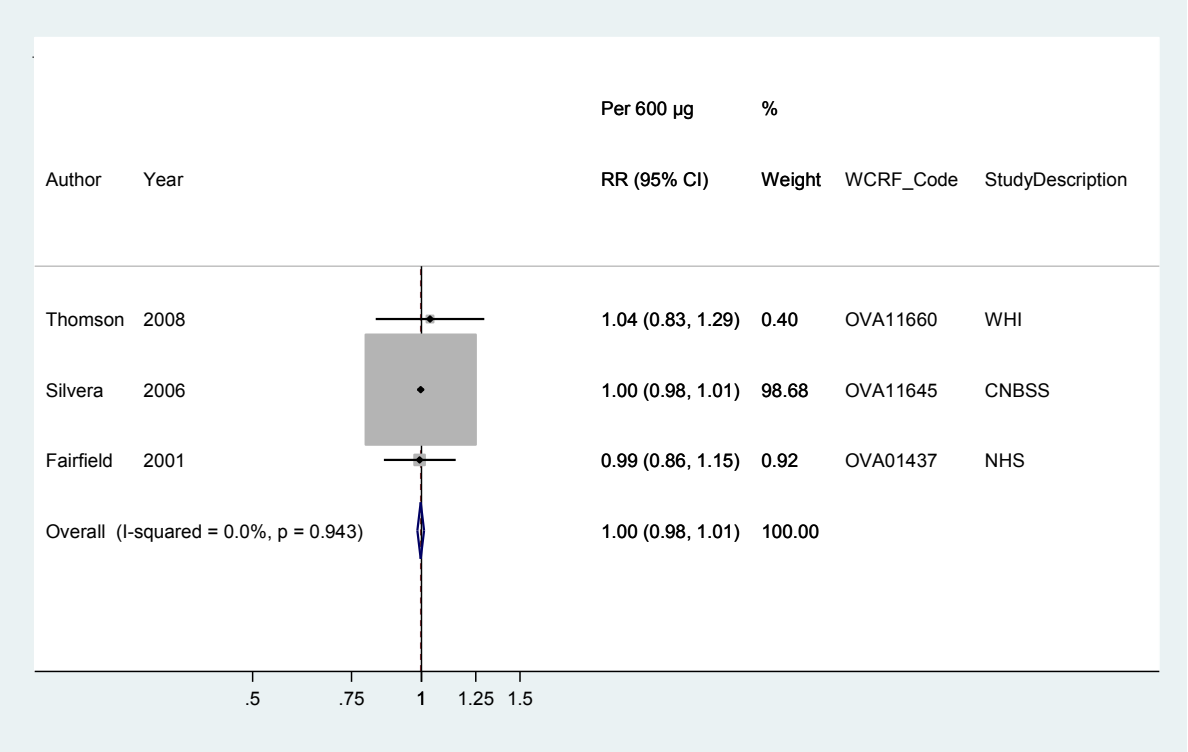


Figure 125 Funnel plot of alpha-carotene intake and ovarian cancer

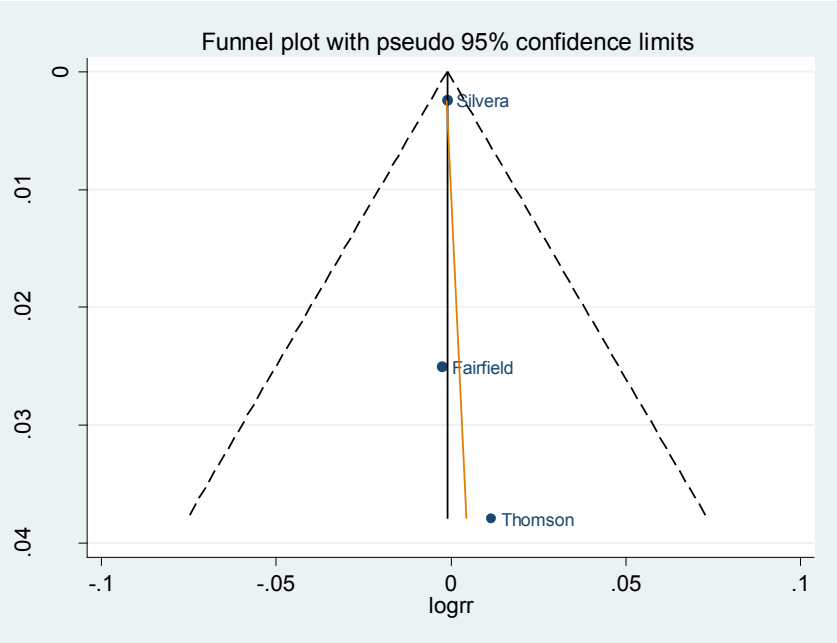
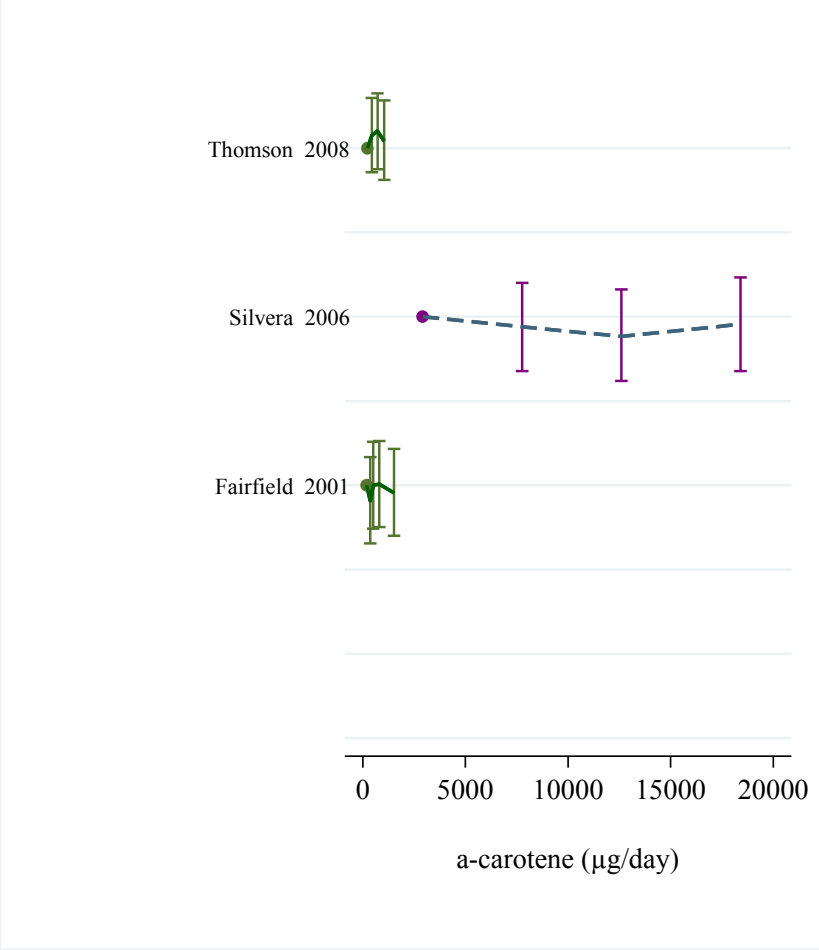


Figure 126 Dose-response graph of alpha-carotene intake and ovarian cancer



5.5.1.2 Total beta-carotene (food and supplement)

Methods

Up to December 2012, reports from three cohort studies were identified; two of them were identified during the CUP and one during the SLR. The CUP meta-analysis included all three studies. The dose-response results are presented for an increment of 1000 µg per day of total beta-carotene intake

Main results

The summary RR per 1000 µg/day was 1.02 (95% CI: 0.99-1.05; I^2= 6.1%, $P_{heterogeneity}$=0.34) for all studies combined. In influence analysis, the RR ranged from 1.01 (95% CI: 0.97-1.05) when excluding the California Teacher's Study (Chang et al, 2007) to 1.03 (95% CI: 1.00-1.06) when excluding the Nurses' Health Study (Fairfield et al, 2001).

Heterogeneity

Low heterogeneity was observed (I^2= 6.1%, p=0.34). Egger's tests did not show evidence of publication bias (p= 0.77), but only three studies were included in the analysis.

Comparison with the Second Expert Report

Only one study on total beta-carotene intake and ovarian cancer was identified during the SLR. This study did not show any association.

Table 133 Studies on total beta-carotene intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	United States	Women's Health Initiative	352	7	1.30	0.94	1.80	>=7605µg/d vs <2331 µg/d
Chang, 2007	United States	California Teacher Study	280	8.1	1.41	0.85	2.33	>4601 µg/d vs <=1409 µg/d

Table 134 Overall evidence on total beta-carotene intake and ovarian cancer

	Summary of evidence
SLR	One prospective cohort study (Nurses' Health Study, Fairfield et al., 2001) suggested no association between total beta-carotene intake and ovarian cancer.
Continuous Update Project	Two cohort studies were identified during the CUP. None of the studies found any association between total beta-carotene intake and ovarian cancer.

Table 135 Summary of results of the dose response meta-analysis of total beta-carotene intake and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	933
Increment unit used	-	Per 1000 μg /day
Overall RR (95%CI)	-	1.02 (0.99-1.05)
Heterogeneity (I^2,p-value)	-	6.1%, p=0.34

*No meta-analysis was conducted in the 2nd report

Table 136 Inclusion/exclusion table for meta-analysis of total beta-carotene intake and ovarian cancer

WCRF Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11654	Chang	2007	Prospective Cohort Study	California Teacher Study	Incidence	No	Yes	Yes	Person/ years per category	-
OVA01437	Fairfield	2001	Prospective Cohort Study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Cases per category Confidence interval re-estimation Person/ years per category	-

Figure 127 Highest versus lowest forest plot of total beta-carotene intake and ovarian cancer

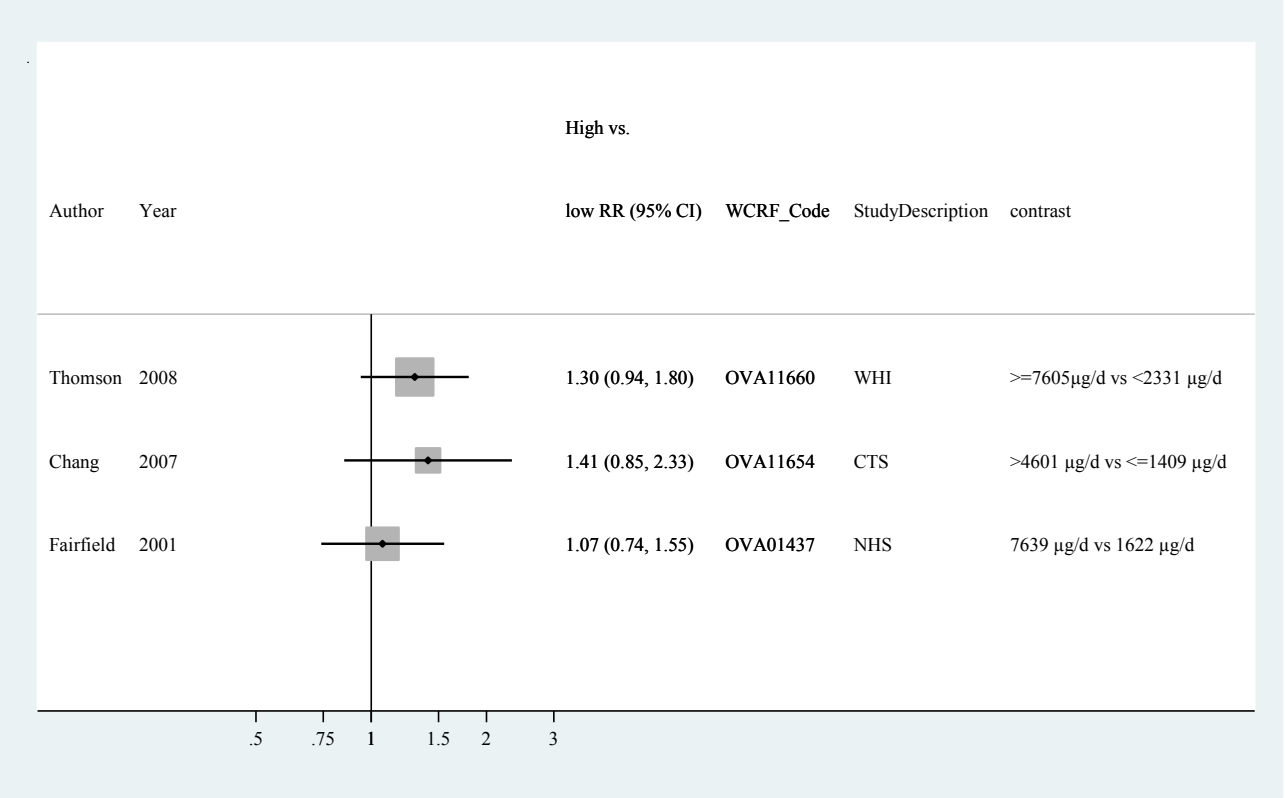


Figure 128 Dose-response meta-analysis of total beta-carotene and ovarian cancer - per 1000 µg /d

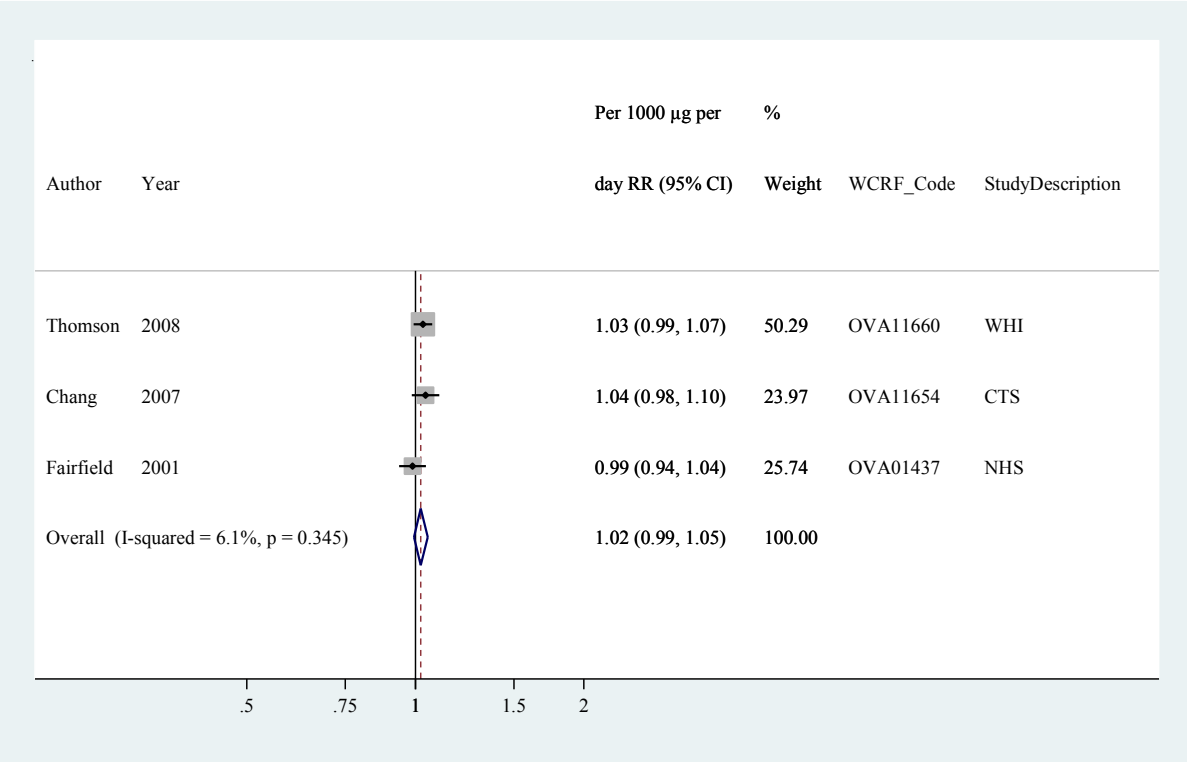


Figure 129 Funnel plot of total beta-carotene intake and ovarian cancer

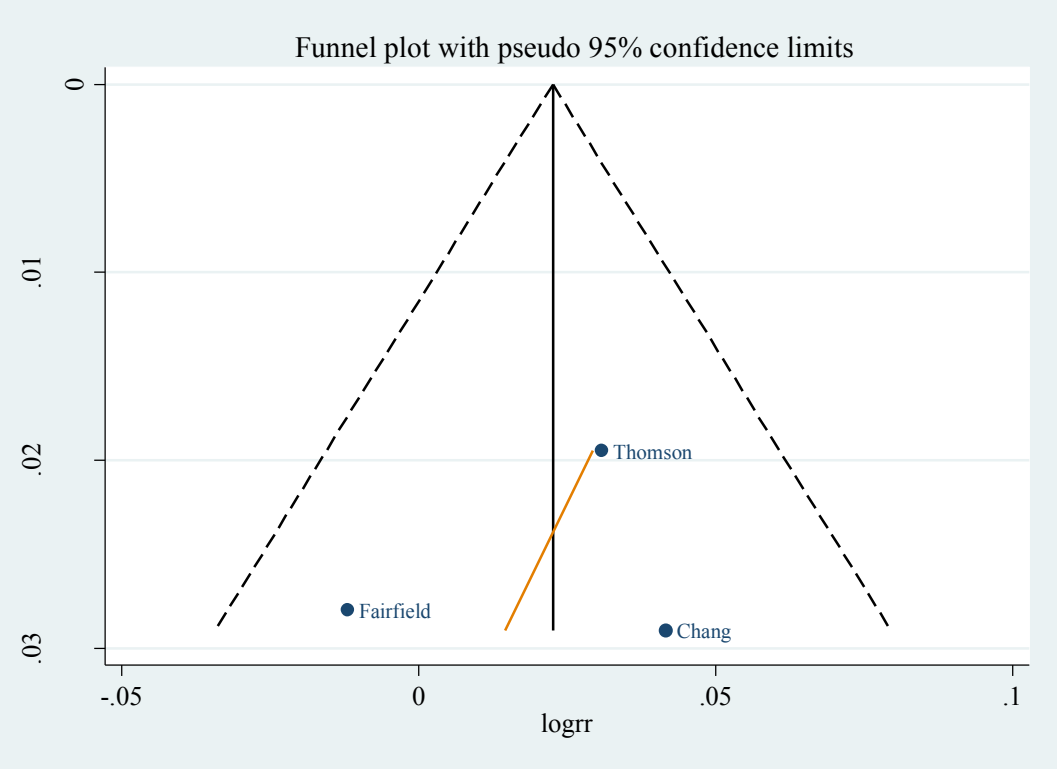
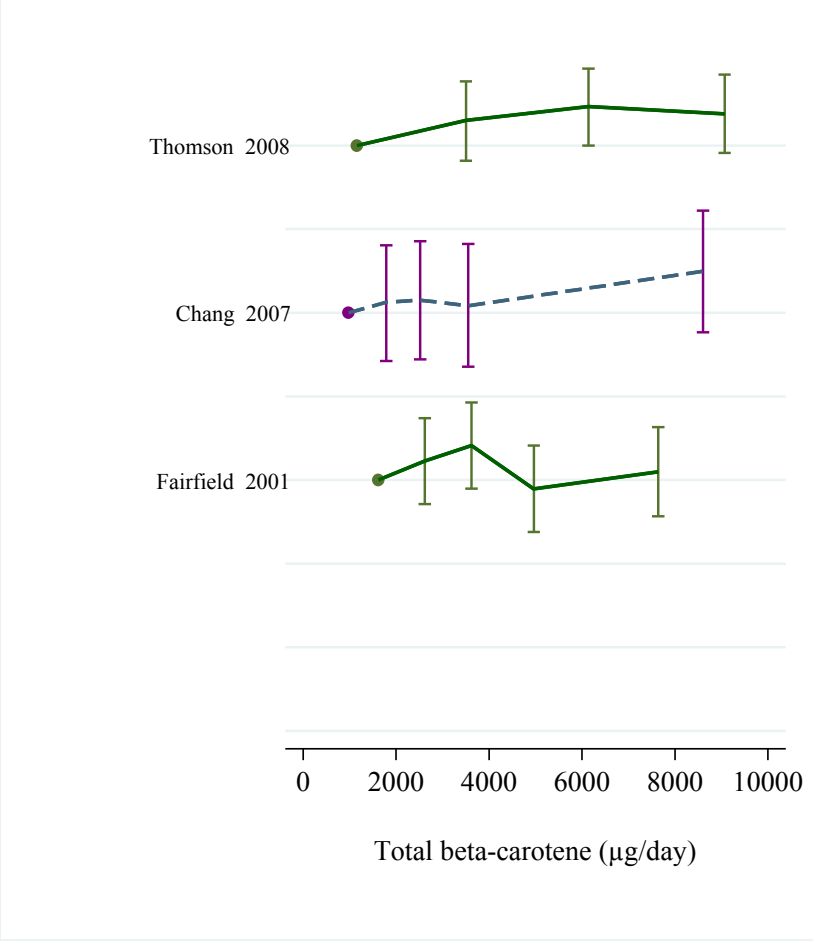


Figure 130 Dose-response graph of total beta-carotene and ovarian cancer



5.5.1.2 Dietary beta-carotene

Methods

Up to December 2012, five cohort studies were identified, three of which were identified during the Continuous Update Project. In one study (Kushi et al, 1999) the intake of dietary beta-carotene in IU was rescaled to µg/day using conversion factor available in Dietary Supplement Ingredient Database (USDA, 2012). Study by Chang et al, 2007 had no intake data and was only used for high versus low analysis. Dose-response analyses were conducted per 2500 µg/day increase.

Main results

The summary RR per 2500 µg/day was 0.99 (95% CI: 0.92 - 1.07, $I^2 = 0\%$, $P_{heterogeneity} = 0.996$) for all studies combined. In influence analysis, the RR did not change significantly when any of the four studies were excluded.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.996$). Egger's tests suggested no evidence of publication bias ($p = 0.78$).

Published pooled analysis

In a published pooled analysis of 10 prospective studies the summary pooled multivariate RR of ovarian cancer per 2500 µg/day beta-carotene intake was 0.98 (95% CI: 0.93-1.03). Multivariate RR for highest versus lowest quintile of beta-carotene was 0.95 (0.82-1.10) and there was no evidence of heterogeneity between the studies ($P_{heterogeneity} = 0.43$) (Koushik et al, 2006).

When the results of the WHI (Thomson et al, 2008) identified in the CUP were added to the pooled analysis published by Koushik et al, 2006 the overall RR for a 2500 µg/day increase in dietary beta-carotene was 0.98 (95% CI: 0.93-1.03).

Table 137 Studies on dietary beta-carotene identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	USA	Women's Health Initiative	352	8.3	1.02	0.74	1.41	>=4122 vs. <1750µg/day
Chang, 2007	USA	California Teachers Study, 1995	280	8.1	1.78	0.83	3.80	Highest vs. lowest
Silvera, 2006	Canada	Canadian National Breast Screening Study	264	16.4	0.97	0.66	1.43	>7000 vs. 0 µg/day

Table 138 Overall evidence on dietary beta-carotene and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR; both studies found no association between dietary beta-carotene intake and ovarian cancer.
Continuous Update Project	Three cohort studies were identified; two of which could be included in the meta-analysis. No associations were found in any of these studies. Overall, four studies were included in the meta-analysis. No association was reported in a published pooled analysis of 10 cohort studies

Table 139 Summary of results of the dose response meta-analysis of dietary beta-carotene intake and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1056
Increment unit used	-	Per 2500µg/day
Overall RR (95%CI)	-	0.99 (0.92 - 1.07)
Heterogeneity (I^2,p-value)	-	0 %, p=0.996
Pooling project and WHI study		
Studies (n)		11
Cases (n)		2364
Increment unit used		Per 2500 µg/day
Overall RR (95%CI)		0.98 (0.93-1.03)

*No meta-analysis was conducted in the 2nd report

Table 140 Inclusion/exclusion table for meta-analysis of dietary beta-carotene intake and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence	No	Yes	Yes	Person/ years per category	-
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study 1995	Incidence	No	No	Yes	-	Only high vs. low data
OVA11645	Silvera	2006	Prospective Cohort study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2001	Prospective Cohort study	Nurses' Health Study (NHS) Cohort 1976-1996	Incidence	Yes	Yes	Yes	Person/ years per category, 95% confidence intervals	-
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category, intake in IU/day rescaled to µg/day, mid-exposure values	-

Figure 131 Highest versus lowest forest plot of dietary beta-carotene intake and ovarian cancer

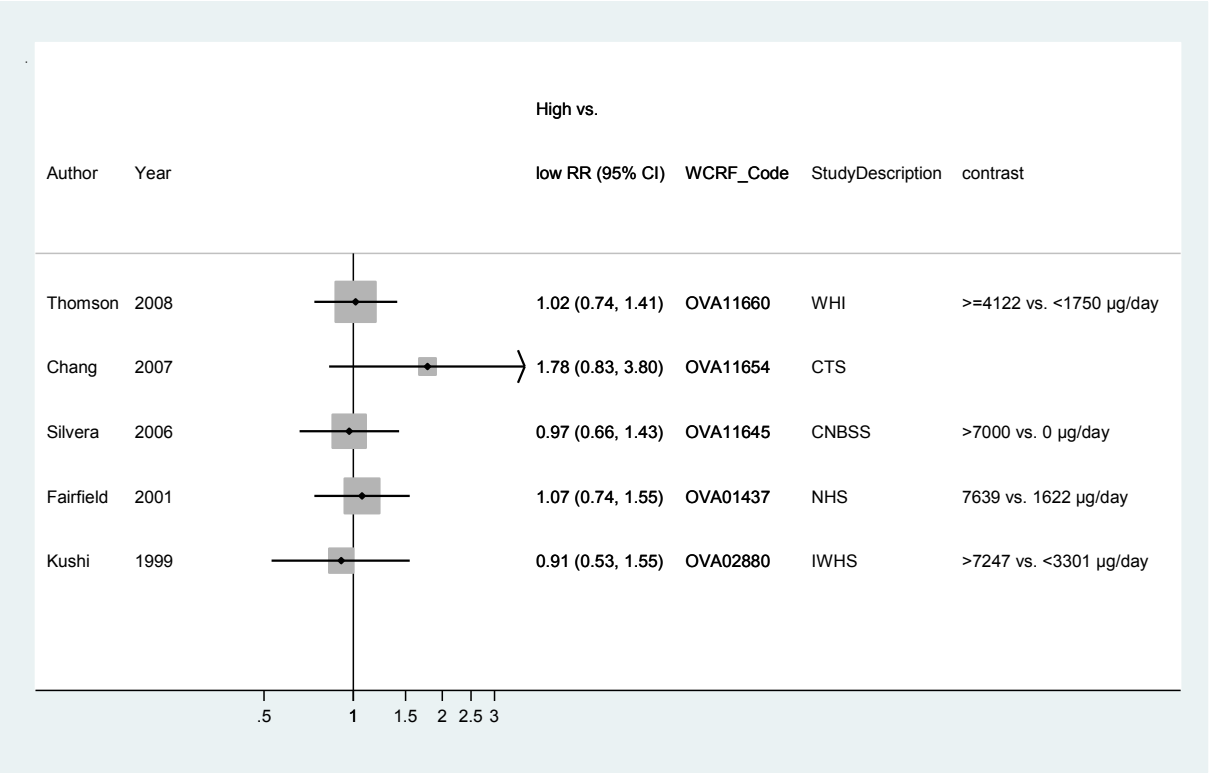


Figure 132 Dose-response meta-analysis of dietary beta-carotene intake and ovarian cancer - per 2500 µg/day

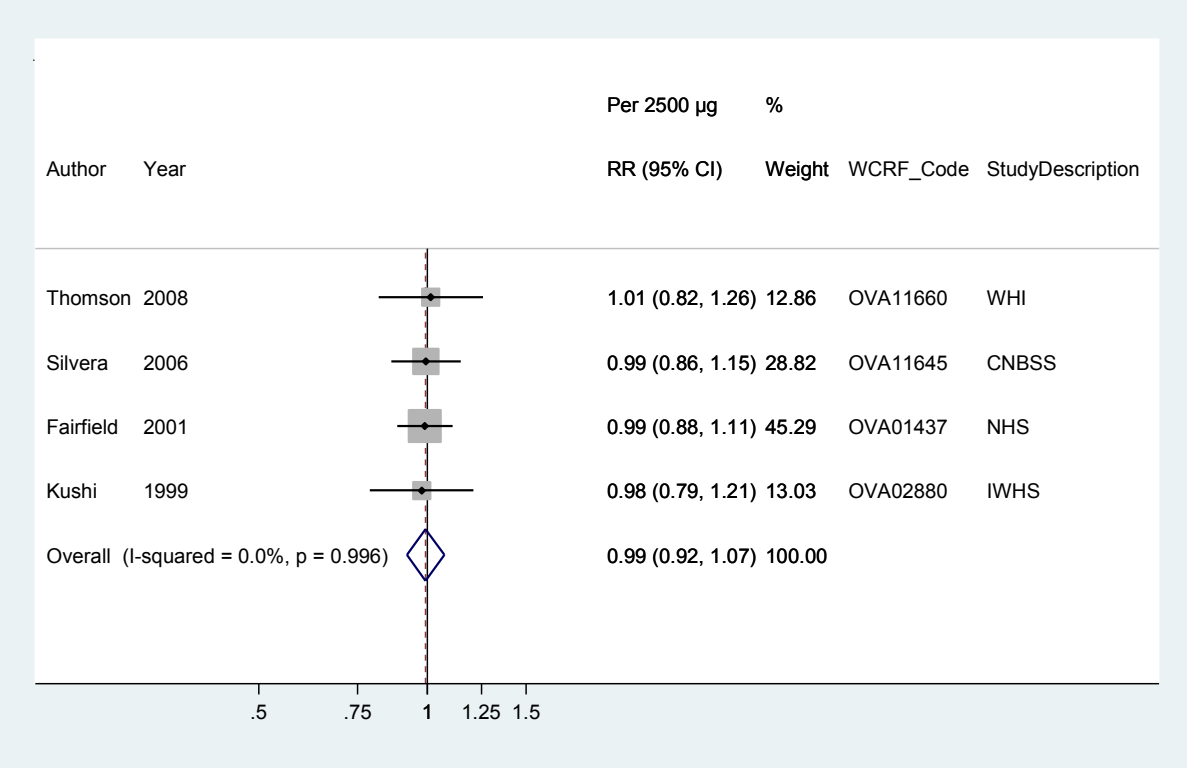


Figure 133 Funnel plot of dietary beta-carotene intake and ovarian cancer

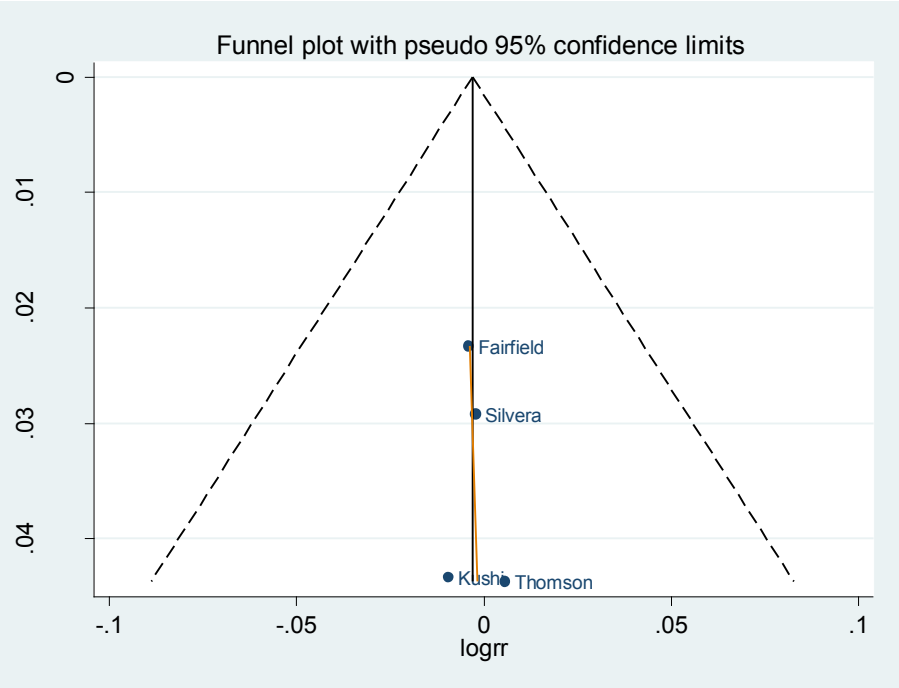
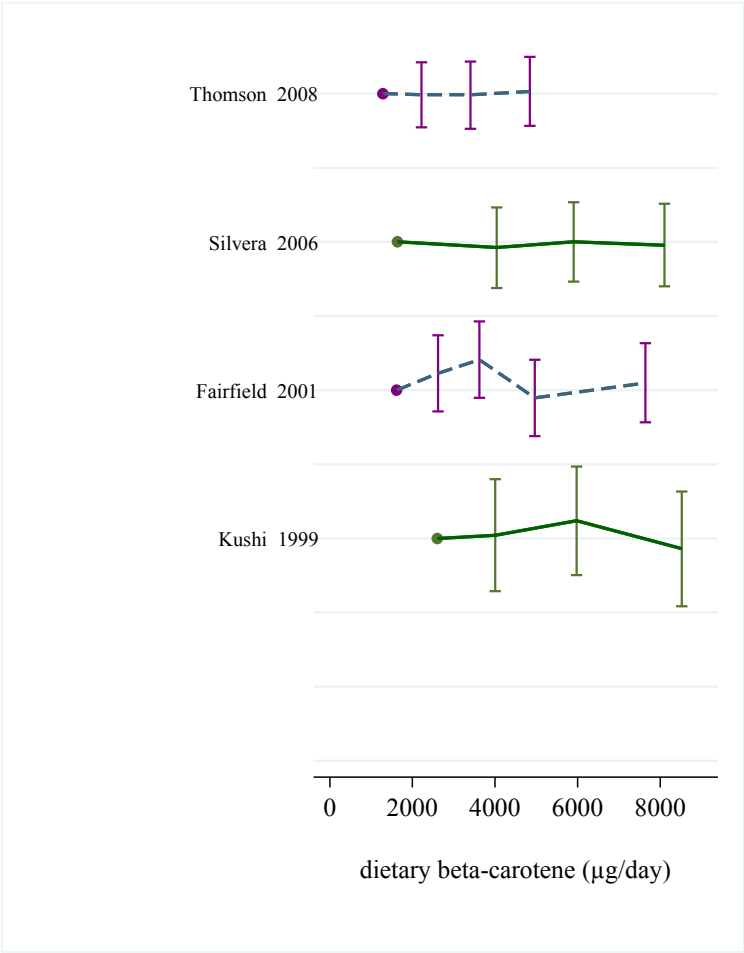


Figure 134 Dose-response graph of dietary beta-carotene intake and ovarian cancer



5.5.1.2 Dietary beta-cryptoxanthin

Methods

Up to December 2012, reports from three cohort studies were identified; two of them were identified during the CUP and one during the SLR. The CUP meta-analysis included all three studies. The dose-response results are presented for an increment of 100 µg per day of dietary beta-cryptoxanthin intake

Main results

The summary RR per 100 µg/day was 1.02 (95% CI: 0.90-1.15; I^2= 0%, $P_{heterogeneity}$=0.99) for all studies combined. In influence analysis, the RR ranged from 1.01 (95% CI: 0.87-1.17) when excluding the Nurses' Health Study (Fairfield et al, 2007) to 1.01 (95% CI: 0.89-1.16) when excluding the Canadian National Breast Cancer Screening Study (Silvera et al, 2006).

Heterogeneity

No heterogeneity was observed (I^2= 0%, p=0.99). Egger's tests did not show evidence of publication bias (p= 0.55), but only three studies were included in the analysis.

Comparison with the Second Expert Report

Only one study on dietary beta-cryptoxanthin intake and ovarian cancer was identified during the SLR. This study did not show any association.

Published meta-analyses or pooling studies

Published results from the Pooling Project of Prospective Studies of Diet and Cancer (Koushik et al, 2006), showed no association between beta-crytoxanthin intake and ovarian cancer, with a multivariate RR of 0.99 (95% CI: 0.97-1.02, $P_{heterogeneity}$=0.93) for a 100 µg /day increment.

When the results of the WHI study (Thomson et al, 2008) were combined with the published pooled analysis (Koushik et al, 2006), the overall RR for a 100 µg/day increase in beta-cryptoxanthin was 0.99 (95% CI: 0.96-1.02; $P_{heterogeneity}$=0.75).

Table 141 Studies on dietary beta-cryptoxanthin intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	United States	Women's Health Initiative	352	7	1.02	0.74	1.41	>=196 µg/day vs <78 µg/day
Silvera, 2006	Canada	Canadian National Breast Cancer Screening Study	264	8.1	1.01	0.67	1.55	>143 µg/day vs 0 µg/day

Table 142 Overall evidence on dietary beta-cryptoxanthin intake and ovarian cancer

	Summary of evidence
SLR	One prospective cohort study (Nurses' Health Study, Fairfield et al., 2001) suggested no association between dietary beta-cryptoxanthin intake and ovarian cancer.
Continuous Update Project	Two cohort studies were identified during the CUP. None of the studies found any association between dietary beta-cryptoxanthin intake and ovarian cancer. No association was reported by the published pooling project of 10 cohorts.

Table 143 Summary of results of the dose response meta-analysis of dietary beta-cryptoxanthin intake and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	917
Increment unit used	-	Per 100 µg /day
Overall RR (95%CI)	-	1.02 (0.90-1.15)
Heterogeneity (I^2,p-value)	-	0%, p=0.99
Pooling project and WHI study		
Studies (n)		11
Cases (n)		2364
Increment unit used		Per 100 µg /day
Overall RR (95%CI)		0.99 (0.96-1.02)

*No meta-analysis was conducted in the 2nd report

Table 144 Inclusion/exclusion table for meta-analysis of dietary beta-cryptoxanthin intake and ovarian cancer

WCRF Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11654	Silvera	2006	Prospective Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2004	Prospective Cohort Study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Cases per category Confidence interval re-estimation Person/ years per category	-

Figure 135 Highest versus lowest forest plot of dietary beta-cryptoxanthin intake and ovarian cancer

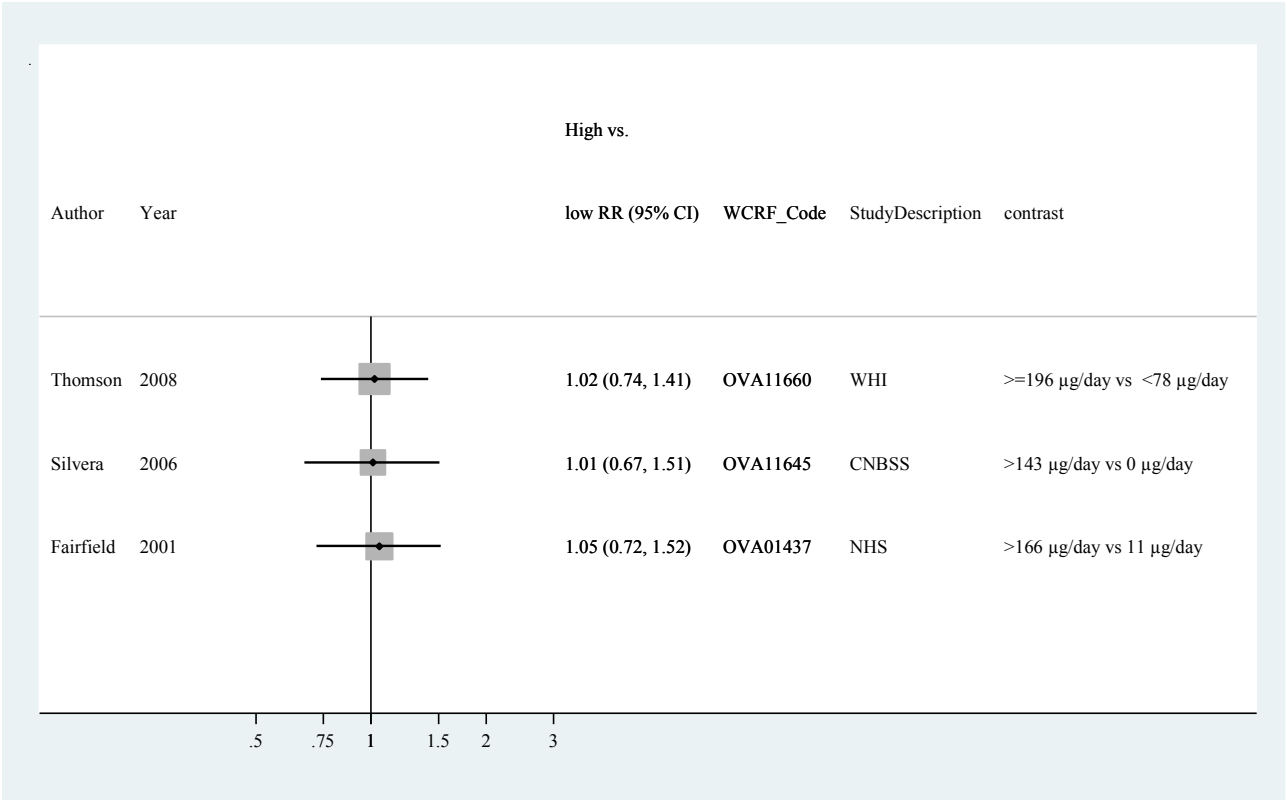


Figure 136 Dose-response meta-analysis of dietary beta-cryptoxanthin and ovarian cancer - per 100 µg /d

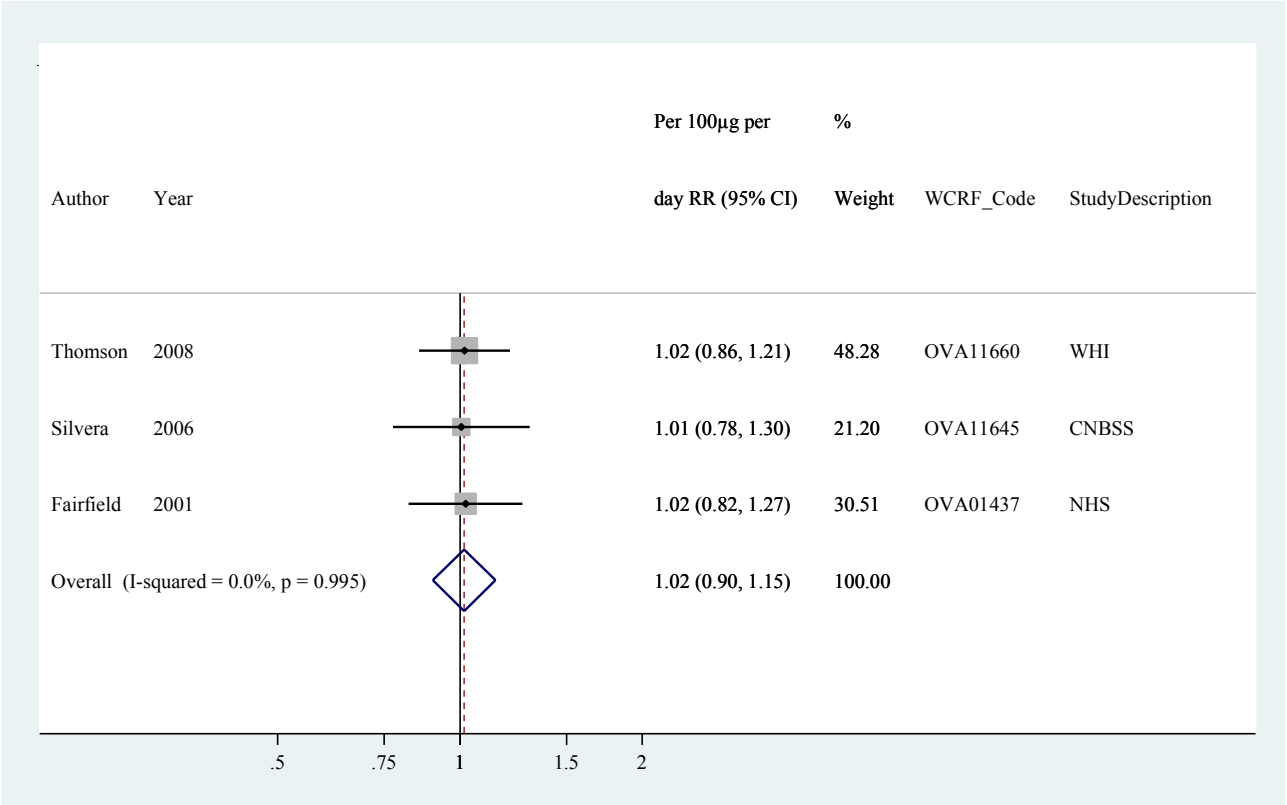


Figure 137 Funnel plot of dietary beta-cryptoxanthin intake and ovarian cancer

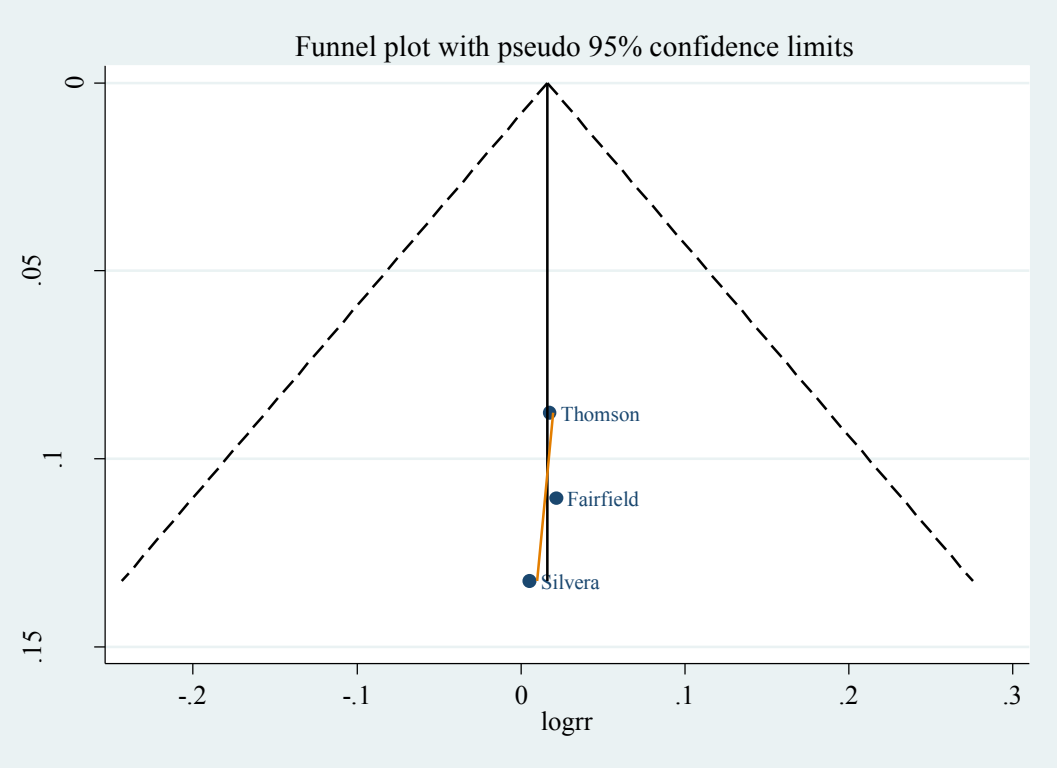
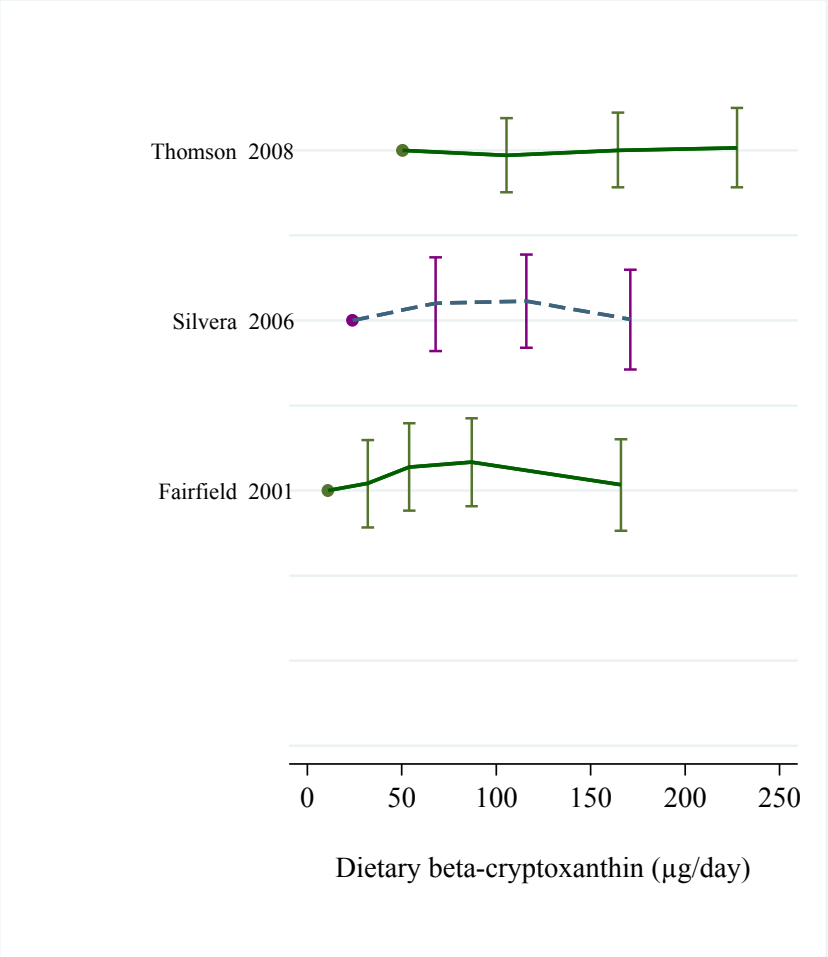


Figure 138 Dose-response graph of dietary beta-cryptoxanthin and ovarian cancer



5.5.2 Dietary lycopene

Methods

Up to December 2012, reports from three cohort studies were identified; two of them were identified during the CUP and one during the SLR. The CUP meta-analysis included all three studies. The dose-response results are presented for an increment of 4000 µg per day of dietary lycopene intake.

Main results

The summary RR per 4000 µg/day was 1.00 (95% CI: 0.93-1.07; I^2= 0%, $P_{heterogeneity}$=0.84) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.92-1.07) when excluding the Women's Health Initiative (Thomson et al, 2008) to 1.02 (95% CI: 0.91-1.14) when excluding the Canadian National Breast Cancer Screening Study (Silvera et al, 2006).

Heterogeneity

No heterogeneity was observed (I^2= 0%, p=0.84). Egger's tests showed evidence of publication bias (p= 0.04), but only three studies were included in the analysis.

Comparison with the Second Expert Report

Only one study on dietary lycopene intake and ovarian cancer was identified during the SLR. This study did not show any association.

Published meta-analyses or pooling studies

Published results from the Pooling Project of Prospective Studies of Diet and Cancer (Koushik et al, 2006), showed no association between lycopene intake and ovarian cancer, with a multivariate RR of 1.01 (95% CI: 0.97-1.05, $P_{heterogeneity}$=0.90) for a 4000 µg /day increment.

When the results of the WHI study (Thomson et al, 2008) were combined with the pooled analysis by Koushik et al, 2006, the overall RR for a 4000 µg/day increase in lycopene was 1.01 (95% CI: 0.97-1.05).

Table 145 Studies on dietary lycopene intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	United States	Women's Health Initiative	352	7	1.02	0.73	1.43	>=6325 µg /d vs <2736 µg /d
Silvera, 2006	Canada	Canadian National Breast Cancer Screening Study	264	8.1	0.92	0.63	1.34	>15000 µg /d vs 0 µg /d

Table 146 Overall evidence on dietary lycopene intake and ovarian cancer

	Summary of evidence
SLR	One prospective cohort study (Nurses' Health Study, Fairfield et al., 2001) suggested no association between dietary lycopene intake and ovarian cancer.
Continuous Update Project	Two cohort studies were identified during the CUP. None of the studies found any association between dietary lycopene intake and ovarian cancer. No association was reported by a pooled analysis of cohort studies.

Table 147 Summary of results of the dose response meta-analysis of dietary lycopene intake and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	824
Increment unit used	-	Per 4000 µg /day
Overall RR (95%CI)	-	1.00 (0.93-1.07)
Heterogeneity (I^2,p-value)	-	0%, p=0.84
Pooling project and WHI study		
Studies (n)		11
Cases (n)		2364
Increment unit used		Per 4000 µg /day
Overall RR (95%CI)		1.01 (0.97-1.05)

*No meta-analysis was conducted in the 2nd report

Table 148 Inclusion/exclusion table for meta-analysis of dietary lycopene intake and ovarian cancer

WCRF Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11654	Silvera	2006	Prospective Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2004	Prospective Cohort Study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Cases per category Confidence interval re-estimation Person/ years per category	-

Figure 139 Highest versus lowest forest plot of dietary lycopene intake and ovarian cancer

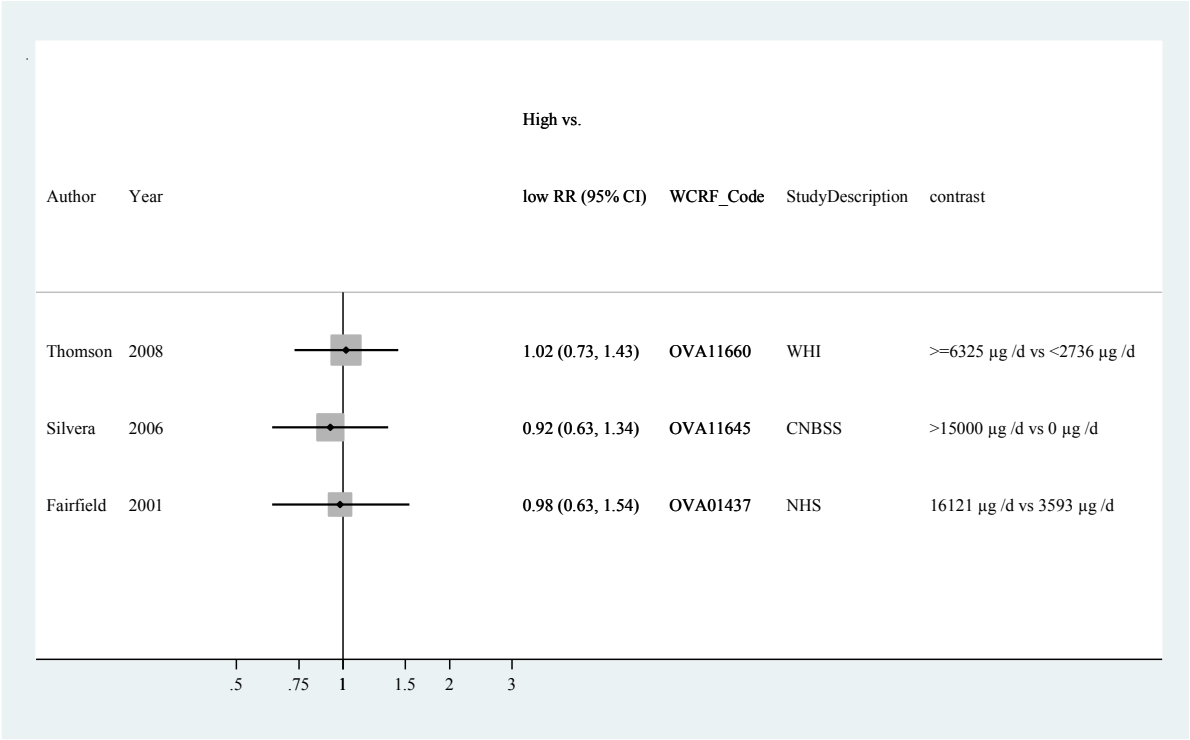


Figure 140 Dose-response meta-analysis of dietary lycopene and ovarian cancer - per 4000 µg /d

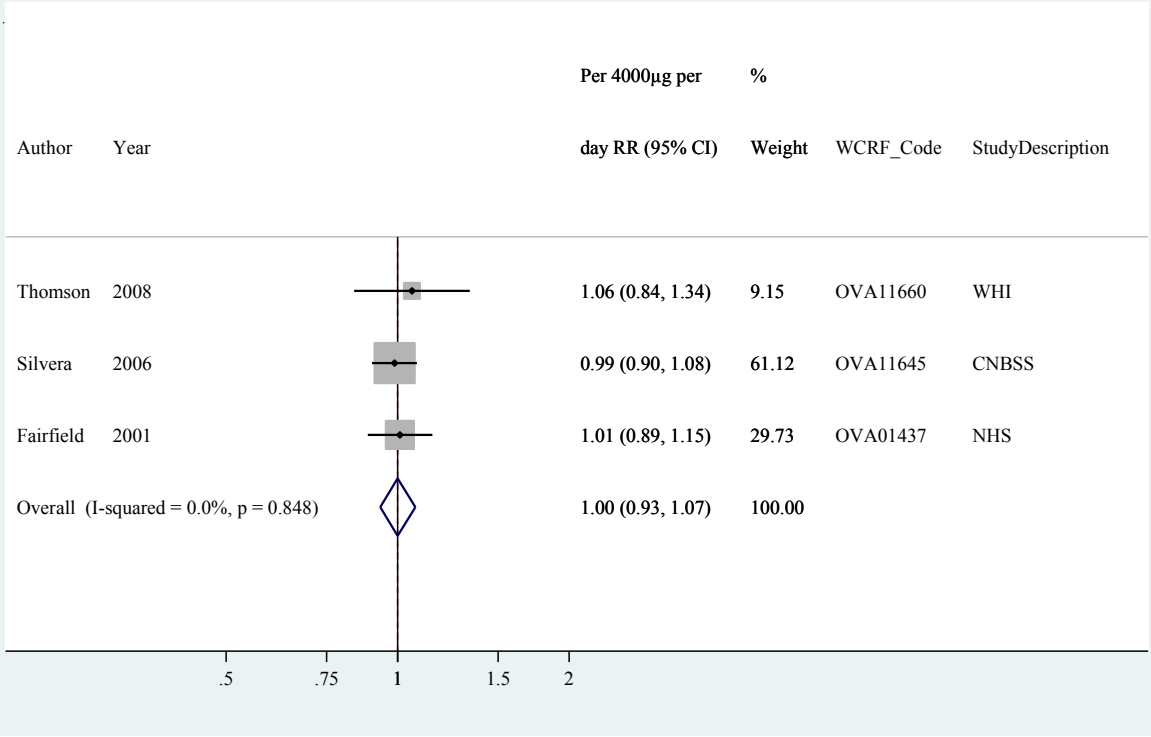


Figure 141 Funnel plot of dietary lycopene intake and ovarian cancer

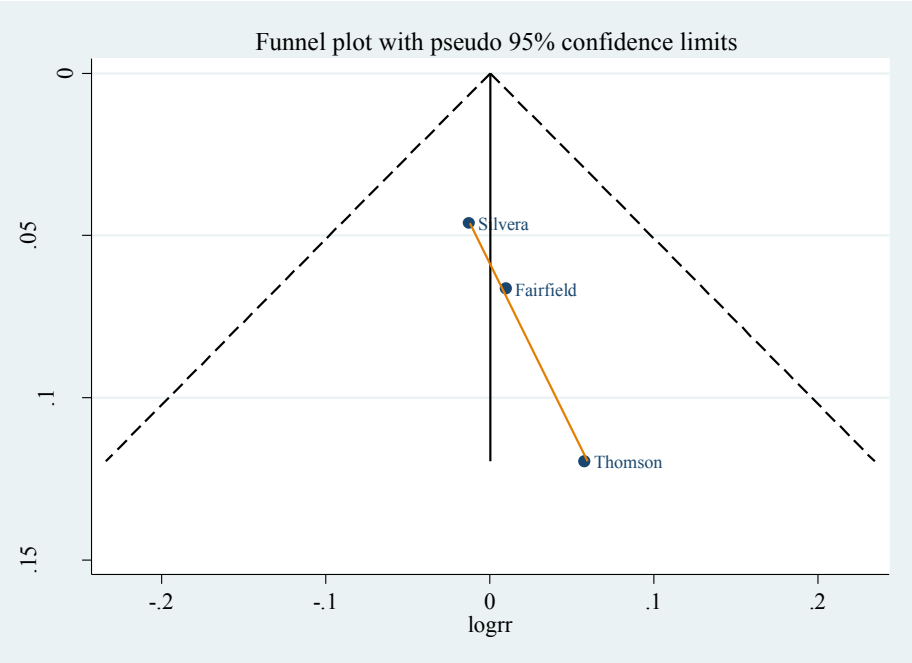
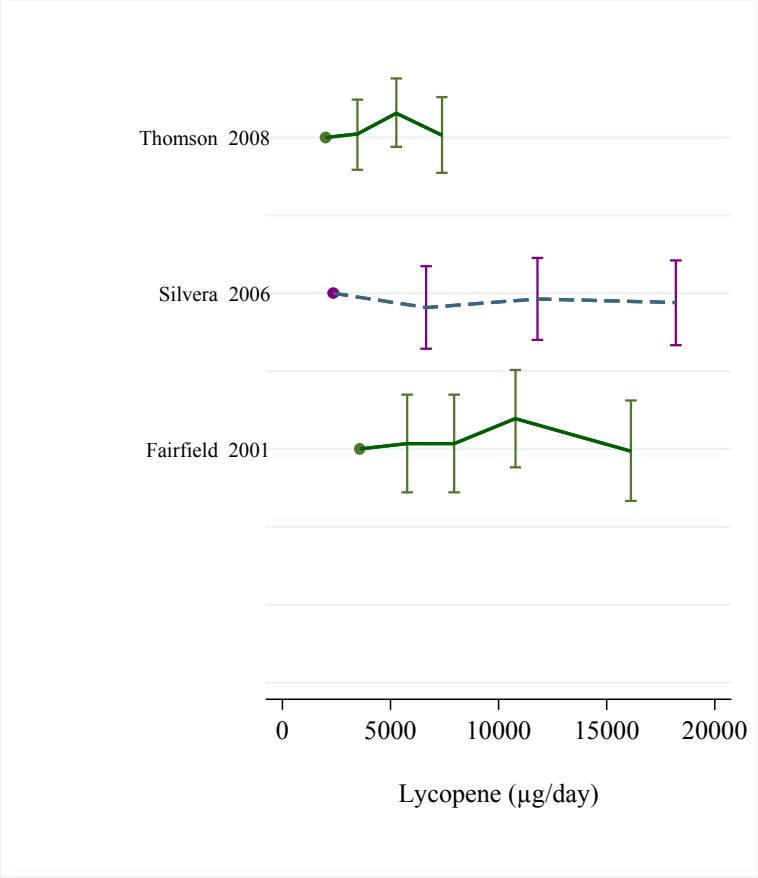


Figure 142 Dose-response graph of dietary lycopene and ovarian cancer



5.5.3 Total folate (diet and supplements)

Methods

Up to December 2012, three studies had been identified, two of them during the Continuous Update Project. The three studies had been included in the dose-response meta-analysis. The increment used was 50 µg /day.

Main results

The summary RR per 50 mcg/day was 1.00 (95% CI: 0.97-1.03) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.95 – 1.02) when excluding the Iowa Women Health Study (Kelemen et al, 2004) to 1.01 (95% CI: 0 .96-1.06) when excluding the California Teachers Study (Chang et al, 2007).

Heterogeneity

There was no evidence of heterogeneity (I^2=0%; p=0.526) and Egger's test detected evidence of publication bias (p = 0. 367) in the limited number of studies.

Table 149 Studies on total folate identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Chang, 2007	USA	California Teachers Study	266	8.1	0.81	0.49	1.32	>711 vs. <272 µg/d
Tworoger, 2006	USA	Nurses' Health Study	481	22	0.84	0.60	1.18	Q5 (median 591 µg /d) vs. Q1 (299 µg/d)

Table 150 Overall evidence on total folate and ovarian cancer

	Summary of evidence
SLR	One publication identified and no association was reported
Continuous Update Project	Two publications were identified. None of them reported significant associations.

Table 151 Summary of results of the dose response meta-analysis of total folate and ovarian cancer

Ovarian cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	908
Increment unit used	-	50 μg /day
Overall RR (95%CI)	-	1.00 (95% CI: 0.97-1.03)
Heterogeneity (I^2,p-value)	-	0% , p=0.526

*No meta-analysis was conducted in the SLR

Table 152 Inclusion/exclusion table for meta-analysis of total folate and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11654	Chang	2007	Prospective Cohort Study	California Teachers Study	Incidence	No	Yes	Yes	Person years per intake category	-
OVA11651	Tworoger	2006	Prospective Cohort Study	Nurses' Health Study	Incidence EOC	No	Yes	Yes	Mid-exposure values	-
OVA10451	Kelemen	2004	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	-

Figure 143Highest versus lowest forest plot of total folate and ovarian cancer

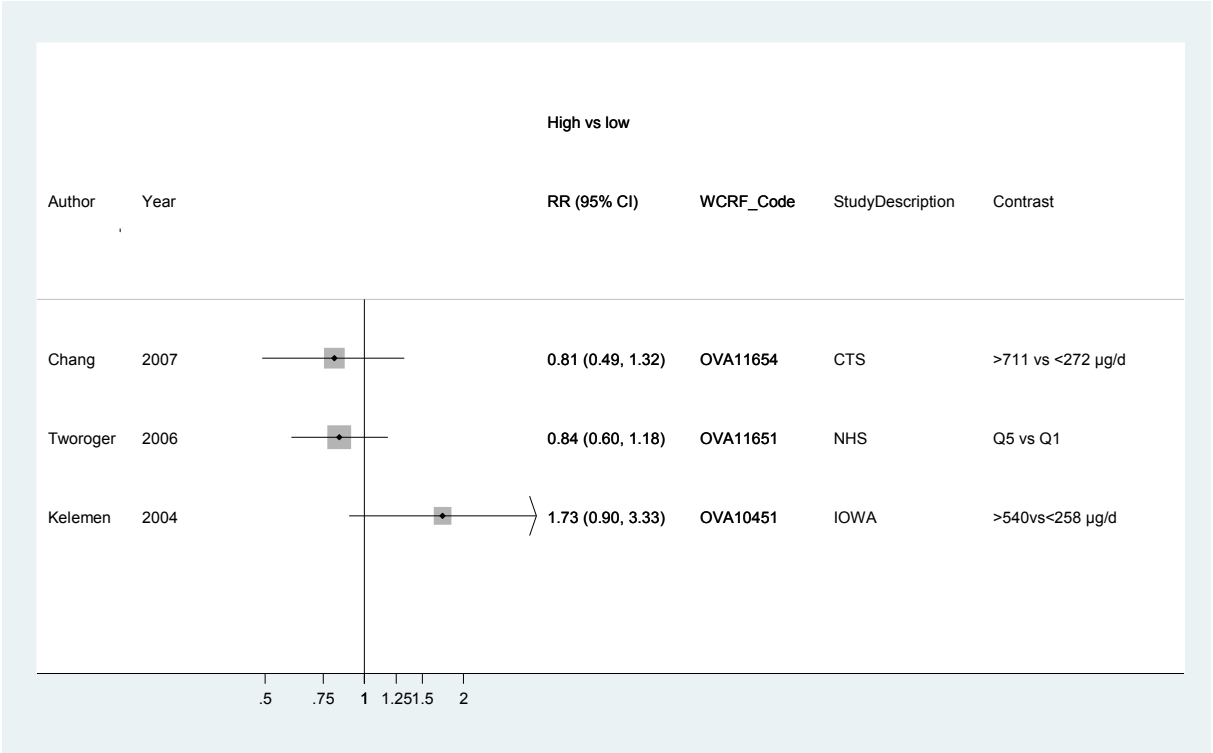


Figure 144 Dose-response meta-analysis of total folate and ovarian cancer - per 50 µg /day

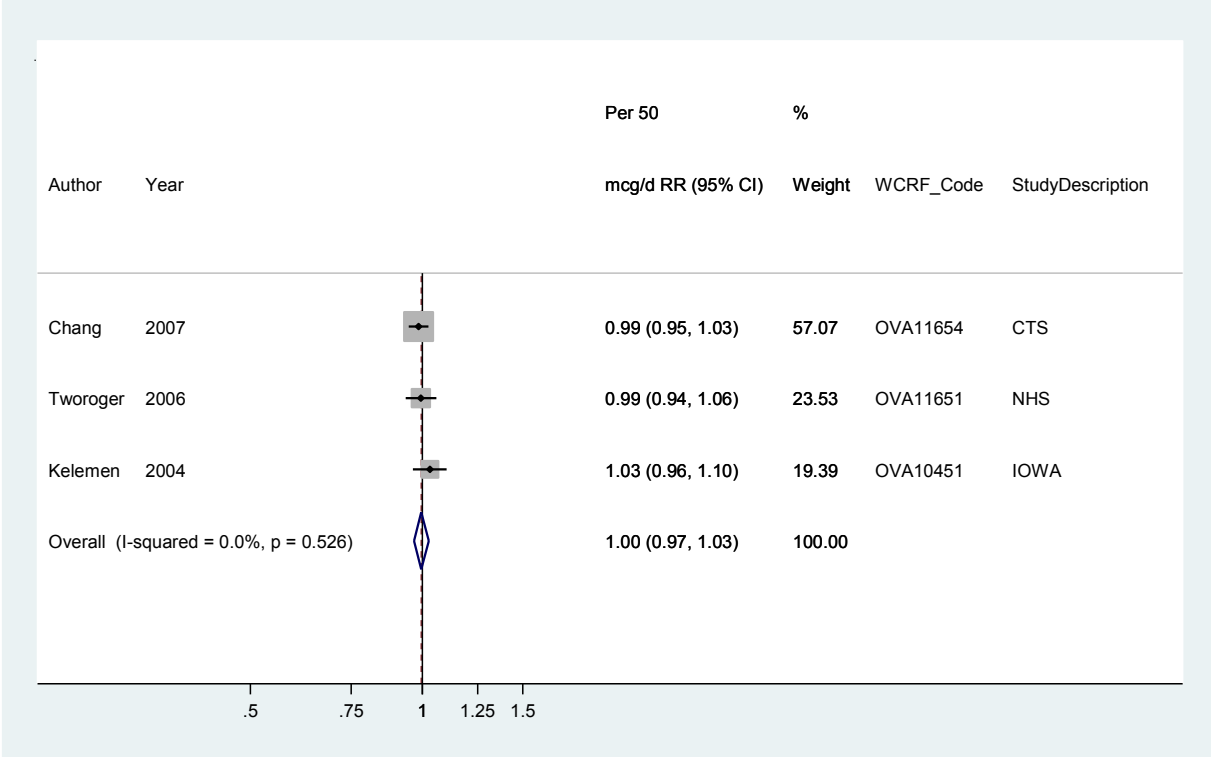


Figure 145 Funnel plot of total folate and ovarian cancer

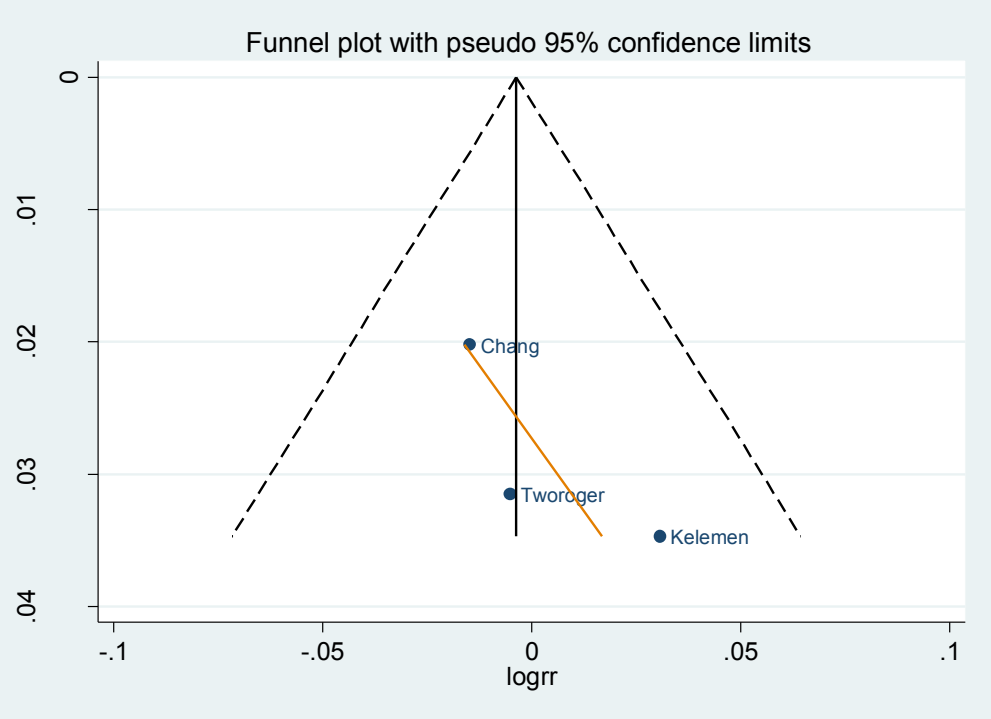
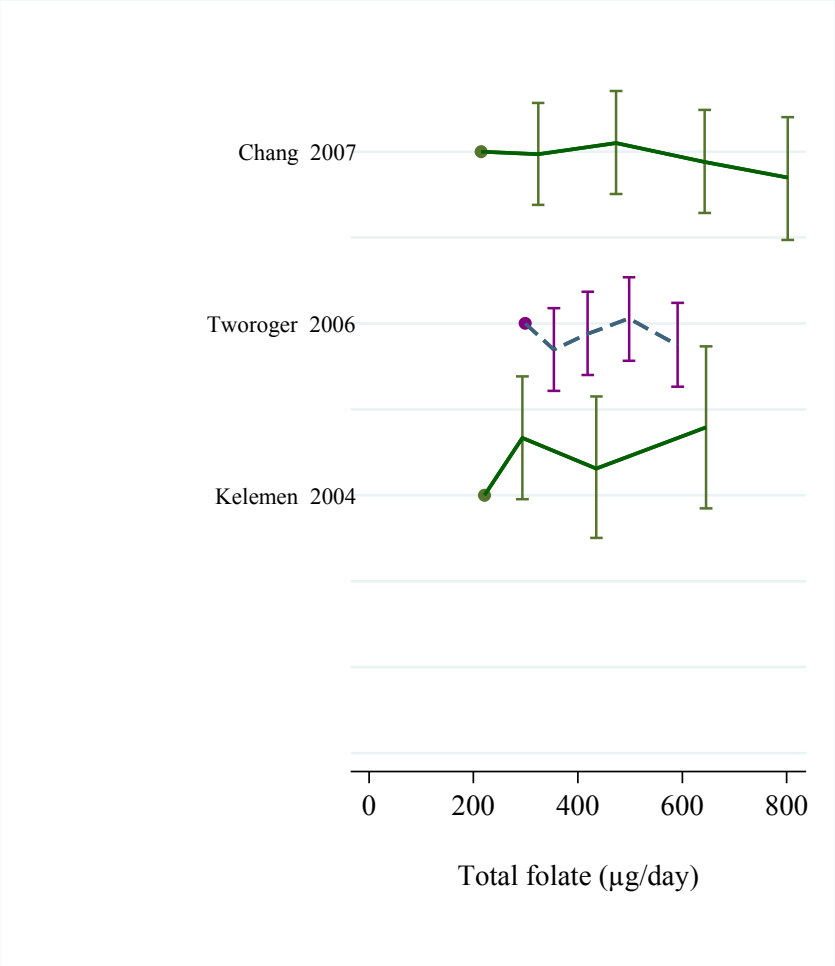


Figure 146 Dose-response graph of total folate and ovarian cancer



5.5.3.1 Dietary folate

Methods

Up to December 2012, four cohort studies (six publications) were identified. Three publications from two cohort studies were identified during the Continuous Update Project. The four studies had been included in the dose-response meta-analysis. The increment used was 50 µg /day.

Main results

The summary RR per 50 µg /day was 0.96 (95% CI: 0.88-1.05) for all studies combined. In influence analysis, the RR ranged from 0.93 (95% CI: 0.79 – 1.10) when excluding the Nurses' Health Study (Tworoger et al, 2006) to 0.98 (95% CI: 0.91-1.06) when excluding the Swedish Mammography Cohort (Larsson et al, 2004).

Heterogeneity

There was moderate heterogeneity (I^2 = 35.4%, $P_{heterogeneity}$ = 0.20) and Egger's test detected evidence of publication bias (p = 0.53) in the limited number of available studies.

Table 153 Studies on dietary folate identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Kabat, 2008	USA	Canadian National Breast Cancer Screening Study	264	16.4	1.05	0.71	1.54	>374 vs. <237 µg /d
Navarro, 2006	USA	Canadian National Breast Cancer Screening Study	264	16.4	0.78	0.44	1.70	>357 vs. <248 µg /day
Tworoger, 2006	USA	Nurses' Health Study	481	22	0.90	0.59	1.36	Q5 (median 460 µg /d) vs. Q1 (198 µg /d)

Table 154 Overall evidence on dietary folate and ovarian cancer

	Summary of evidence
SLR	Three publications of two cohort studies were identified. None of them reported significant associations.
Continuous Update Project	Three publications of two cohort studies were identified. None of the studies reported significant associations. The results from the four studies were included in the meta-analysis.

Table 155 Summary of results of the dose response meta-analysis of dietary folate and ovarian cancer

Ovarian cancer incidence		
	SLR	Continuous Update Project
Studies (n)	2	4
Cases (n)	413	1158
Increment unit used	100 µg /day	50 µg /day
Overall RR (95%CI)	0.98 (0.92-1.04)	0.96 (0.88-1.05)
Heterogeneity (I^2,p-value)	72.9	35.4%, p=0.20

Table 156 Inclusion/exclusion table for meta-analysis of dietary folate and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
OVA11681	Kabat	2008	Prospective Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	No	No	No	-	Navarro, 2006 had more complete information
OVA11624	Navarro	2006	Prospective Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	
OVA11651	Tworoger	2006	Prospective Cohort Study	Nurses' Health Study	Incidence EOC	No	Yes	Yes	Mid-exposure values	
OVA09696	Larsson	2004	Prospective Cohort Study	Swedish Mammography Study	Incidence	Yes	Yes	Yes	-	
OVA10451	Kelemen	2004	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
OVA02880	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Superseded by Kelemen, 2004

Figure 147 Highest versus lowest forest plot of dietary folate and ovarian cancer

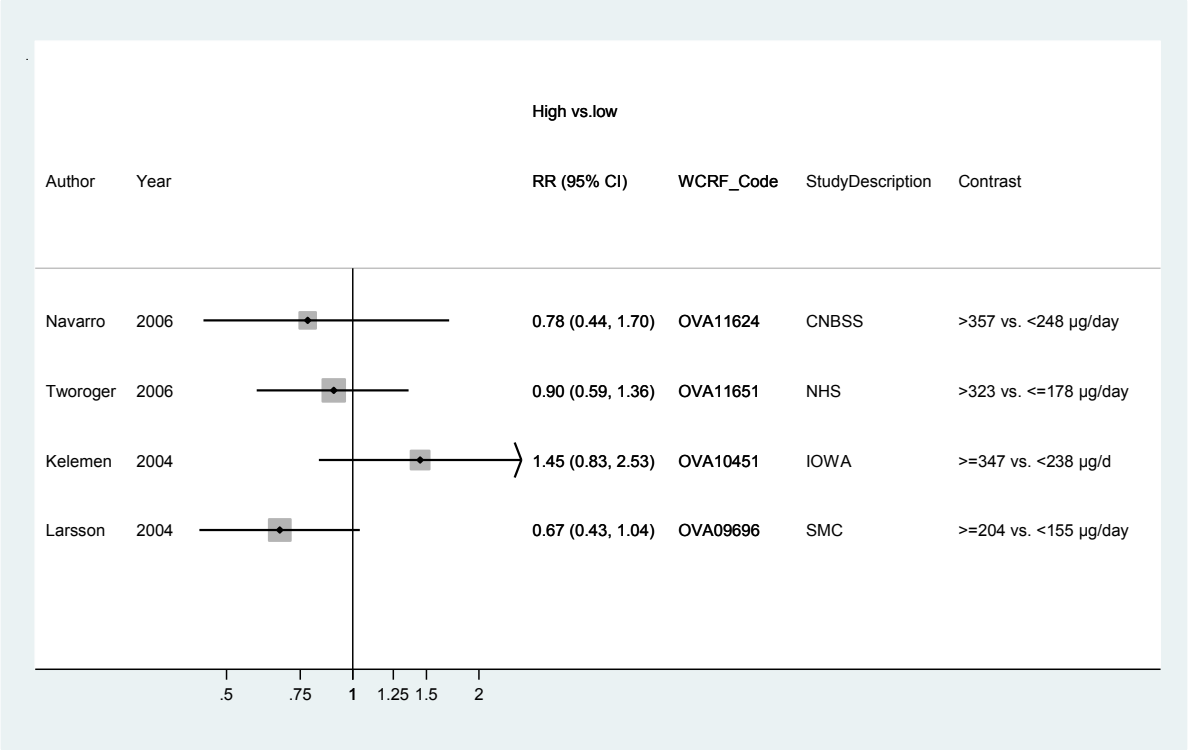


Figure 148 Dose-response meta-analysis of dietary folate and ovarian cancer - per 50 µg /day

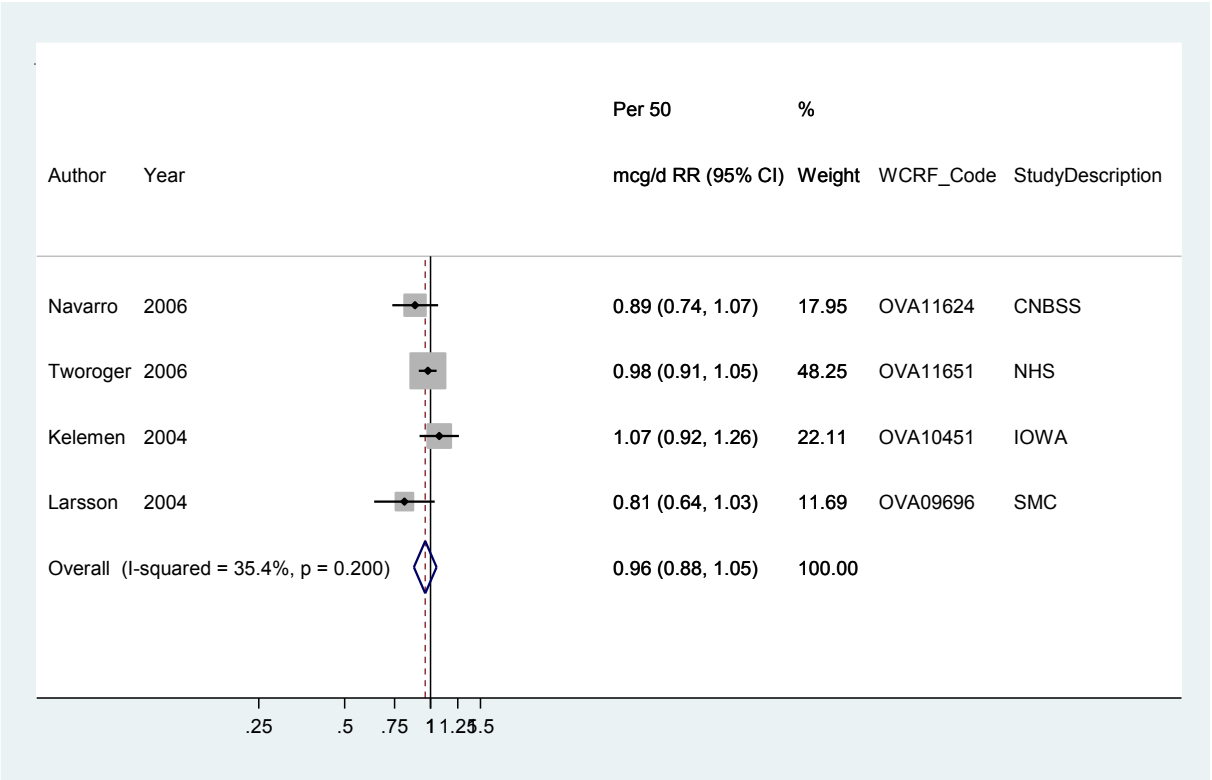


Figure 149 Funnel plot of dietary folate and ovarian cancer

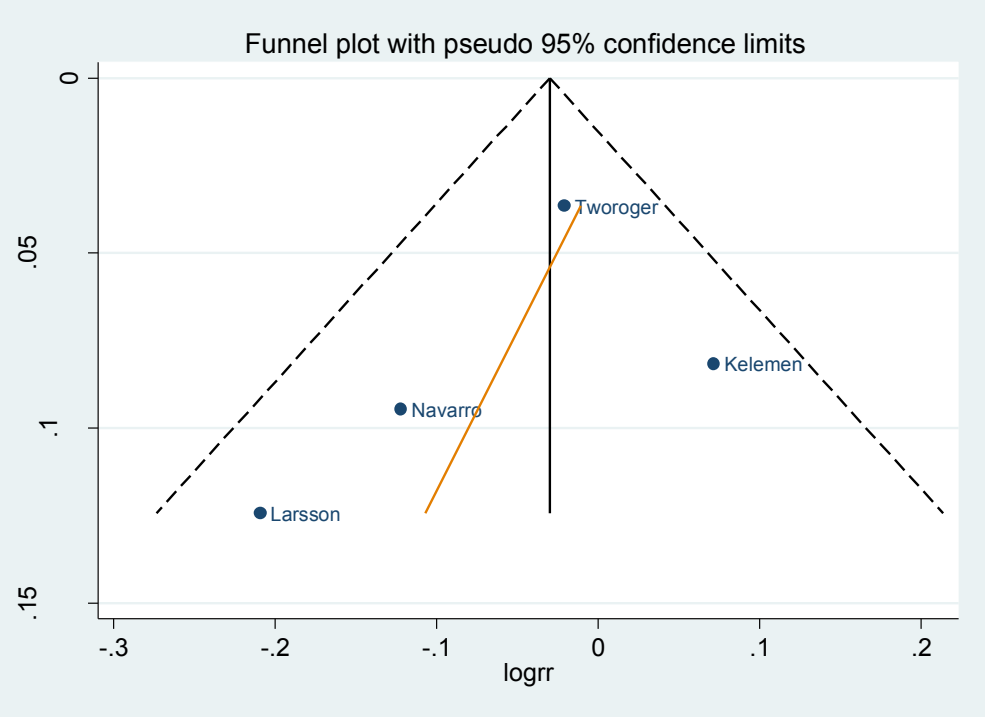
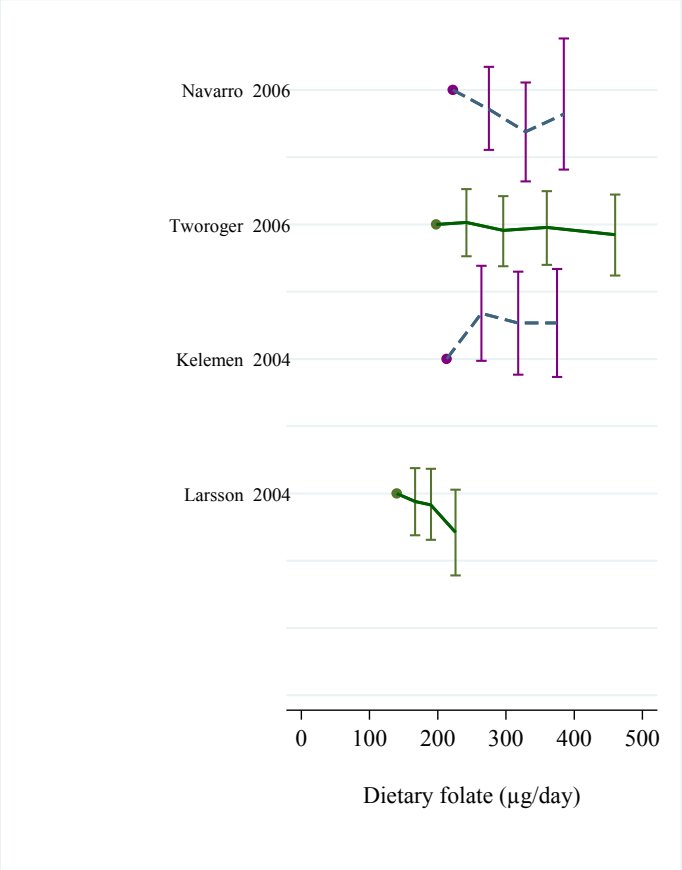


Figure 150 Dose-response graph of dietary folate and ovarian cancer



5.5.3.4 Methionine

Three studies were identified (one in the SLR). None of the studies reported significant associations. The data in the publications was not enough to conduct dose-response meta-analysis. Study results are described to complement the analysis on folate.

In the IWS (Kelemen et al,. 2004), the associations of methionine intake with ovarian cancer were in opposite directions in subgroups of women according to their folate intake: among women with folate intake <330 µg/d, the highest (≥7.3 g/d) compared to the lowest (<4.6 g/d) quartile of energy-adjusted methionine intake was not associated with risk of ovarian cancer (RR, 0.81; 95% CI, 0.41–1.62; p trend, 0.45). Among women with folate intake ≥331 µg/ d, the highest compared to lowest quartile of methionine intake was 1.66 (95% CI, 0.84–3.26; p for trend,0.16).

In the CNBSS (Navarro et al, 2006), the hazard ratio for the highest versus the lowest quartile methionine intake level was 0.79 (95% CI=0.53–1.19). The association between folate intake and risk of ovarian cancer appeared to differ somewhat by strata of methionine intake, with no association among women with methionine intakes ≤ 2 g/day, but evidence of a 35% decrease in risk of ovarian cancer associated with the highest versus the lowest quartile level of folate intake among women with methionine intakes >2 g/day (HR= 0.65; 95% CI=0.28–1.49). No significant interaction was observed (P=0.98).

In the NHS (Tworoger et al, 2006), dietary methionine was not related to ovarian cancer risk (HR 1.8 vs. 1.7 g/day (mean) = 0.93 95% CI: (0.68- 1.28).

5.5.9.1 Total vitamin C (food and supplements)

Methods

Up to December 2012, reports from four cohort studies were identified. The CUP meta-analysis included four studies (three studies identified during the CUP and one study identified during the 2007 SLR. The dose-response results are presented for an increase of 200 mg/d.

Main results

The summary RR per 200 mg/day was 1.03 (95% CI: 0.98-1.08; I^2= 0%, $P_{heterogeneity}$=0.71) for all studies combined. In influence analysis, the RR ranged from 1.01(95% CI: 0.95-1.08) when excluding the California Teachers Study (Chang et al, 2007) to 1.04 (95% CI: 0.99-1.10) when excluded the Nurses' Health Study (Fairfield et al, 2001).

Heterogeneity

No heterogeneity was observed (I^2=0%, p=0.71). Egger's tests did not show evidence of publication bias (p=0.99). These tests lack power because only four studies were included in the meta-analysis.

Comparison with the Second Expert Report

One study was identified during the SLR, showing no association with ovarian cancer.

Table 157 Studies on Total vitamin C identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	United States	Women Health Initiative	352	7	1.22	0.89	1.67	>=555 mg/d vs. <90 mg/d
Chang, 2007	United States	California Teachers Study	280	8.1	1.96	1.11	3.46	1222 mg/d vs. 51 mg/d
Silvera, 2006	Canada	Canadian National Breast Screening Study	264	7.2	1.11	0.75	1.66	>247 mg/d vs. <122 mg/d

Table 158 Overall evidence on total vitamin C and ovarian cancer

	Summary of evidence
SLR	One study was identified during the SLR. Fairfield et al, 2001 showed no association with ovarian cancer.
Continuous Update Project	Three cohort studies were identified; all of them could be included in the meta-analysis. Overall, the meta-analysis included four studies.

Table 159 Summary of results of the dose response meta-analysis of total vitamin C and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1197
Increment unit used	-	Per 200 mg/day
Overall RR (95%CI)	-	1.03 (0.98-1.08)
Heterogeneity (I^2,p-value)	-	0%, p=0.71

*No meta-analysis was conducted in the 2nd report

Table 160 Inclusion/exclusion table for meta-analysis of Total vitamin C and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11660	Thomson	2008	Prospective Cohort Study	Women Health Initiative	Incidence Invasive cancer	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11654	Chang	2007	Prospective Cohort Study	California Teachers Study	Incidence	No	Yes	Yes	Person/ years per category	-
OVA11645	Silvera	2006	Prospective Cohort Study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2001	Prospective Cohort Study	Nurses' Health Study	Incidence EOC	Yes	Yes	Yes	Confidence intervals estimation Person/ years per category	-

Figure 151 Highest versus lowest forest plot of total vitamin C and ovarian cancer

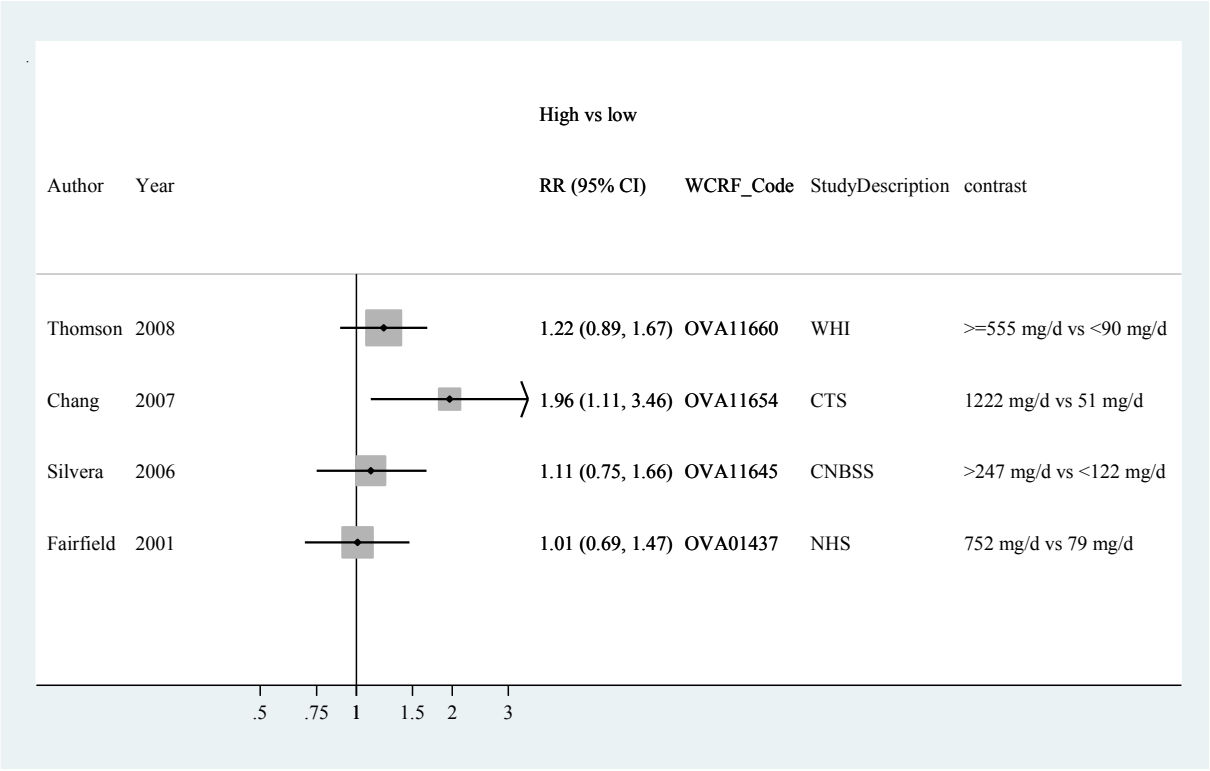


Figure 152 Dose-response meta-analysis of total vitamin C and ovarian cancer - per 200 mg/day increase

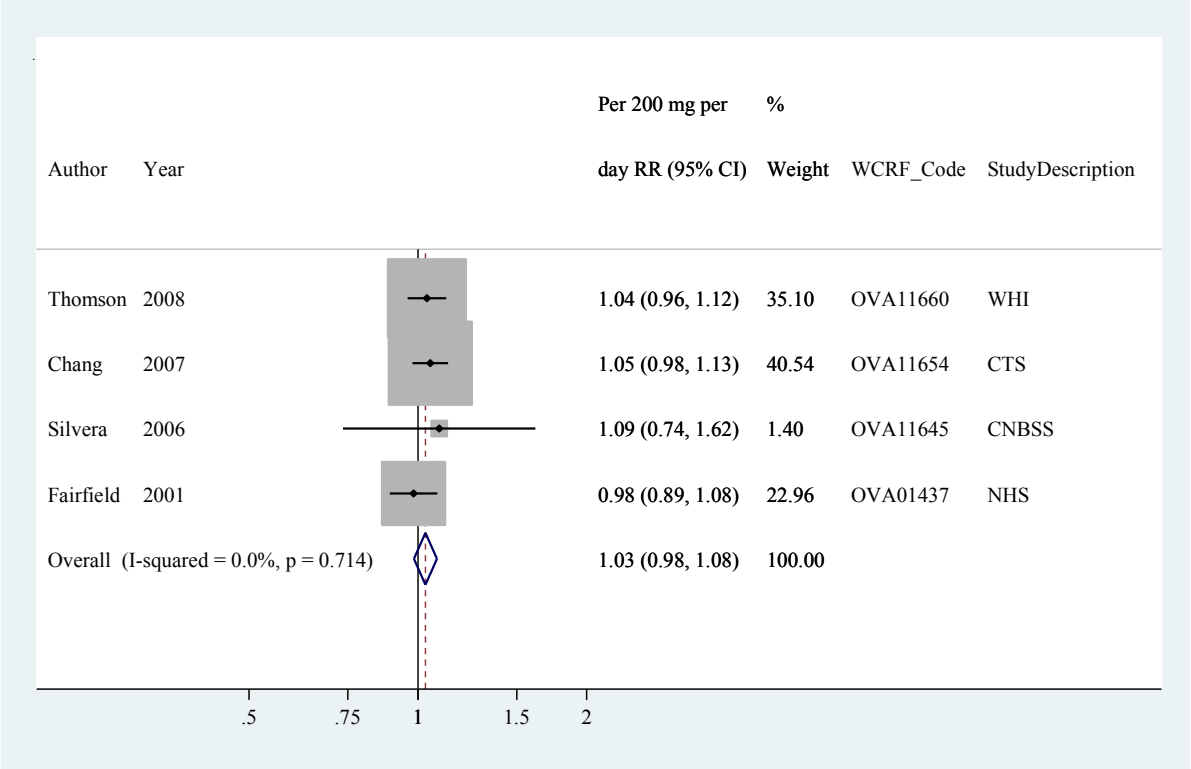


Figure 153 Funnel plot of total vitamin C and ovarian cancer

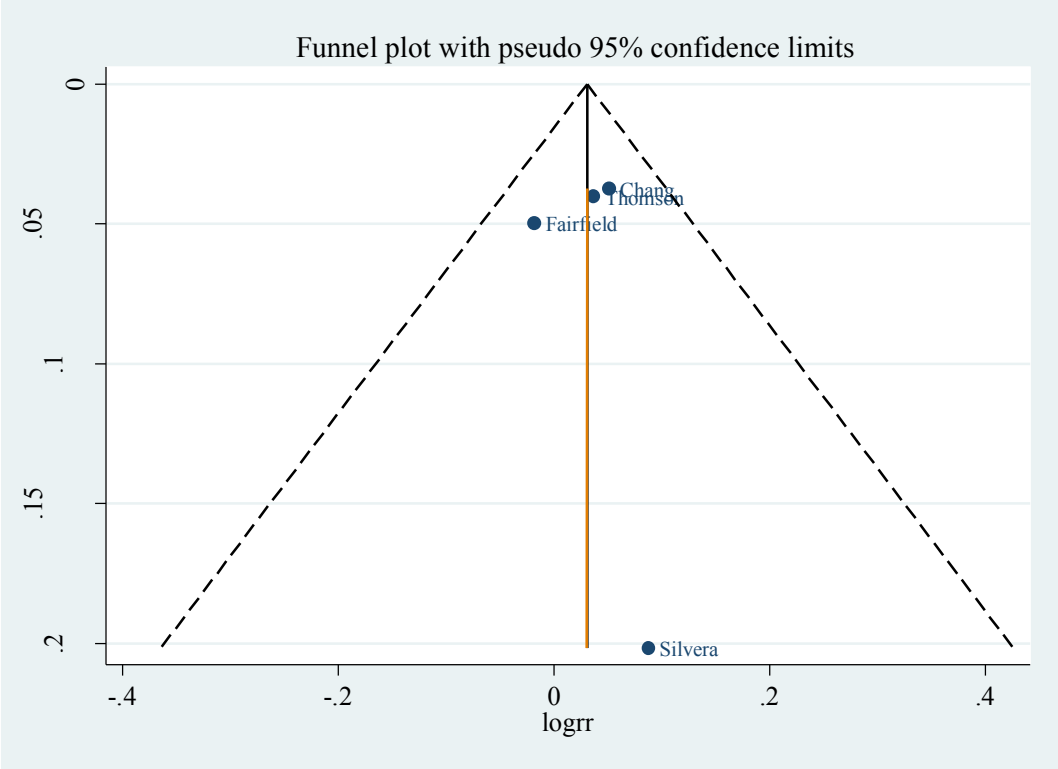
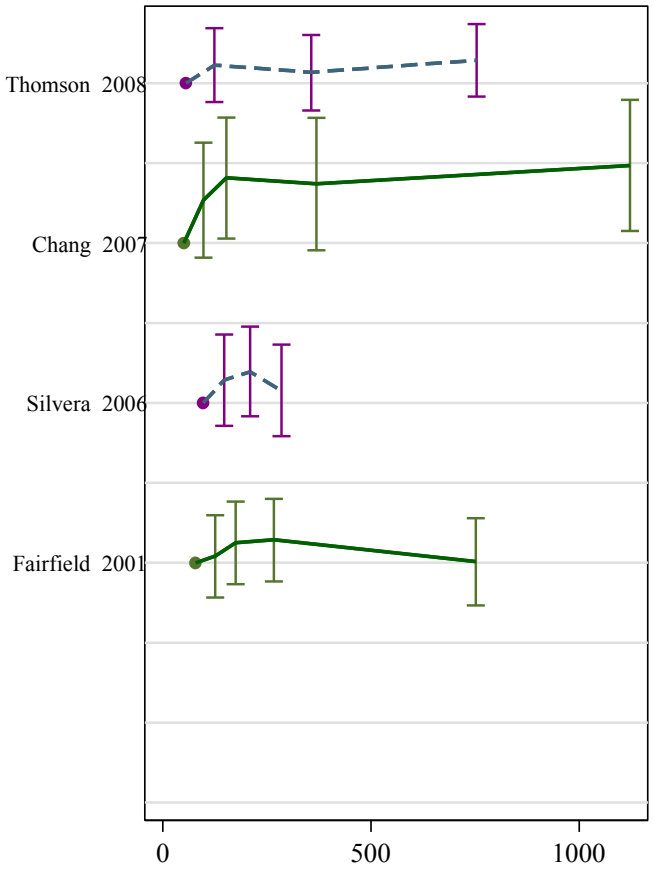


Figure 154 Dose-response graph of total vitamin C and ovarian cancer



5.5.9.2 Dietary vitamin C

Methods

Up to December 2012, reports from five cohort studies were identified. The CUP meta-analysis included four studies (two studies identified during the CUP and two studies identified during the 2007 SLR). The dose-response results are presented for an increment of 25 mg/d.

Main results

The summary RR per 25 mg/day was 1.00 (95% CI: 0.97-1.03; I^2= 0%, $P_{heterogeneity}$=0.87) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.96-1.02) when excluding the Nurses' Health Study (Fairfield et al, 2001) to 1.00 (95% CI: 0.97-1.03) when excluded the Canadian National Breast Screening Study (Silvera et al, 2007)

Heterogeneity

No heterogeneity was observed (I^2=0%, p=0.87). Egger's tests did not show evidence of publication bias (p=0.70). These tests lack power because only four studies were identified.

Comparison with the Second Expert Report

Two studies were identified during the SLR; none of them suggested association with ovarian cancer.

Table 161 Studies on dietary vitamin C identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	United States	Women Health Initiative	352	7	1.07	0.77	1.48	>=130 mg/d vs. <58 mg/d
Chang, 2007	United States	California Teachers Study	280	8.1	1.50	0.71	3.19	Highest vs. lowest quintile
Silvera, 2006	Canada	Canadian National Breast Screening Study	264	7.2	0.90	0.58	1.37	>206 mg/d vs <115 mg/d

Table 162 Overall evidence on dietary vitamin C and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR (Fairfield et al, 2001 and Kushi et al, 1999). None of them suggested association with ovarian cancer.
Continuous Update Project	Three additional cohort studies were identified. Overall, four studies could be included in the final meta-analysis.

Table 163 Summary of results of the dose response meta-analysis of dietary vitamin C and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1056
Increment unit used	-	Per 25 mg/day
Overall RR (95%CI)	-	1.00 (0.97-1.03)
Heterogeneity (I^2,p-value)	-	0%, p=0.87

*No meta-analysis was conducted in the 2nd report

Table 164 Inclusion/exclusion table for meta-analysis of dietary vitamin C and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11660	Thomson	2008	Prospective Cohort Study	Women Health Initiative	Incidence Invasive cancer	No	Yes	Yes	Mid-exposure values Person/ years per category	-
OVA11654	Chang	2007	Prospective Cohort Study	California Teachers Study	Incidence	No	No	Yes	-	Two categories
OVA11645	Silvera	2006	Prospective Cohort Study	Canadian National Breast Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2001	Prospective Cohort Study	Nurses' Health Study	Incidence EOC	Yes	Yes	Yes	Confidence intervals estimation Person/ years per category	-
OVA02880	Kushi	1999	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category Mid-exposure values	-

Figure 155 Highest versus lowest forest plot of dietary vitamin C and ovarian cancer

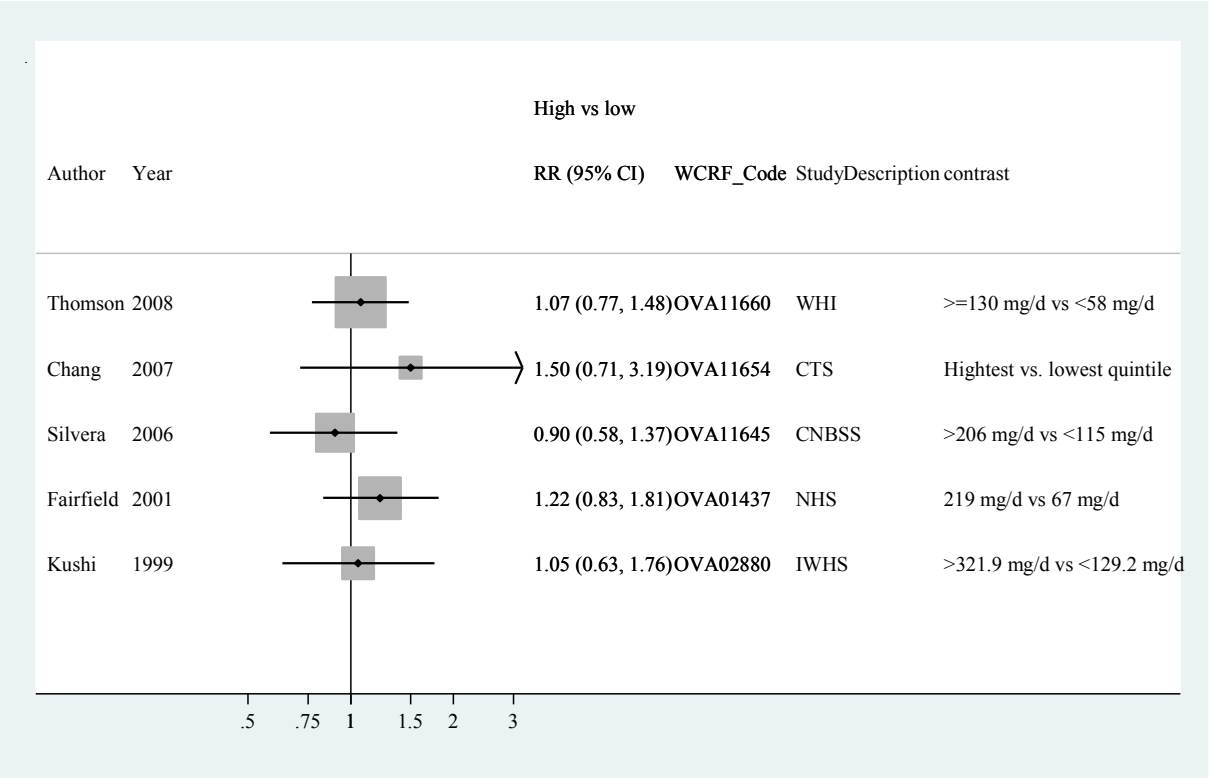


Figure 156 Dose-response meta-analysis of dietary vitamin C and ovarian cancer - per 25 mg/day

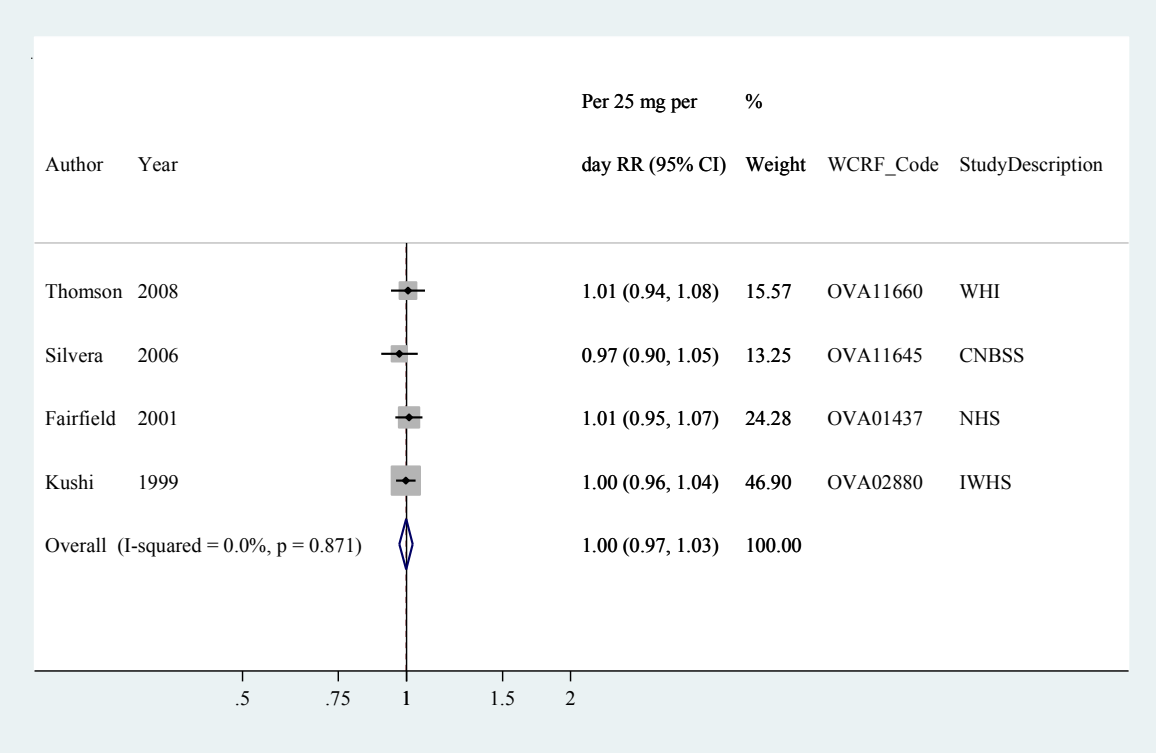


Figure 157 Funnel plot of dietary vitamin C and ovarian cancer

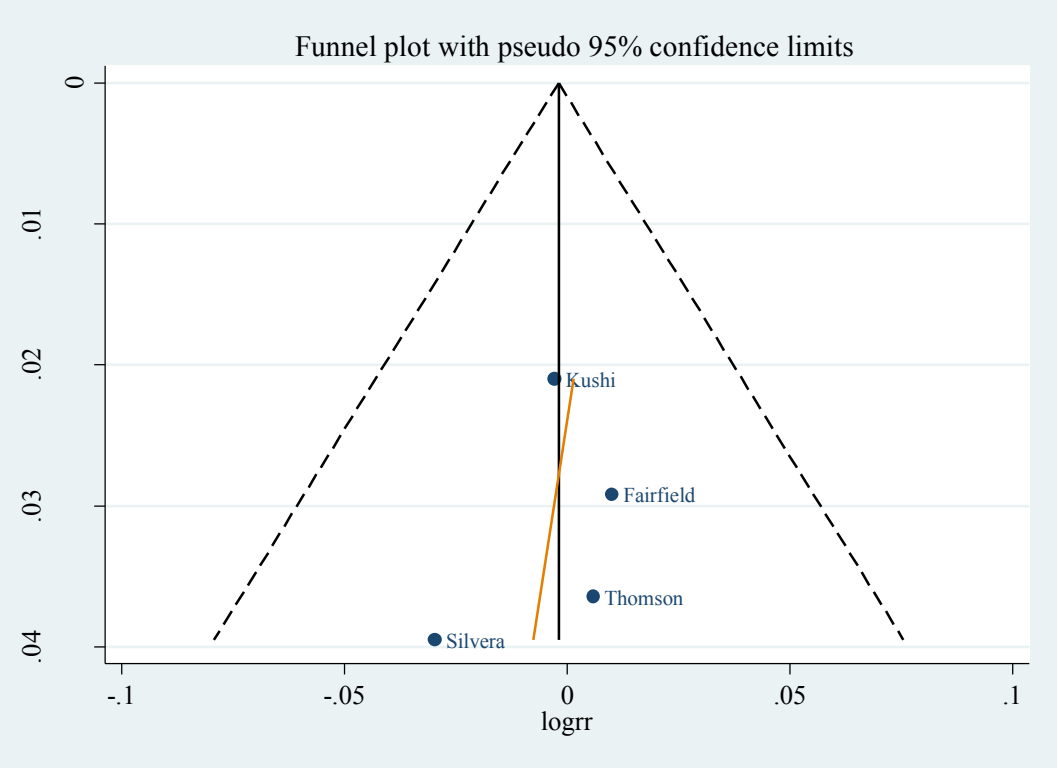
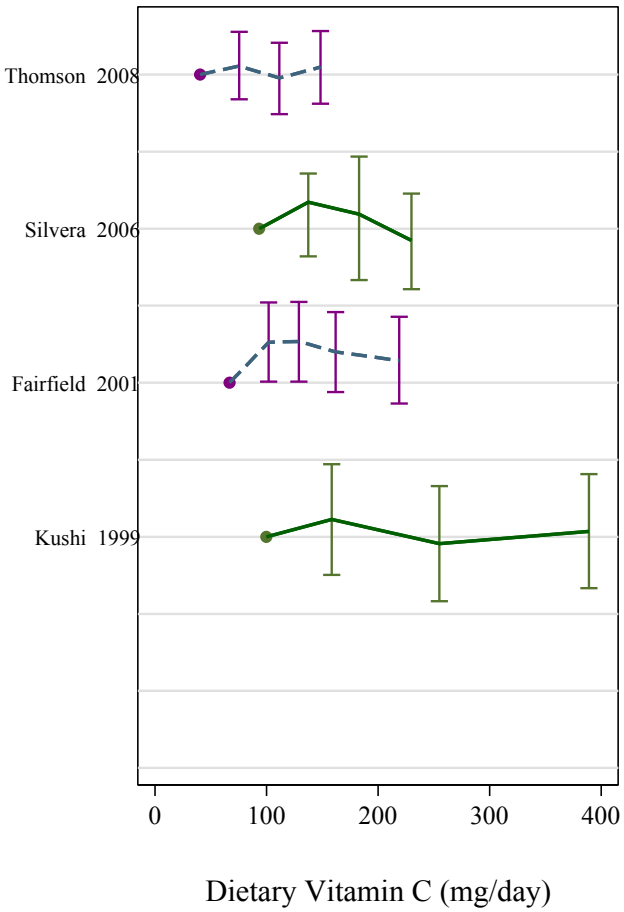


Figure 158 Dose-response graph of dietary vitamin C and ovarian cancer



5.5.10.1 Serum vitamin D

Methods

Up to December 2012, reports from five cohort studies were identified in three publications. The CUP meta-analysis included five studies (all studies identified during the CUP). For the dose-response analyses results were converted to a common scale of exposure level (nmol per litre). The dose-response results are presented for an increment of 10 nmol/L.

Main results

The summary RR per 10 nmol/L was 1.01 (95% CI: 0.87-1.17; I^2= 0%, $P_{heterogeneity}$=0.85) for all studies combined. In influence analysis, the RR ranged from 0.96 (95% CI: 0.80-1.14) when excluding the New York University Women's Health Study (Arslan et al, 2009) to 1.03 (95% CI: 0.87-1.21) when excluding the Northern Sweden Health and Disease Study (Arslan et al, 2009).

Heterogeneity

No heterogeneity was observed (I^2=0%, p=0.85). Egger's tests did not show evidence of publication bias (p=0.68).

Cohort Consortium Vitamin D Pooling Project of Rarer Cancers

In a pooled analysis of 7 prospective cohort studies (Zheng et al, 2010), circulating 25(OH) D concentrations were not associated with ovarian cancer risk. Compared with women with 25(OH) D concentrations of 50–<75nmol/L, the ORs were 1.21 (95% CI: 0.87, 1.70) among women with <37.5 nmol/L, 1.03 (95% CI: 0.75, 1.41) for women with 37.5–<50 nmol/L, and 1.11 (95% CI: 0.79, 1.55) for women with >=75 nmol/L. Stratified analysis did not change the main results. However, stratified analyses by body mass index suggested a possible inverse association between circulating vitamin D and ovarian cancer risk among overweight and obese women.

When the CUP added the results of the Finnish Maternity Cohort (Toriola et al, 2010), the Northern Sweden Health and Disease Study (Arslan 2009) and the Women Health Study (Tworoger, 2007) to the pooled analysis by Zheng et al (2010), the overall RR for a 10 nmol/L increase in circulating vitamin D was 1.00 (95% CI: 0.97-1.04; $P_{heterogeneity}$=0.93).

Table 165 Studies on serum vitamin D identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Toriola, 2010	Finland	Finnish Maternity Cohort	201	10	0.89	0.36	2.18	>=53.1nmol/L vs. <26.4 nmol/L
Arslan, 2009	United States	New York University Women's Health Study	71	6	1.50	0.53	4.23	>=57.8 nmol/L vs <=36.7 nmol/L
Arslan, 2009	Sweden	Northern Sweden Health and Disease Study	97	6	0.83	0.38	1.81	>=44.8 nmol/L vs <=34.0 nmol/L
Tworoger, 2007	United States	Nurses' Health Study	161	14	0.84	0.47	1.52	>=32.5ng/mL vs <20.6 ng/mL
Tworoger, 2007	United States	Women Health Study	63	12	0.88	0.28	2.82	>=27.7 ng/mL vs <17.4 ng/mL

Table 166 Overall evidence on serum vitamin D and ovarian cancer

	Summary of evidence
SLR	No studies were identified during the SLR.
Continuous Update Project	Five cohort studies were identified; all of them could be included in the meta-analysis.

Table 167 Summary of results of the dose response meta-analysis of serum vitamin D and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	593
Increment unit used	-	Per 10 nmol/litre
Overall RR (95%CI)	-	1.01 (0.87-1.17)
Heterogeneity (I^2,p-value)	-	0%, p=0.85

*No meta-analysis was conducted in the 2nd report

Table 168 Inclusion/exclusion table for meta-analysis of serum vitamin D and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11665	Toriola	2008	Nested case-control study	Finnish Maternity Cohort	Incidence	No	Yes	Yes	Risk rate re-estimation Person/ years per category Mid-exposure values	-
OVA11630	Arslan	2009	Nested case-control study	New York University Women's Health Study	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11631	Arslan	2009	Nested case-control study	Northern Sweden Health and Disease Study	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11663	Tworoger	2007	Nested case-control study	Nurses' Health Study	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11664	Tworoger	2007	Nested case-control study	Women Health Study	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-

Figure 159 Highest versus lowest forest plot of serum vitamin D and ovarian cancer

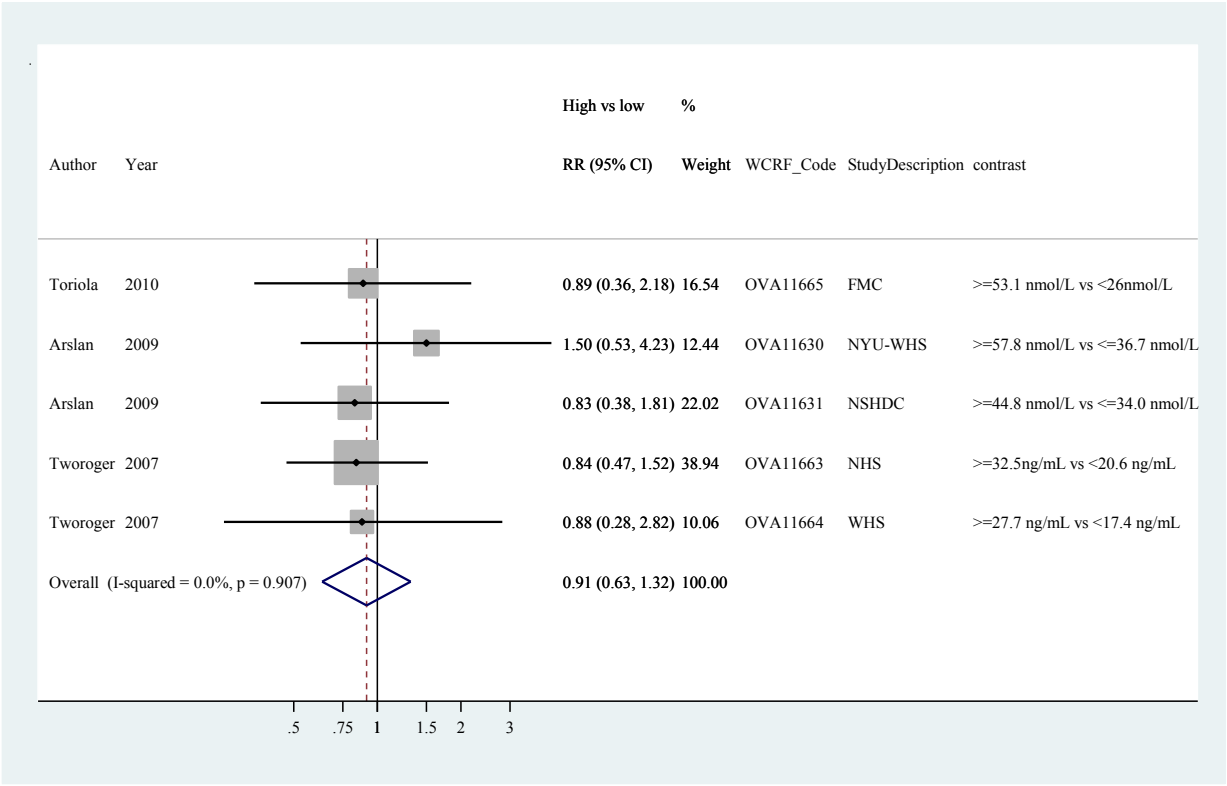


Figure 160 Dose-response meta-analysis of serum vitamin D and ovarian cancer - per 10 nmol/L

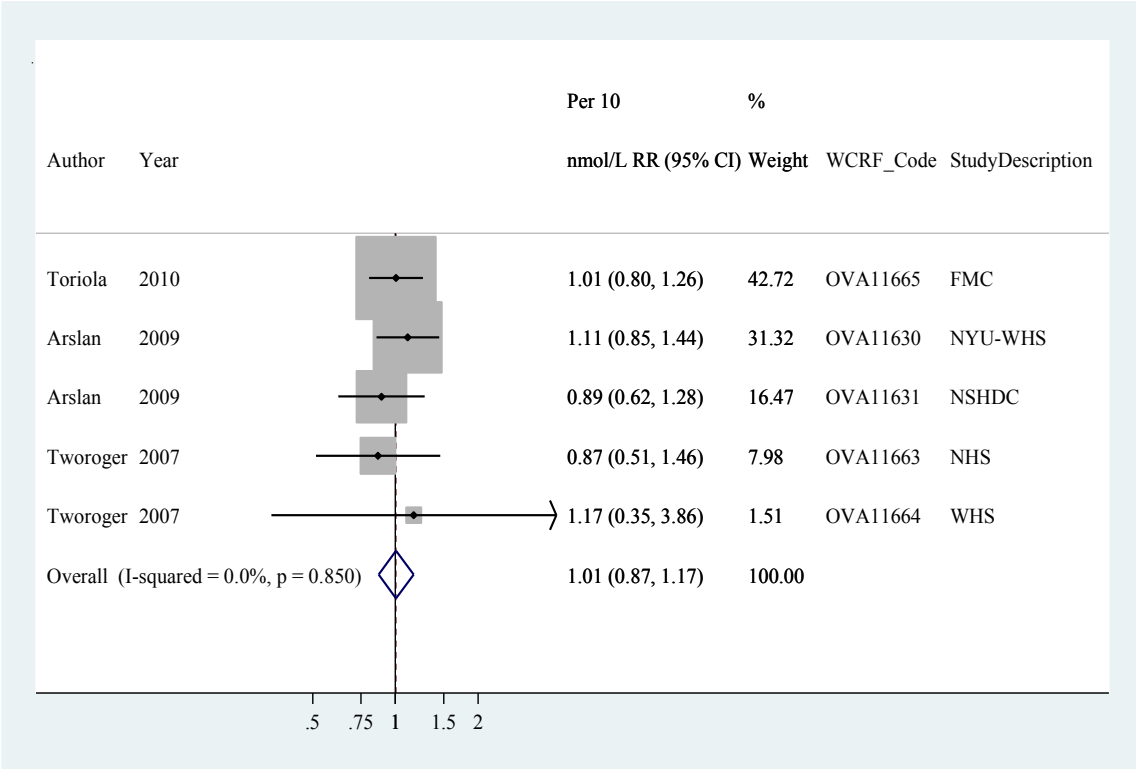


Figure 161 Funnel plot of serum vitamin D and ovarian cancer

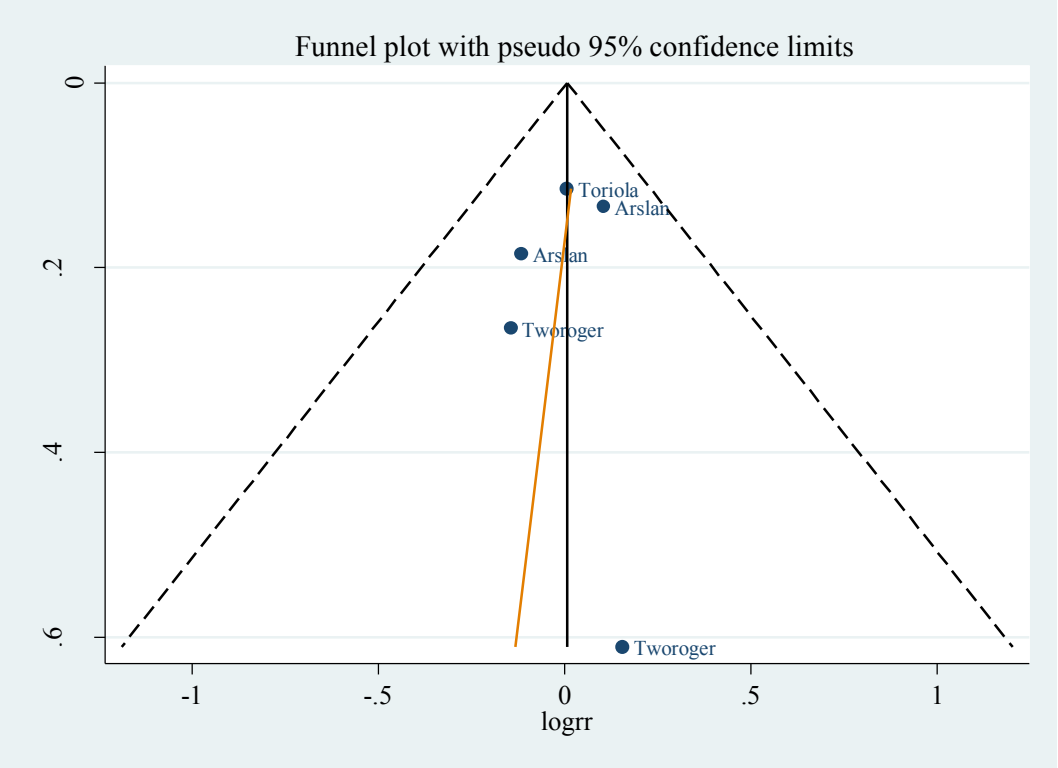
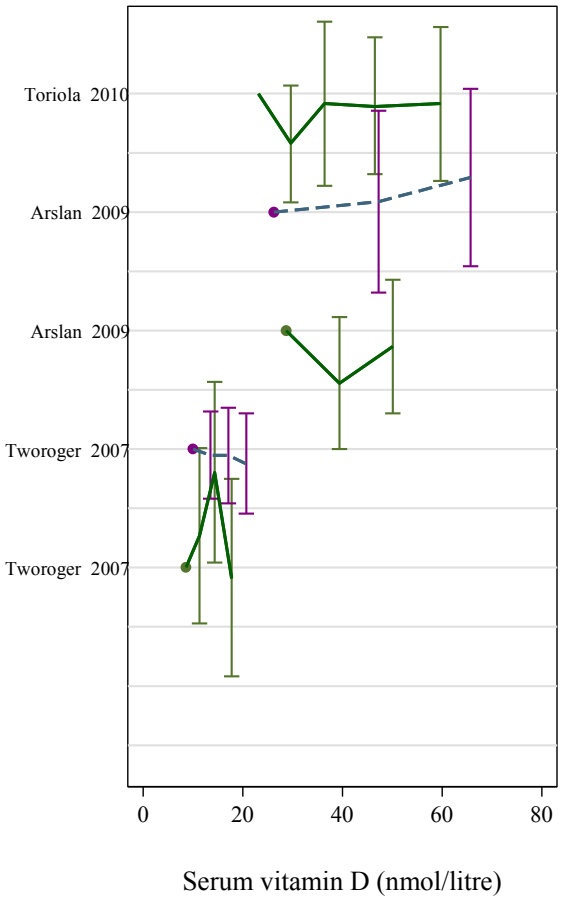


Figure 162 Dose-response graph of serum vitamin D and ovarian cancer



5.5.11.1 Total Vitamin E (diet and supplements)

Methods

Up to December 2012, reports from four cohort studies were identified. The CUP meta-analysis included four studies (three studies identified during the CUP and one study identified during the 2007 SLR). For the dose-response analyses, total vitamin E intake was converted to a common exposure level scale (mg per day). The dose-response results are presented for an increase of 50 mg/day.

Main results

The summary RR per 50 mg/day was 1.01 (95% CI: 0.98-1.03; I^2= 0%, $P_{heterogeneity}$=0.61) for all studies combined. In influence analysis, the RR ranged from 0.99 (95% CI: 0.94-1.05) when excluding the Women's Health Initiative (Thompson et al, 2008) to 1.00 (95% CI: 0.97-1.03) when excluding the California Teacher's Study (Chang, 2007).

Heterogeneity

No heterogeneity was observed (I^2=0%, p=0.61). Egger's tests did not show evidence of publication bias (p=0.97). These tests lack power because only four studies were included in the meta-analysis.

Comparison with the Second Expert Report

Only one study was identified during the SLR. This study suggested no association with ovarian cancer

Table 169 Studies on total vitamin E identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	USA	Women's Health Initiative	451	8.3	1.22	0.89	1.66	>=403.2 mg/d ATE vs. <7.4 mg/d ATE*
Chang, 2007	USA	California Teachers Study	280	8.1	1.46	0.76	2.79	295 mg/d vs 6 mg/d
Silvera 2006	Canada	Canadian National Breast Cancer Screening	264	16.4	1.24	0.85	1.82	>28 mg/d vs <17 mg/d

*ATE: alpha-tocopherol equivalents

Table 170 Overall evidence on total vitamin E and ovarian cancer

	Summary of evidence
SLR	One study was identified during the SLR. No association was observed in the study identified during the SLR, the Nurses' Health Study cohort (Fairfield et al., 2001).
Continuous Update Project	Three cohort studies were identified; all of them could be included in the meta-analysis. Overall, the CUP meta-analysis included four articles

Table 171 Summary of results of the dose response meta-analysis of total vitamin E and ovarian cancer

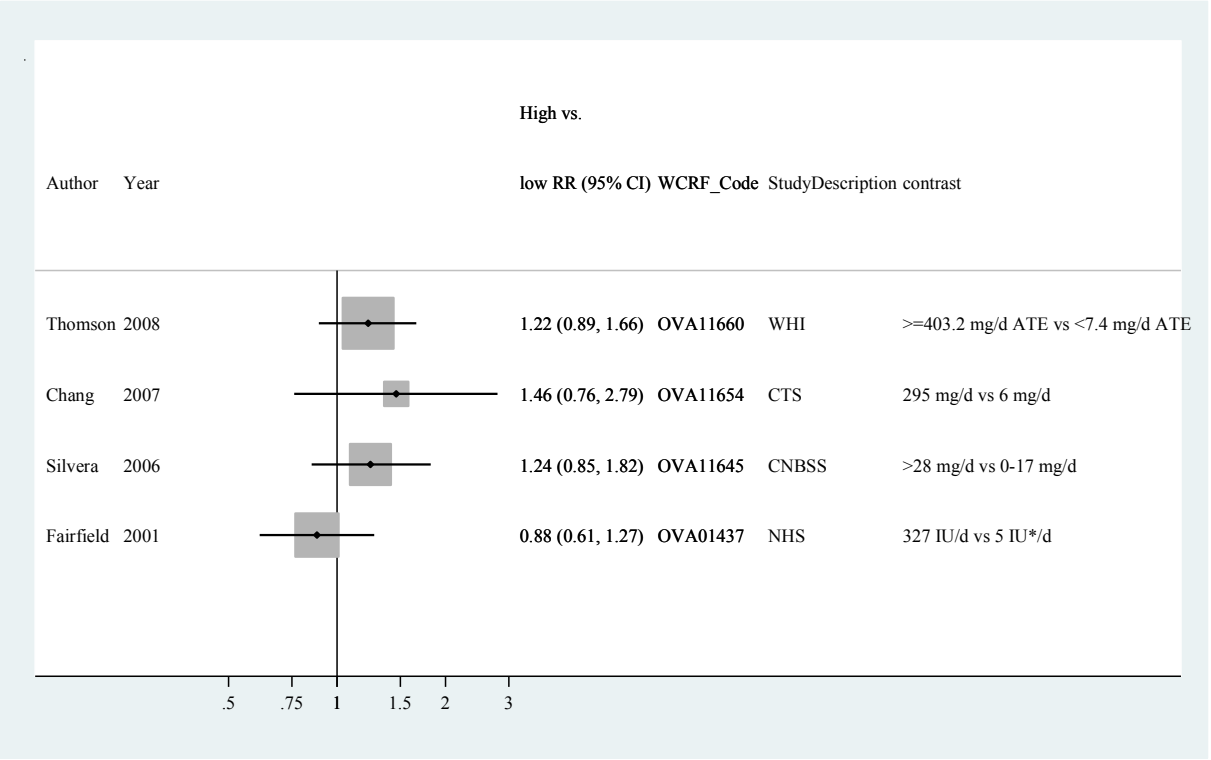
Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1296
Increment unit used	-	Per 50 mg/day
Overall RR (95%CI)	-	1.01 (0.98-1.03)
Heterogeneity (I^2,p-value)	-	0%, p=0.61

*No meta-analysis was conducted in the 2nd report

Table 172 Inclusion/exclusion table for meta-analysis of total vitamin E and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence Invasive cancer	No	Yes	Yes	Person/ years per category Mid-exposure values	-
OVA11654	Chang	2007	Prospective Cohort study	California Teachers Study	Incidence	No	Yes	Yes	Person/ years per category	-
OVA11645	Silvera	2006	Prospective Cohort study	Canadian National Breast Cancer Screening	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2001	Prospective Cohort study	Nurses' Health Study	Incidence EOC	Yes	Yes	Yes	Person/ years per category Confidence intervals	-

Figure 163 Highest versus lowest forest plot of total vitamin E and ovarian cancer



*IU: International Units

Figure 164 Dose-response meta-analysis of total vitamin E and ovarian cancer incidence- per 50 mg/d

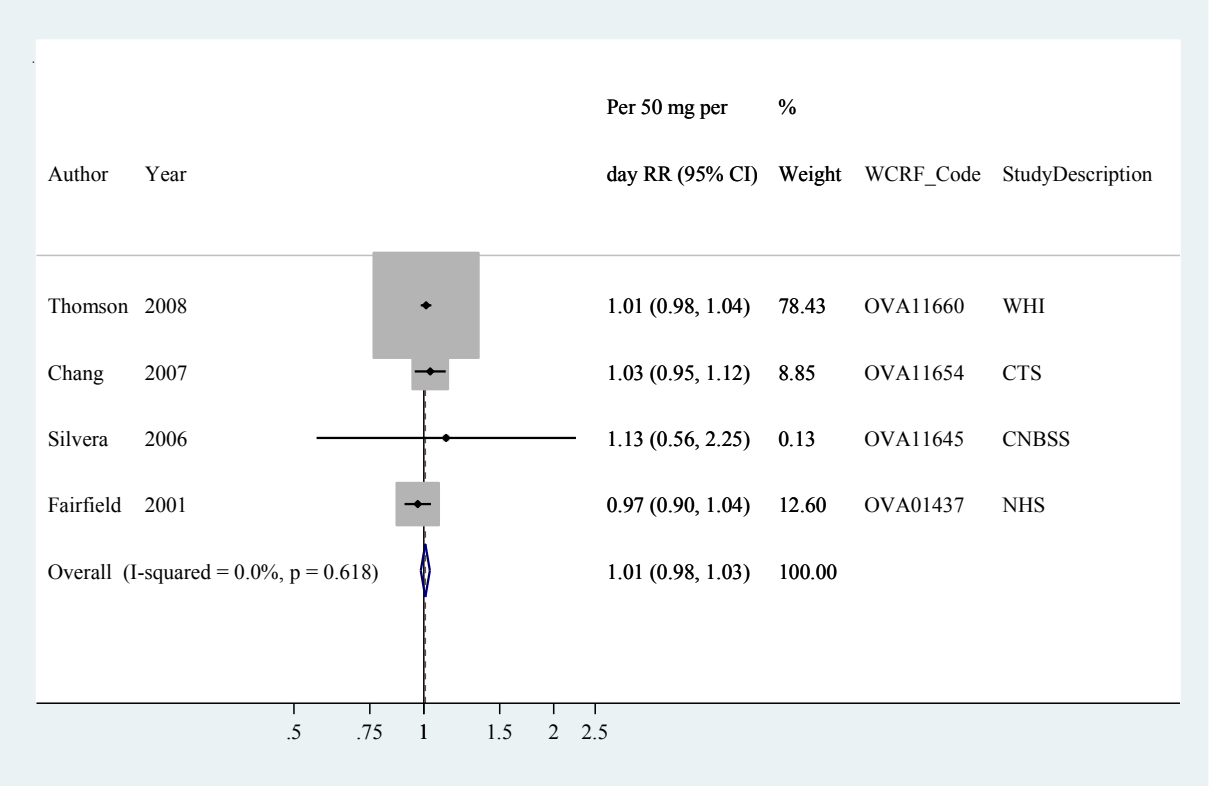


Figure 165 Funnel plot of total vitamin E and ovarian cancer

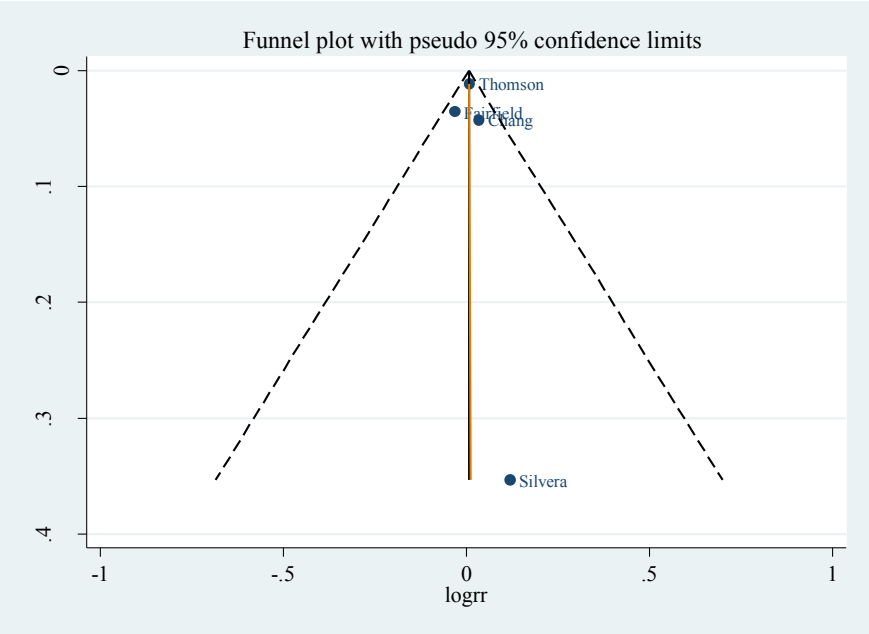
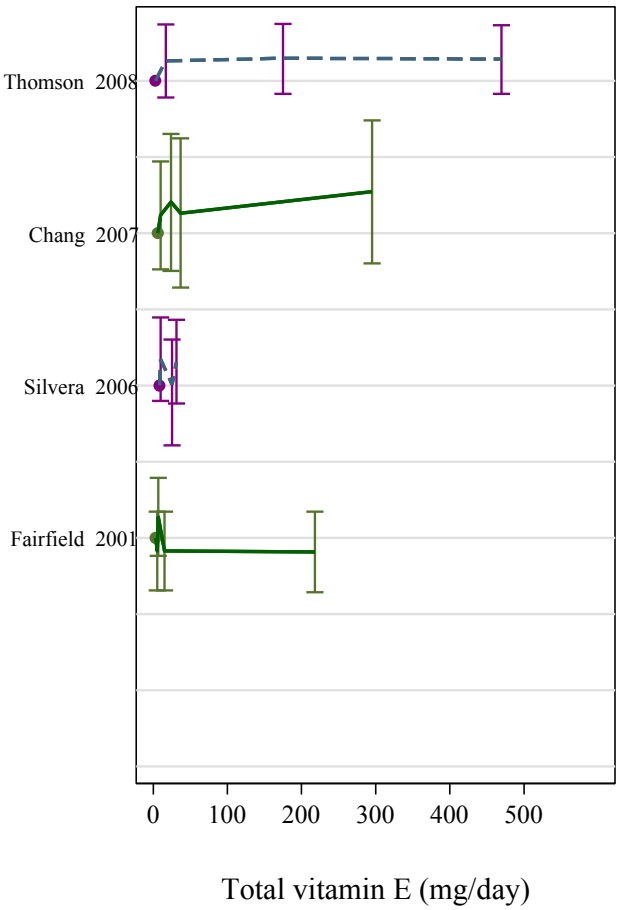


Figure 166 Dose-response graph of total vitamin E and ovarian cancer



5.5.11.2 Dietary Vitamin E

Methods

Up to December 2012, reports from four cohort studies were identified. The CUP meta-analysis included all four studies (two studies identified during the 2007 SLR and two studies identified during the CUP). For the dose-response analyses results were converted to a common level of exposure scale of 10 mg per day. The dose-response results are presented for an increment of 10 mg/day.

Main results

The summary RR per 10 mg/day was 1.05 (95% CI: 0.92-1.19; I^2= 4.1%, $P_{heterogeneity}$=0.37) for all studies combined. In influence analysis, the RR ranged from 1.02 (95% CI: 0.90-1.16) when excluding the Nurses' Health Study (Fairfield et al, 2001), to 1.14 (95% CI: 0.81-1.60) when excluding the Canadian National Breast Cancer Screening (Silvera et al, 2006)

Heterogeneity

Low heterogeneity was observed (I^2=4.1%, p=0.37). Egger's tests did not show evidence of publication bias (p=0.35). These tests lack power as only four studies are included in the analysis

Comparison with the Second Expert Report

Two studies were identified during the SLR. One of them, suggested significant increased risk (RR = 1.52; 95% CI: 1.04-2.21).

Table 173 Studies on dietary vitamin E identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Thomson, 2008	USA	Women's Health Initiative	451	8.3	1.05	0.71	1.57	>=9.4 mg/d ATE vs. <4.9 mg/d ATE*
Silvera, 2006	Canada	Canadian National Breast Cancer Screening	264	16.4	0.87	0.57	1.31	>25 mg/d vs. <17 mg/d

*ATE: alpha-tocopherol equivalents

Table 174 Overall evidence on dietary vitamin E and ovarian cancer

	Summary of evidence
SLR	Two studies were identified during the SLR, the Nurses' Health Study (Fairfield et al., 2001), showed a significant increased risk (RR = 1.52; 95% CI: 1.04-2.21)
Continuous Update Project	Two cohort studies were identified and overall four studies were included in the CUP meta-analysis.

Table 175 Summary of results of the dose response meta-analysis of dietary vitamin E and ovarian cancer

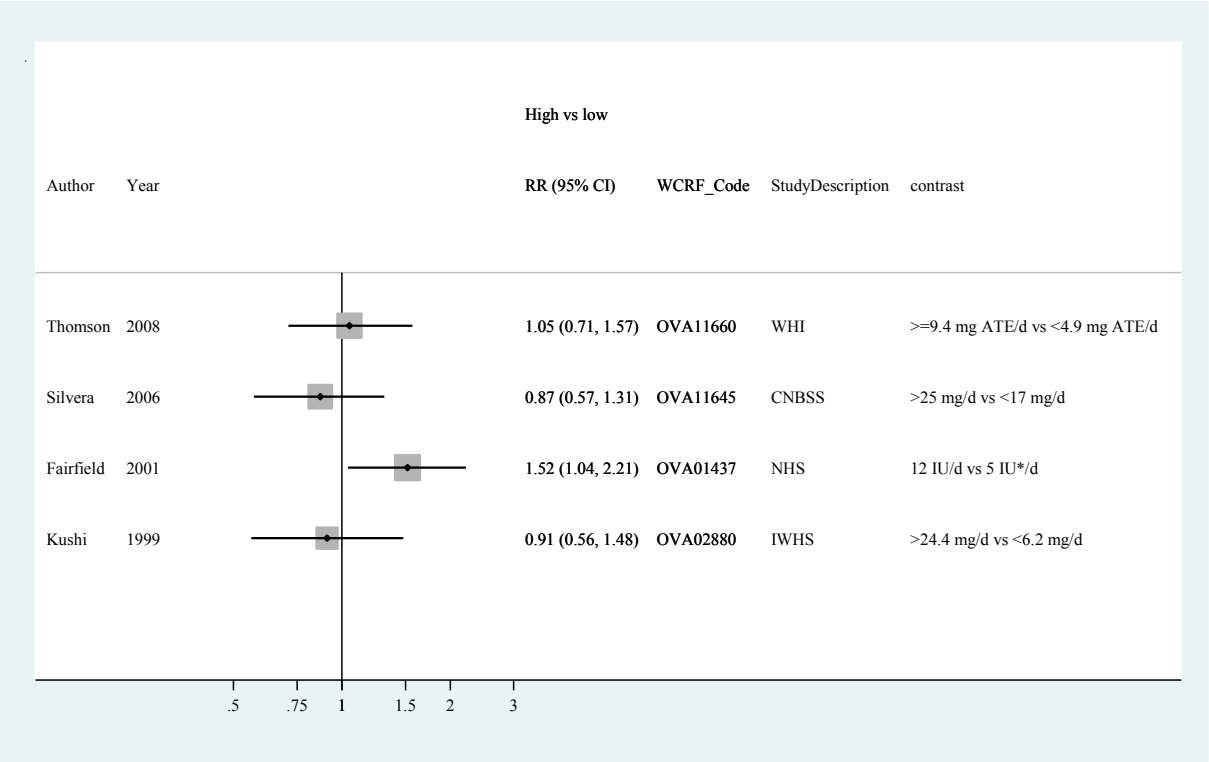
Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1155
Increment unit used	-	Per 10 mg/day
Overall RR (95%CI)	-	1.05 (0.92-1.19)
Heterogeneity (I^2,p-value)	-	4.1%, p=0.37

*No meta-analysis was conducted in the 2nd report

Table 176 Inclusion/exclusion table for meta-analysis of dietary vitamin E and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11660	Thomson	2008	Prospective Cohort study	Women's Health Initiative	Incidence Invasive	No	Yes	Yes	Mid-exposure values	-
OVA11645	Silvera	2006	Prospective Cohort study	Canadian National Breast Cancer Screening	Incidence	No	Yes	Yes	Mid-exposure values	-
OVA01437	Fairfield	2001	Prospective Cohort study	Nurses' Health Study	Incidence EOC	Yes	Yes	Yes	Person/ years per category Mid-exposure values Confidence intervals	-
OVA	Kushi	1999	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category Mid-exposure values	

Figure 167 Highest versus lowest forest plot of dietary vitamin E and ovarian cancer



*IU: International Units

Figure 168 Dose-response meta-analysis of dietary vitamin E and ovarian cancer - per 10 mg/d increase

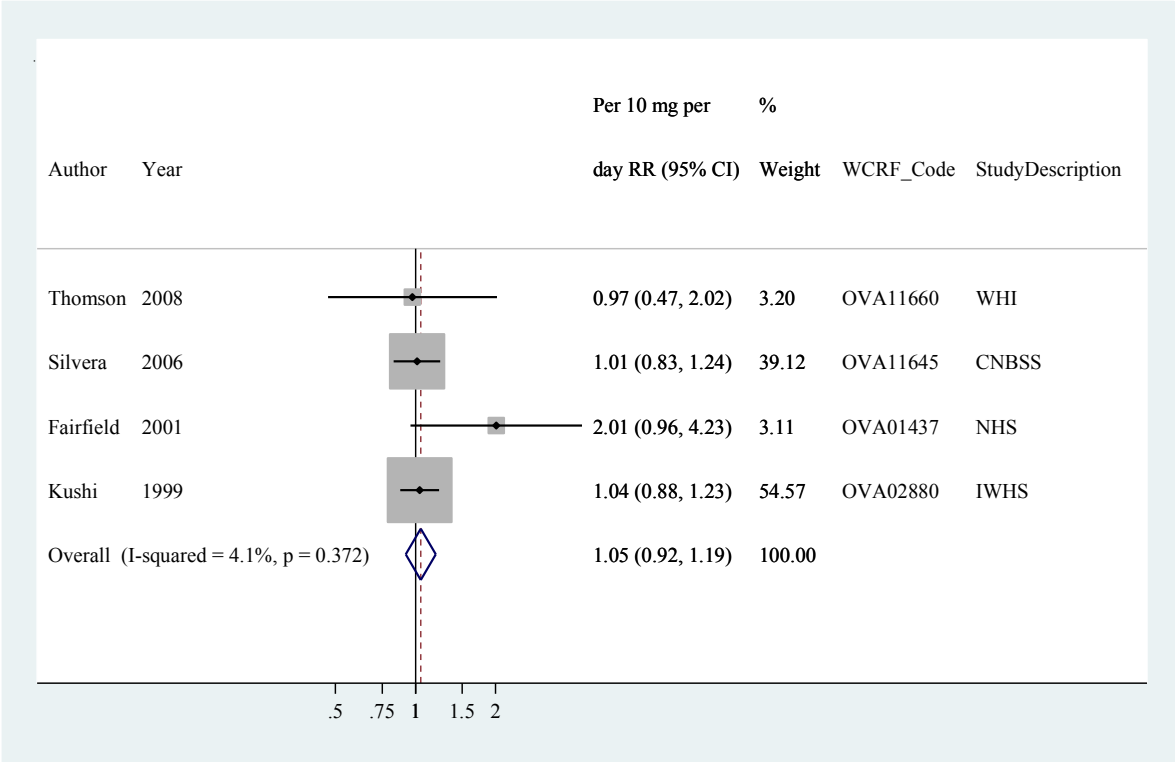


Figure 169 Funnel plot of dietary vitamin E and ovarian cancer

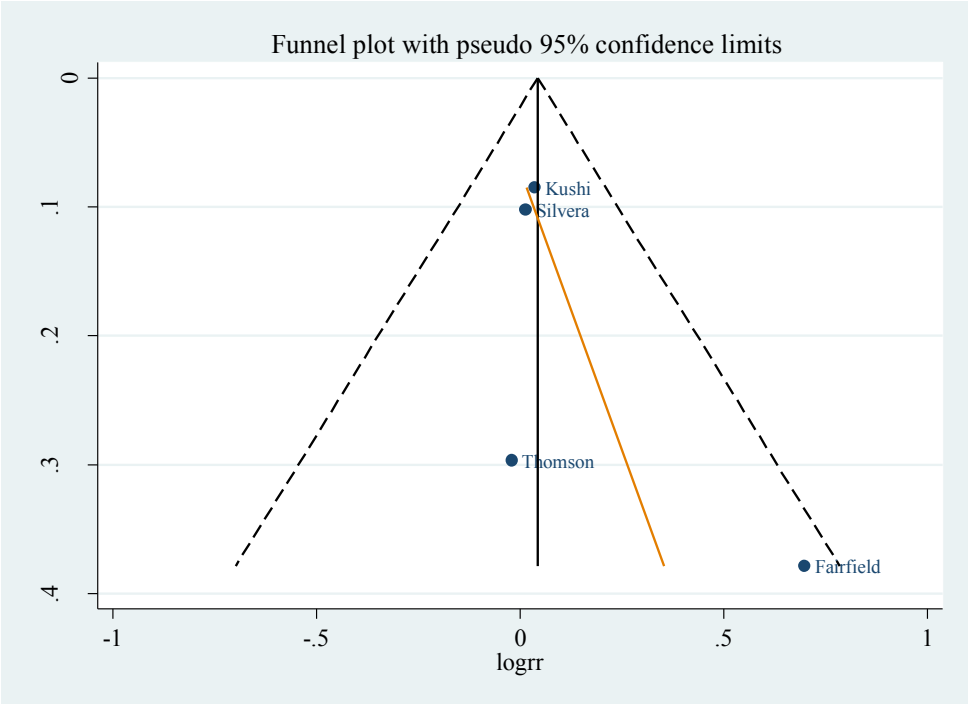
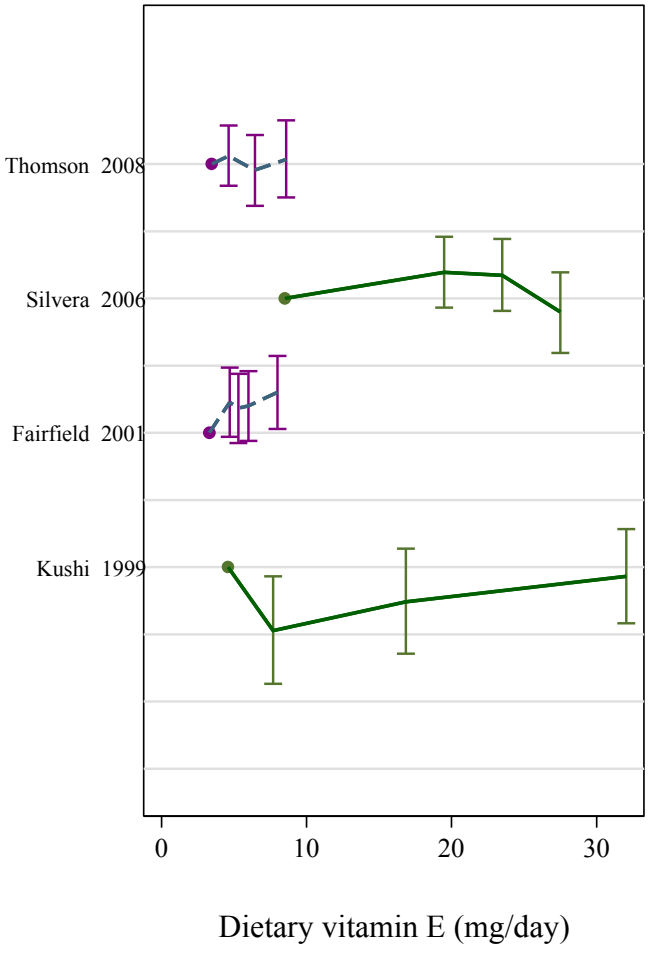


Figure 170 Dose-response graph of dietary vitamin E and ovarian cancer



5.6.3.1 Total calcium (food and supplements)

Methods

Up to December 2012, reports from four cohort studies were identified; three of them were identified during the CUP and one during the SLR. The CUP meta-analysis included three studies, all of them identified during the CUP. The dose-response results are presented for an increment of 200 mg per day of total calcium.

Main results

The summary RR per 200 mg/day was 1.00 (95% CI: 0.97-1.04; I^2= 10.2%, $P_{heterogeneity}$=0.32) for all studies combined. In influence analysis, the RR ranged from 0.97 (95% CI: 0.91-1.03) when excluding the National Institute of Health- American Association of Retired Persons (Park et al, 2009) to 1.01 (95% CI: 0.97-1.04) when excluding the Breast Cancer Detection Demonstration Project (Koralek et al, 2006).

Heterogeneity

Low heterogeneity was observed (I^2= 10.2%, p=0.32). Egger's tests did not show evidence of publication bias (p= 0.19) but only three studies were included.

Comparison with the Second Expert Report

The only study on total calcium intake and ovarian cancer identified in the SLR did not show any association.

Published pooled analysis

A pooled analysis of 12 cohort studies found no association between total calcium and ovarian cancer risk, pooled RR=1.08 (95% CI: 0.84-1.38, $p_{heterogeneity}$=0.37) for ≥1,300 vs. <500 mg/d (Genkinger et al, 2006). The RR for an increase of 350 mg was 1.01 (95% CI=0.99-1.02).

If the results of the NIH-AARP (Park et al, 2009) and the CTS (Chang et al, 2007) are pooled with the summary results of the pooled analysis of 12 cohorts (Genkinger et al, 2006), the relative risk estimate for an increase of 350 mg of total calcium is (RR=1.00; 95% CI=1.00-1.03).

Table 177 Studies on total calcium intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Park, 2009	United States	National Institute of Health-American Association of Retired Persons	515	7	1.14	0.85	1.52	1881 mg/d vs 494 mg/d
Chang, 2007	United States	California Teacher Study	280	8.1	0.90	0.57	1.43	>1127 mg/d vs <=461 mg/d
Koralek, 2006	United States	Breast Cancer Detection Demonstration Project	146	8.3	0.65	0.36	1.16	1696 mg/d vs 406 mg/d

Table 178 Overall evidence on total calcium intake and ovarian cancer

	Summary of evidence
SLR	One study was identified during the SLR, showing no association between total calcium intake and ovarian cancer.
Continuous Update Project	Three cohort studies were identified during the CUP. Three studies were included in the meta-analysis. None of the studies found an association between total calcium intake and ovarian cancer.

Table 179 Summary of results of the dose response meta-analysis of total calcium intake and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	941
Increment unit used	-	Per 200 mg/day
Overall RR (95%CI)	-	1.00 (0.97-1.04)
Heterogeneity (I^2,p-value)	-	10.2%, p=0.32

*No meta-analysis was conducted in the 2nd report

Table 180 Inclusion/exclusion table for meta-analysis of total calcium intake and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11694	Park	2009	Prospective Cohort Study	National Institute of Health-American Association of Retired Persons	Incidence	No	Yes	Yes	Cases per category Person/ years per category	
OVA11654	Chang	2007	Prospective Cohort Study	California Teacher Study	Incidence	No	Yes	Yes	Person/ years per category	
OVA11662	Koralek	2006	Prospective Cohort Study	Breast Cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Person/ years per category	
OVA11491	Fairfield	2004	Prospective Cohort Study	Nurses' Health Study	Incidence	Yes	No	Yes	-	Only RR for the highest vs lowest category

Figure 171 Highest versus lowest forest plot of total calcium intake and ovarian cancer

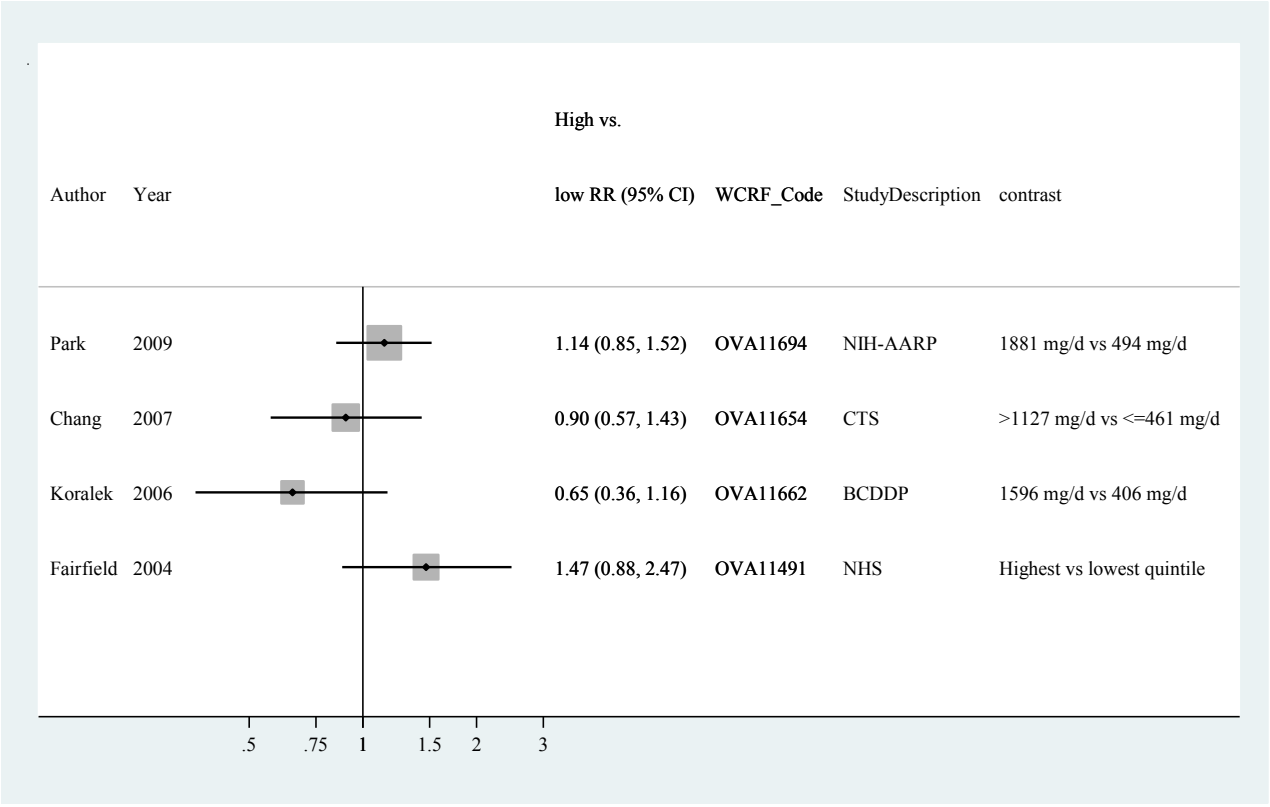


Figure 172 Dose-response meta-analysis of total calcium and ovarian cancer - per 200 mg/d

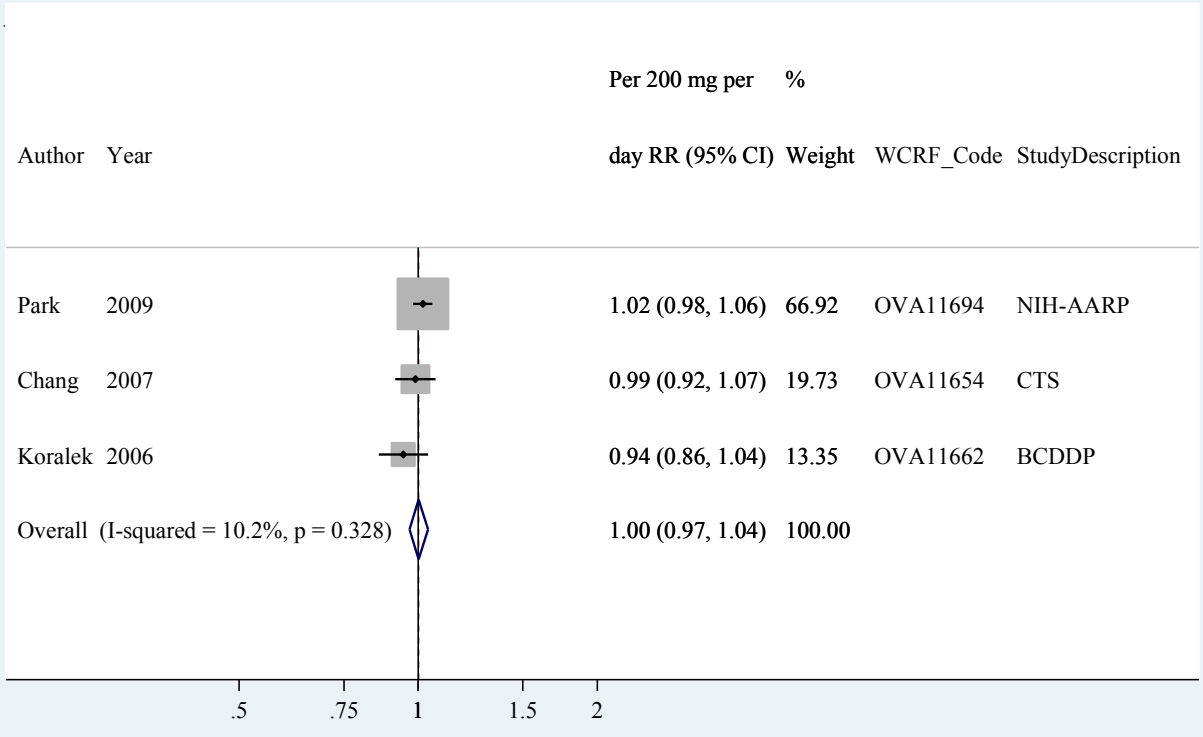


Figure 173 Funnel plot of total calcium intake and ovarian cancer

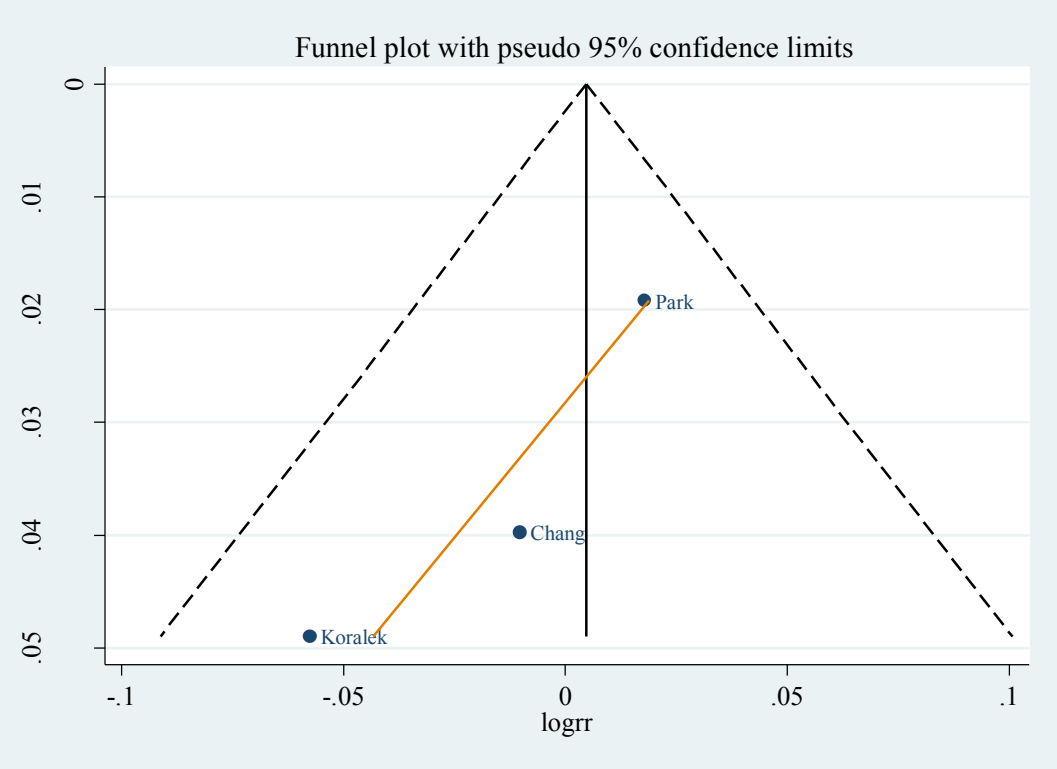
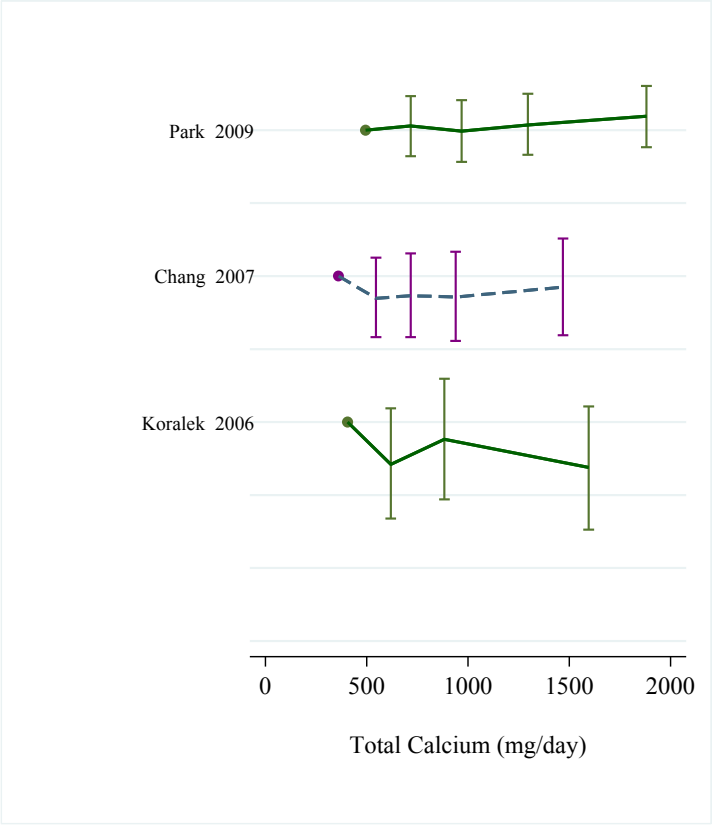


Figure 174 Dose-response graph of total calcium and ovarian cancer



5.6.3.2 Dietary calcium

Methods

Up to December 2012, reports from four cohort studies were identified; two of them were identified during the CUP and two during the SLR. The CUP meta-analysis included three studies, two of them identified during the CUP and one identified during the SLR. The dose-response results are presented for an increment of 200 mg per day of dietary calcium intake.

Main results

The summary RR per 200 mg/day was 0.99 (95% CI: 0.90-1.10; I^2= 59.1%, $P_{heterogeneity}$=0.08) for all studies combined. In influence analysis, the RR ranged from 0.95 (95% CI: 0.81-1.10) when excluding the Iowa Women's Health Study (Kushi et al, 1999) to 1.03 (95% CI: 0.97-1.10) when excluding the Breast Cancer Detection Demonstration Project (Koralek et al, 2006).

Heterogeneity

High heterogeneity was observed (I^2= 59.1%, p=0.08). Egger's tests did not show evidence of publication bias (p= 0.50) but the number of studies is limited.

Comparison with the Second Expert Report

The SLR identified two studies on dietary calcium intake and ovarian cancer. None of these studies showed any association.

Published pooled analysis

A pooled analysis of 12 cohort studies found no association between dietary calcium intake and ovarian cancer risk, pooled RR=1.17 (95% CI: 0.93-1.47, $p_{heterogeneity}$=0.53) for ≥1,300 vs. <500 mg/d (Genkinger et al, 2006). The RR for an increase of 350 mg was 1.03 (95% CI=0.97-1.09).

If the results of the NIH-AARP (Park et al, 2009) are pooled with the summary results of the pooled analysis of 12 cohorts (Genkinger et al, 2006), the relative risk estimate for an increase of 350 mg of dietary calcium remains unchanged (RR= 1.03; 0.95% CI= 0.97-1.09).

Table 181 Studies on dietary calcium intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Park, 2009	United States	National Institute of Health- American Association of Retired Persons	515	7	1.02	0.75	1.37	1101 mg/d vs 409 mg/d
Koralek, 2006	United States	Breast Cancer Detection Demonstration Project	146	8.3	0.67	0.43	1.04	946 mg/d vs 359 mg/d

Table 182 Overall evidence on dietary calcium intake and ovarian cancer

	Summary of evidence
SLR	The Nurses' Health Study and the Iowa Women's' cohort reported no association of calcium with ovarian cancer (Kushi et al., 1999, Fairfield et al., 2004).
Continuous Update Project	Two additional cohort studies were identified during the CUP. Overall, three studies were included in the meta-analysis. None of the studies found any association between dietary calcium intake and ovarian cancer.

Table 183 Summary of results of the dose response meta-analysis of dietary calcium intake and ovarian cancer

Ovarian cancer incidence and mortality		
	SLR	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	800
Increment unit used	-	Per 200 mg/day
Overall RR (95%CI)	-	0.99 (0.90-1.10)
Heterogeneity (I^2,p-value)	-	59.1%, p=0.08

*No meta-analysis was conducted in the 2nd report

Table 184 Inclusion/exclusion table for meta-analysis of dietary calcium intake and ovarian cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
OVA11694	Park	2009	Prospective Cohort Study	National Institute of Health-American Association of Retired Persons	Incidence	No	Yes	Yes	Cases per category Person/ years per category	
OVA11662	Koralek	2006	Prospective Cohort Study	Breast Cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Person/ years per category	
OVA11491	Fairfield	2004	Prospective Cohort Study	Nurses' Health Study	Incidence	Yes	No	Yes	-	Only RR for highest versus lowest category
OVA02880	Kushi	1999	Prospective Cohort Study	Iowa Women Health Study	Incidence	Yes	Yes	Yes	Person/ years per category and mid-exposure values	

Figure 175 Highest versus lowest forest plot of dietary calcium intake and ovarian cancer

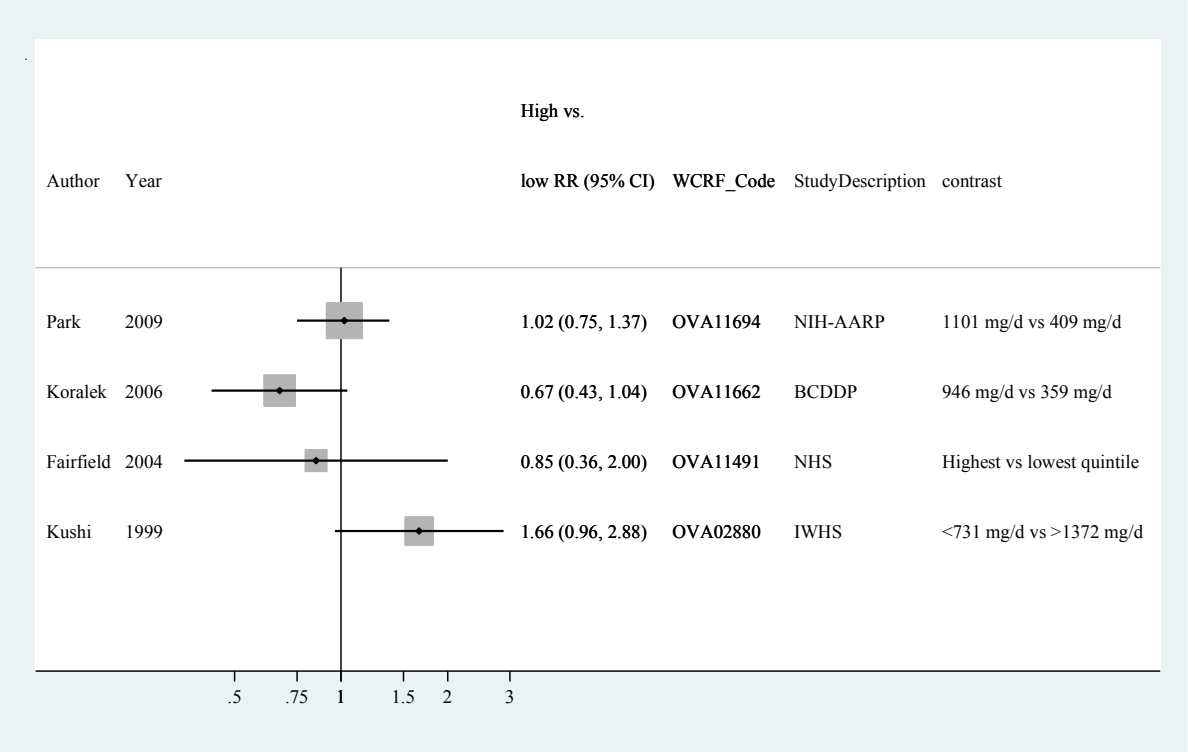


Figure 176 Dose-response meta-analysis of dietary calcium and ovarian cancer - per 200 mg/d

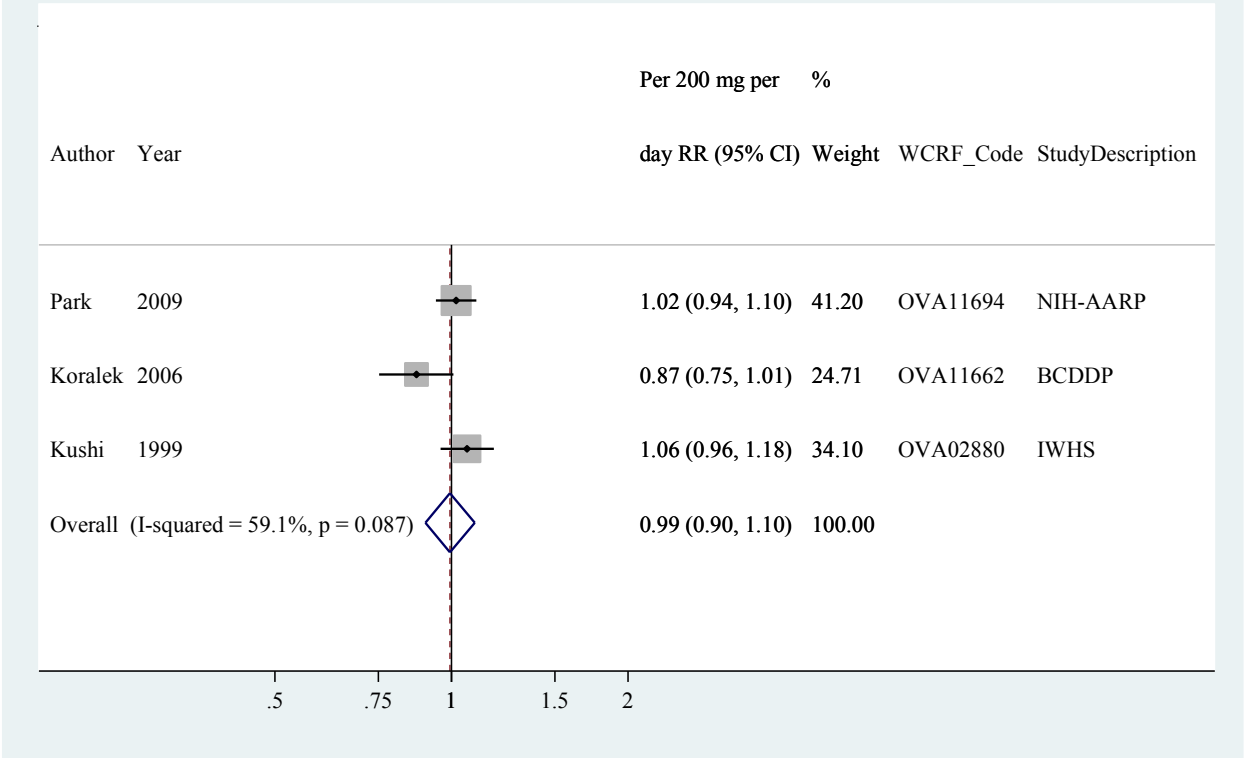


Figure 177 Funnel plot of dietary calcium intake and ovarian cancer

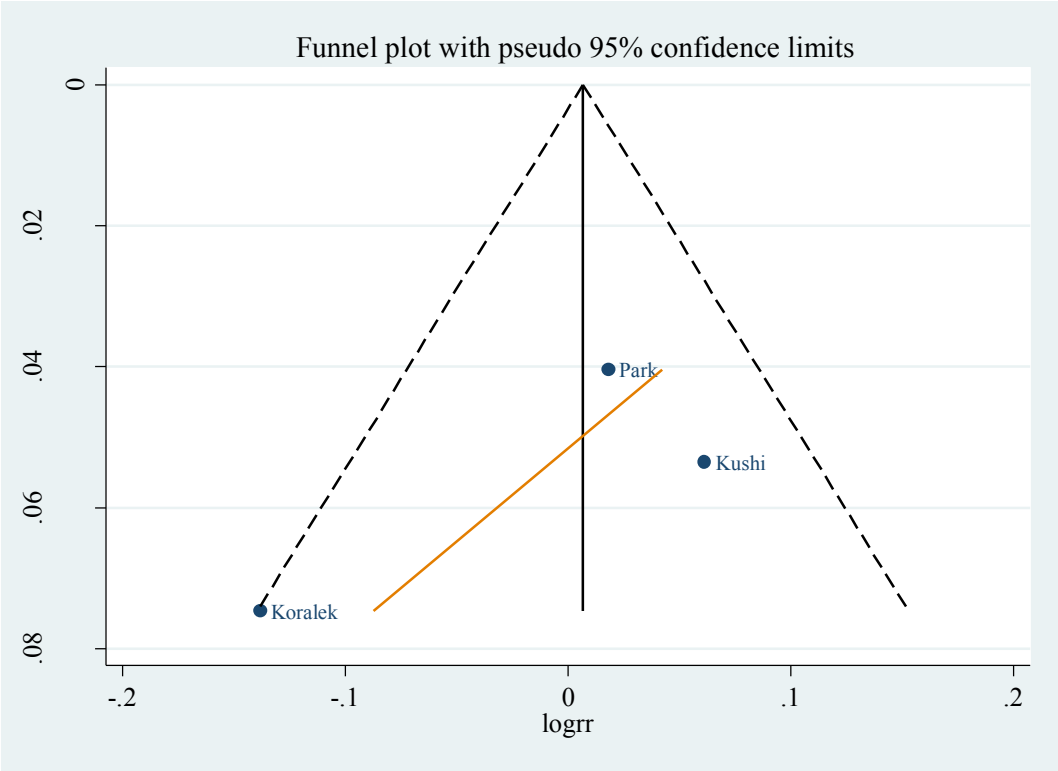
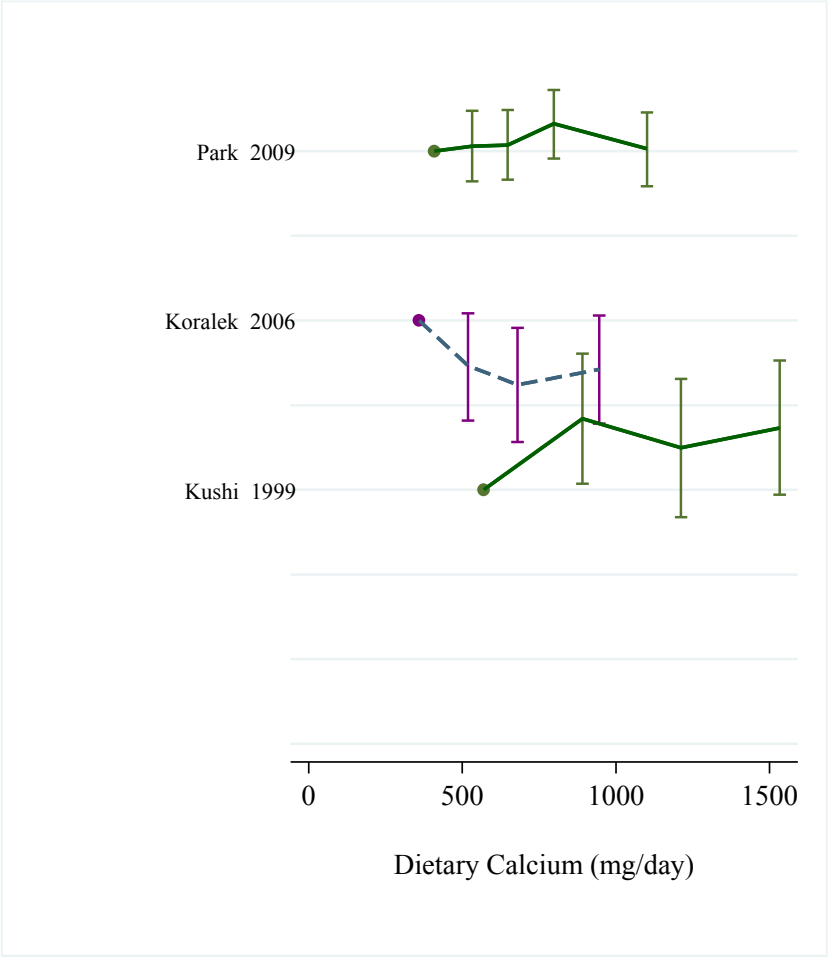


Figure 178 Dose-response graph of dietary calcium and ovarian cancer



6 Physical activity

No meta-analysis was possible for total physical activity, occupational and household activities, walking, physical activity intensity and physical inactivity. Study results are described below as a complement of the meta-analyses on leisure time activity.

6.1 Total physical activity

None of the two studies identified reported a significant association between total physical activity levels and ovarian cancer risk. In the Breast Cancer Detection Demonstration Project (121 cases) ovarian cancer the relative risk for >65 MET h/day vs. ≤ 48.4 MTS h/day was 0.70 (95% CI: 0.41–1.21, P trend = 0.13) (Hannan et al., 2004) and in the EPIC study, the relative risk comparing active vs inactive women was 1.32 (95% CI: 0.93-1.88; P trend=0.26) (Lahmann et al, 2009).

6.1.1.1 Ocupational

In the EPIC study (Lahmann et al, 2009) ovarian cancer was not related to occupational activity (RR manual/heavy manual versus sedentary= 1.07; 95% CI: 0.76-1.52).

6.1.1.3 Household

In the EPIC study (Lahmann et al, 2009) ovarian cancer was not related to household activitiy (RR >85 vs <26 MET h/week= 1.00; 95% CI: 0.77-1.29)

6.1.1.4 Walking

Walking was positively related to ovarian cancer risk in the Melbourne Collaborative Cohort Study (RR ≥3 times/weeks vs. none=1.62; 95% CI: 1.04-2.52, 113 cases) (Chionh et al., 2010).

6.1.3 Intensity of physical activity

In the Breast Cancer Detection Demonstration Project the relative risk of ovarian cancer for vigorous activities (>2 h/day vs. none) was 0.71 (95% CI: 0.42-1.30) (Hannan et al., 2004) and in the NIH-AARP Diet and Health Study (Yang et al., 2011) the relative risk for vigorous physical activity 3 or more times per week compared to never/rarely was 0.99 (95% CI: 0.83-1.18)

6.2 Physical inactivity

In the CPSII (Patel et al., 2006), prolonged duration of sedentary behaviour was associated with an increased risk of ovarian cancer (HR for _6 vs. <3 hours per day: 1.55, 95% CI: 1.08-2.22; P trend ≤ 0.01(but in the NIH-AARP Diet and Health Study, the relative risk of ovarian cancer in women entirely inactive compared to those with neither moderate nor vigorous activity was 0.87 (95% CI: 0.53–1.43) (Leitzmann et al., 2009).

6.1.1.2 Leisure-time physical activity

Methods

A total of 11 cohort studies (12 publications) on leisure-time physical activity and ovarian cancer risk have been published up to 2012, 8 of which were identified in the CUP. Because many studies did not provide a quantity of physical activity or provided results in <3 categories and because the remaining studies reported the quantities of physical activity in different measures (MET-hrs, hrs/wk) it was only possible to conduct dose-response analyses in MET-hrs/wk.

Main results

The summary RR per 20 MET-hrs per week was 1.05 (95% CI: 0.97-1.14, I^2=0%, $p_{heterogeneity}$=0.76).

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.76.

Published meta-analysis

A meta-analysis of 6 case-control studies and 7 cohort studies found summary RR of 0.81 (95% CI: 0.57-1.17) for high vs. low recreational physical activity in cohort studies with significant heterogeneity, p=0.004 (Olsen et al, 2007).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating recreational physical activity to ovarian cancer risk was limited and no conclusion was possible.

Table 185 Studies on leisure-time physical activity identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Weiderpass, 2011	Japan	Japan Public Health Centre-based Prospective Study	86 cases	16 years	1.1	0.6	1.7	Yes vs. no
Chionh, 2010	Australia	Melbourne Collaborative Cohort Study	113 cases	10.2 years	2.21	1.16	4.24	High vs. none
Leitzmann, 2009	USA	NIH-AARP Diet and Health Study	309 cases	7 years	1.10	0.82	1.48	Moderate and vigorous activity vs. neither
Lahmann, 2008	Europe	EPIC	731 cases	9.3 years	1.18	0.94	1.47	>42 vs. <12 MET-hrs/wk
Sakauchi, 2007	Japan	Japan Collaborative Cohort Study	77 deaths	13.3 years	0.51	0.24	1.07	≥1-2 hrs/wk vs. seldom
Biesma, 2006	Netherlands	Netherlands Cohort study	252 cases	11.3 years	0.72	0.48	1.06	>90 vs. <30 min/d
Weiderpass, 2006	Sweden	Women's Lifestyle and Health Study	264 cases	11.1 years	1.03	0.64	1.66	Vigorous vs. moderate
Patel, 2006	USA	Cancer Prevention Study II	314 cases	~10 years follow-up	0.73	0.40	1.34	≥31.5 MET-hrs/wk vs. none

Table 186 Overall evidence on leisure-time physical activity and ovarian cancer

SLR	Summary of evidence
2005 SLR	Three cohort studies (four publications) had reported on leisure-time physical activity and ovarian cancer. All of these reported no significant association.
Continuous Update Project	Eight cohort studies have been identified. Of these, one study found a significant increase in risk with greater recreational activity and the remaining studies found non-significant associations.

Table 187 Summary of results of the dose-response meta-analysis of leisure-time physical activity and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1422
RR (95% CI)	-	1.05 (0.97-1.14)
Increment	-	Per 20 MET-hrs/wk
Heterogeneity (I^2, p-value)	-	0%, p=0.76

*No meta-analysis was conducted in the 2nd report

Table 188 Inclusion/exclusion table for meta-analysis of leisure-time physical activity and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11669	Weiderpass	2011	Prospective Study	Japan Public Health Center-based Prospective Study	Incidence	No	No	Yes		Only two categories of exposure
OVA11629	Chionh	2010	Prospective Study	Melbourne Collaborative Cohort Study	Incidence	No	No	Yes		No quantification of physical activity
OVA11652	Leitzmann	2009	Prospective Study	NIH-AARP Diet and Health Study	Incidence	No	No	Yes		No quantification of physical activity
OVA11641	Lahmann	2008	Prospective Study	EPIC	Incidence	No	Yes	Yes	Midpoints, person-years	
OVA11661	Sakauchi	2007	Prospective Study	Japan Collaborative Cohort Study	Mortality	No	No	Yes		Only two categories of exposure
OVA11618	Biesma	2006	Prospective Study	Netherlands Cohort study	Incidence	No	No	Yes		Too few studies to conduct analyses by min/day
OVA11625	Patel	2006	Prospective Study	Women's Lifestyle and Health Study	Incidence	No	Yes	Yes	Midpoints	
OVA11634	Weiderpass	2006	Prospective Study	Cancer Prevention Study II	Incidence	No	No	Yes		No quantification of physical activity
OVA10078	Schnohr	2005	Prospective Study	Copenhagen Centre for Prospective Population Studies	Incidence	Yes	No	Yes		No quantification of physical activity
OVA09688	Anderson	2004	Prospective Study	Iowa Women's Health Study	Incidence	Yes	No	Yes		No quantification of physical activity
OVA00455	Bertone	2001	Prospective Study	Nurses' Health Study	Incidence	Yes	Yes	Yes	Midpoints, person-years	
OVA03556	Mink	1996	Prospective Study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with OVA09688 (Anderson et al, 2004)

Figure 179 Highest versus lowest forest plot of leisure-time physical activity and ovarian cancer

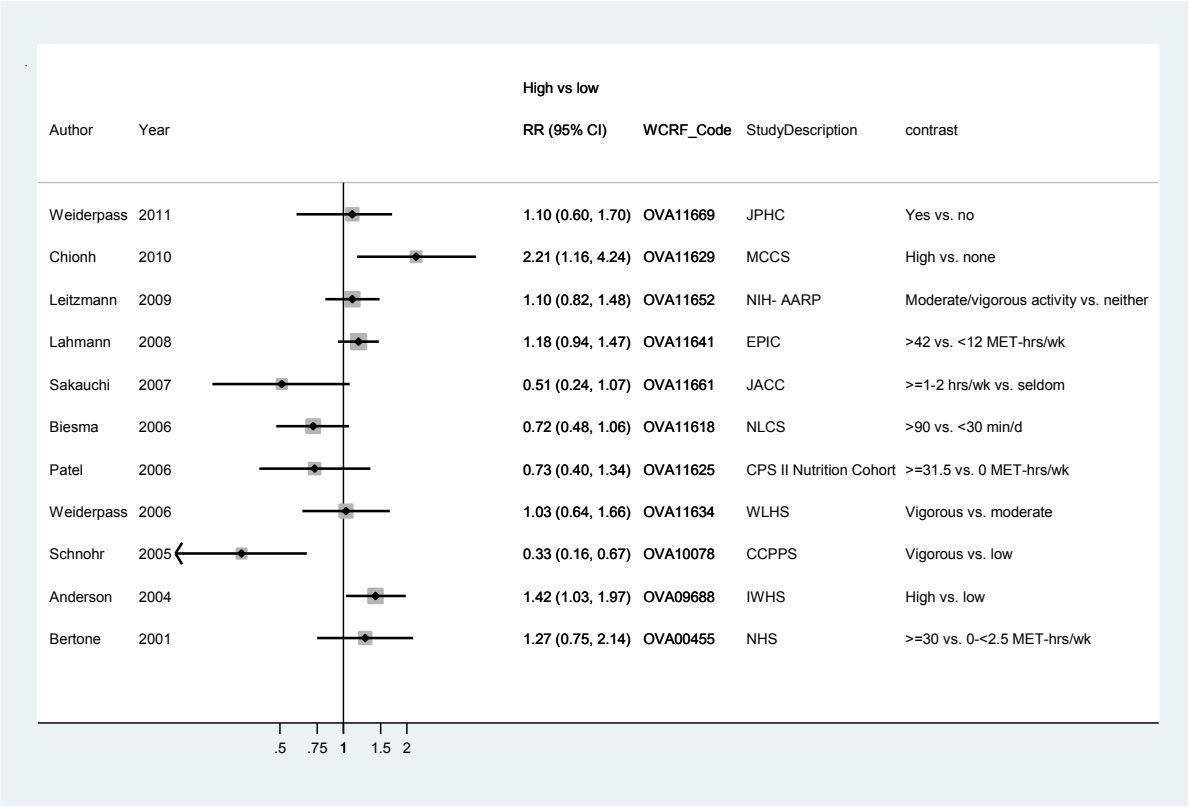


Figure 180 Dose-response meta-analysis of leisure-time physical activity and ovarian cancer, per 20 MET-hrs/wk

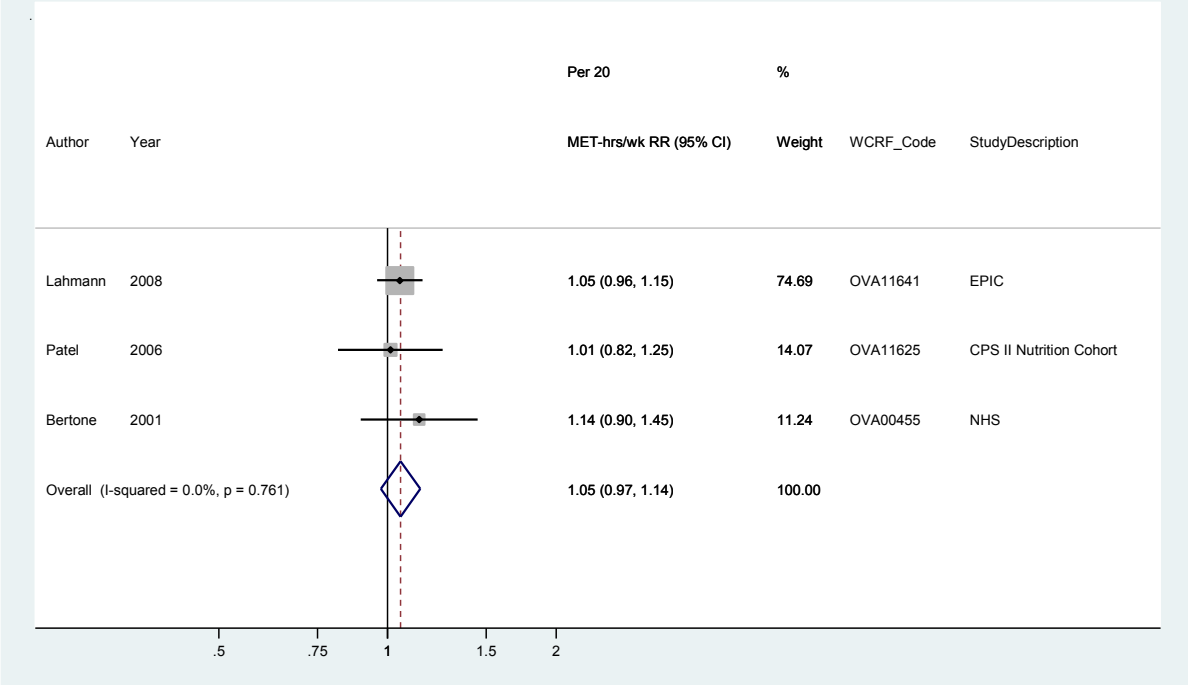
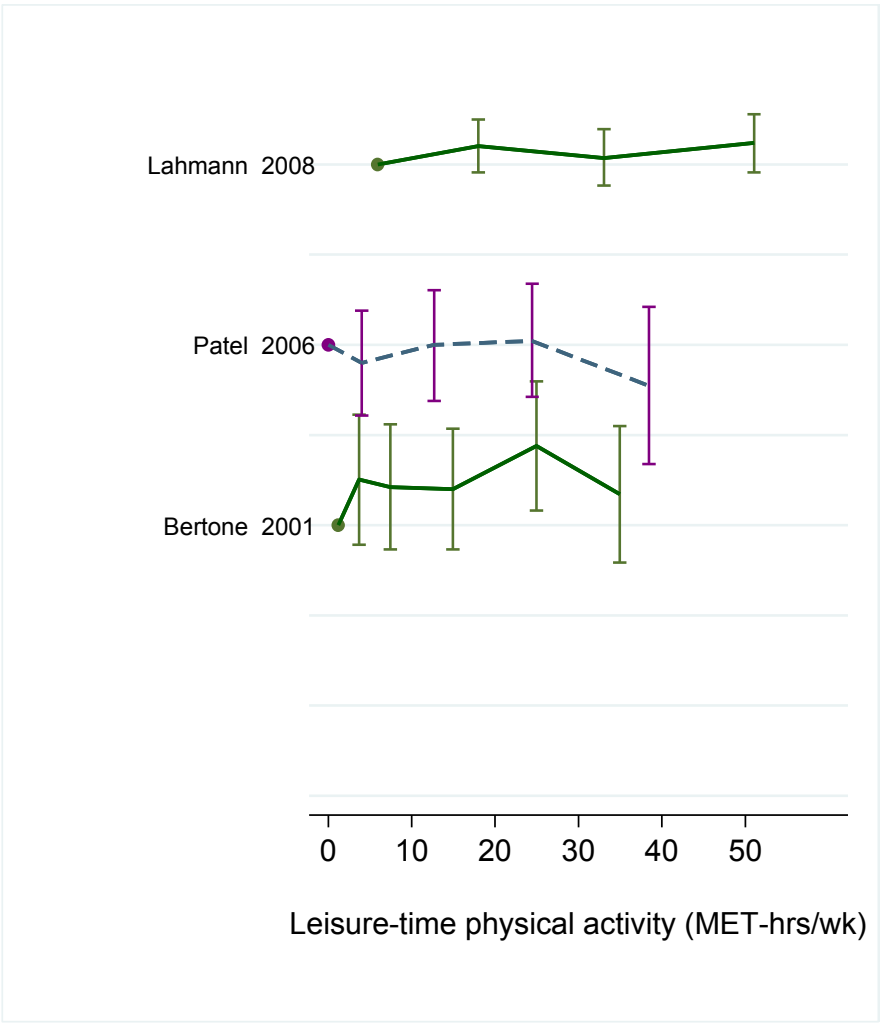


Figure 181 Dose-response graph of leisure-time physical activity and ovarian cancer



8 Anthropometry

8.1.1 BMI

Methods

A total of 26 prospective studies (31 publications) have been published on BMI and ovarian cancer risk up to 2012, of which 17 prospective studies (18 publications) were identified in the CUP. Dose-response analyses were conducted per 5 BMI units. When the category corresponding to underweight (BMI<18.5) was not used as the reference category, the relative risks estimates associated to this category were not included in the meta-analysis. This is because the number of cases with BMI<18.5 was low and rescaling the dose-response association using this category as reference would have resulted in unstable estimates. We also conducted a sensitivity analysis recalculating the risk estimates so that the lowest category always was used as a reference category using the method by Hamling et al, 2008 but this did not change the results. A subgroup analysis was conducted by menopausal status, and for some studies which conducted analyses stratified by age group (≥50 vs. <50 years for example) we used this as a proxy for menopausal status (Tornberg et al, 1994, Engeland et al, 2003, Lundqvist, et al, 2007). For the study by Engeland, results for ages, 20-29, 30-39, 40-49 years were combined and for ages 50-59, 60-69, 70-74 years were combined using a fixed effects model.

A potential non-linear dose-response meta-analysis was explored using fractional polynomial models (Royston, 2000).

Main results

The summary RR per 5 BMI units was 1.06 (95% CI: 1.02-1.11, I^2=55.1%, $p_{heterogeneity}$=0.001). In the sensitivity analysis when recalculating all the risk estimates in studies where the lowest category was not used as the reference category, the risk estimate was identical and heterogeneity statistics were similar (1.06 (95% CI: 1.02-1.11, I^2=54.1%, $p_{heterogeneity}$=0.001). There was borderline evidence of funnel plot asymmetry with Egger's test, p=0.05. In analyses stratified by menopausal status, the summary RR was 1.10 (95% CI: 0.99-1.22, I^2=59.6%, $p_{heterogeneity}$=0.03) for premenopausal women, and 1.04 (95% CI: 1.00-1.09, I^2=45.9%, $p_{heterogeneity}$=0.05) for postmenopausal women.
The nonlinear analysis shows that there is a statistically significant increase in risk of ovarian cancer for BMI higher than >28.4 kg/m^2 ($p_{nonlinarity}$<0.0001) (that is the point where the curve shows a significant association).
In an additional analysis we included the non-overlapping studies from the CUP meta-analysis together with the results of the pooled analysis (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012) and the summary RR per 5 BMI units was 1.06 (95% CI: 1.00-1.12, I^2=37.9%, $p_{heterogeneity}$=0.07).

Heterogeneity

There was evidence of substantial heterogeneity, I^2=55.1%, $p_{heterogeneity}$=0.001. In influence analysis, there was no evidence of heterogeneity when the large Norwegian Tuberculosis

Screening Study (Engeland et al, 2003) was excluded (I^2=21% and p for heterogeneity=0.19) and the summary RR increased slightly to 1.07 (95% CI: 1.04-1.11).

Published pooled analyses and meta-analyses

Another meta-analysis of 17 case-control studies and 11 cohort studies found a summary RR of 1.30 (95% CI: 1.12-1.50, $p_{heterogeneity}$=0.001) for obesity and 1.16 (95% CI: 1.01-1.32, $p_{heterogeneity}$=0.001) for overweight (Olsen et al, 2007). The associations were stronger in case-control studies than cohort studies and when analysing cohort studies separately (9550 cases), the summary RR was 1.12 (95% CI: 0.95-1.32 $p_{heterogeneity}$=0.04) for obesity and 1.07 (95% CI: 0.92-1.25, $p_{heterogeneity}$=0.14) for overweight.

A pooled analysis of 12 cohort studies including 531583 women and 2036 cases found a RR of 1.03 (95% CI: 0.86-1.22) for BMI 30 compared with BMI of 18.5-23 (Schouten et al, 2008). The pooled RR was 1.72 (95% CI: 1.02-2.89) for premenopausal women and 1.07 (95% CI: 0.87-1.33) for postmenopausal women.

A meta-analysis of 13 prospective studies (12208 cases, 2703734 participants) reported a summary risk estimate of 1.03 (95% CI: 0.99-1.08, I^2=55%, $p_{heterogeneity}$=0.30) for a 5 unit increment in BMI (Renehan et al, 2008).

A pooled analysis of 47 studies with 25157 cases and 81311 controls (17 of which were prospective studies) studies reported a pooled RR of 1.05 (95% CI: 1.03-1.07) per 5 unit increase in BMI (excluding results from 6 hospital-based case-control studies) (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). In categorical analyses the pooled RR was 1.13 (95% CI: 1.06-1.20) for a BMI of ≥30 compared with <22.5 (mean: 33.6 vs. 20.6). Restricting the analysis to the 17 prospective studies (10643 cases and 44731 controls) showed a pooled RR of 1.03 (95% CI: 1.00-1.06) per 5 unit increase in BMI.

Comparison with the Second Expert Report

In the systematic review of the 2007 Expert Report, the evidence relating body fatness to ovarian cancer risk was considered either of too low quality, considered too inconsistent, or the number of studies were too few to allow conclusions to be reached.

Table 189 Studies on BMI identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Weiderpass, 2012	Japan	Japan Public Health Center-based Prospective Study	86	16 years	0.8 1.00	0.2 0.94	3.3 1.08	>29.9 vs. 20-22.9 Per unit
Brändstedt, 2011	Sweden	Malmo Diet and Cancer Cohort	93	13.1 years	0.90	0.47	1.75	≥30 vs. <25
Yang, 2011	USA	NIH-AARP Diet and Health Study	849	~9.8 years	1.15	0.98	1.35	≥30 vs. <30
Andreotti, 2010	USA	Agricultural Health Study	48	>10 years	0.48	0.14	1.63	≥30 vs. <25
Kotsopoulos, 2010	USA	Nurses' Health Study 1	732	30 years	1.11	0.85	1.45	≥30 vs. <21
Kotsopoulos, 2010	USA	Nurses' Health Study 2	130	16 years	1.36	0.80	2.33	≥30 vs. <21
Chionh, 2010	Australia	Melbourne Collaborative Cohort Study	113	10.2 years	1.58 1.22	0.96 1.00	2.62 1.48	30 vs. 25-29 Per 5 units
Canchola, 2010	USA	California Teachers Study	277	12.1 years	1.2 0.54 0.61	0.72 0.21 0.26	2.0 1.39 1.45	≥30 vs. <25, never used HT ≥30 vs. <25, HT ≤5 years ≥30 vs. <25, HT >5 years
Lahmann, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	611	8.9 years	1.27 1.33 1.05	0.98 1.05 1.01	1.63 1.68 1.08	>27.9 vs. <22.2 ≥30 vs. <25 Per 2 units
Leitzmann, 2009	USA	NIH-AARP Diet and Health Study	303	7 years	1.26	0.94	1.68	≥30 vs. <25
Song, 2008	Korea	Korean Cancer Prevention Study	176	8.75 years	0.93 1.04	0.32 0.99	2.67 1.09	≥30 vs. 21-22.9 Per 1 unit
Lundqvist, 2007	Sweden, Finland	Sweden, Finland Co-twin study	313	26.3 years	0.7 1.00 0.8 1.06	0.3 0.96 0.2 1.02	1.5 1.04 2.6 1.11	≥30 vs. 18.5-<25.0 Per 1 unit, older subjects ≥30 vs. 18.5-<25.0 Per 1 unit, younger subjects
Sakauchi,	Japan	Japan	77	13.3	1.69	0.99	2.87	≥25.0 vs.

2007		Collaborative Cohort Study		years				18.5-25.0
Reeves, 2007	United Kingdom	Million Women's Study	2406	5.4 years	1.12 1.14	1.02 1.03	1.23 1.27	≥30 vs. 22.5-24.9 Per 10 units
Kiani, 2006	USA	Adventist Health Study	71	Up to 16 years	1.33	0.72	2.47	≥25.9 vs. ≤23.2
Lacey, 2006	USA	NIH-AARP Diet and Health Study	214	~4 years	1.07	0.68	1.39	≥30 vs. <25
Lacey, 2006	USA	Breast Cancer Detection Demonstration Project Follow-Up Study	346	14.5 years	1.55	0.84	2.84	≥35 vs. 18.5-24.9
Kuriyama, 2005	Japan	Miyagi Cohort Study	20	9 years	0.85	0.19	3.81	27.5-29.9 vs. 18.5-24.9
Rapp, 2005	Austria	VHM & PP	121	9.9 years	1.25	0.75	2.08	≥30 vs. 18.5-24.9

Table 190 Overall evidence on BMI and ovarian cancer

SLR	Summary of evidence
2005 SLR	Thirteen prospective studies reported on BMI and ovarian cancer. One combined analysis of three nested case-control studies reported an inverse association between BMI and ovarian cancer risk, while six studies reported no significant association, one study reported a marginally significant positive association and three studies reported significant increases in risk or a significant p-value for trend.
Continuous Update Project	Of the seventeen studies identified in the CUP, four reported significant associations, although in one of these a positive association was observed only among younger subjects. None of the remaining studies showed any significant associations, although several showed non-significant positive associations.

Table 191 Summary of results of the dose-response meta-analysis of BMI and ovarian cancer

Ovarian cancer		
	SLR	Continuous Update Project
Studies (n)	7[1]	25[2]
Cases (n)	8801	15899
RR (95% CI)	1.00 (0.99-1.01)	1.06 (1.02-1.11)
Quantity	Per 2 units	Per 5 units
Heterogeneity (I^2, p-value)	62.1%, p=not available	55.1%, p=0.001

[1]Number of risk estimates = 5
[2]Number of risk estimates = 22

Table 192 Inclusion/exclusion table for meta-analysis of BMI and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11669	Weiderpass	2012	Prospective cohort study	Japan Public Health Center-based Prospective Study	Incidence	No	Yes	Yes	Midpoints, person-years	
OVA11644	Brändstedt	2011	Prospective cohort study	Malmo Diet and Cancer Cohort study	Incidence	No	No	No		Overlap with Lahmann et al OVA11636
OVA11672	Yang	2011	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	No	No		Overlap with Leitzmann et al, 2009 OVA11623 which provided results by three categories (Yang et al, presented results only as dichotomized variable)
OVA11691	Andreotti	2010	Prospective cohort study	Agricultural Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 1	Incidence	No	Yes	Yes	Midpoints	
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 2	Incidence	No	Yes	Yes	Midpoints	
OVA11629	Chionh	2010	Prospective cohort study	Melbourne Collaborative Cohort Study	Incidence	No	Yes	Yes	Midpoints	
OVA11627	Canchola	2010	Prospective cohort study	California Teachers Study	Incidence	No	Yes	Yes	Midpoints, RRs were recalculated using the lowest	

									category of BMI as reference within each stratum of HT	
OVA11636	Lahmann	2009	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA11623	Leitzmann	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints	
OVA11688	Song	2008	Prospective cohort study	Korean Cancer Prevention Study	Incidence	No	Yes	Yes	Midpoints	
OVA11657	Lundqvist	2007	Prospective cohort study	Sweden, Finland Co-twin study	Incidence	No	Yes	Yes	Midpoints, person-years	
OVA11661	Sakauchi	2007	Prospective cohort study	Japan Collaborative Cohort Study	Mortality	No	No	No		Overlap with Niwa et al, 2005 OVA09951, which was used because it analysed incidence instead of mortality
OVA11653	Reeves	2007	Prospective cohort study	Million Women's Study	Incidence Mortality	No	Yes	Yes	Midpoints, person-years	
OVA11647	Kiani	2006	Prospective cohort study	Adventist Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
OVA11655	Lacey	2006	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	No	No		Overlap with Leitzmann et al, 2009, OVA11623, which had a larger number of cases
OVA12070	Lukanova	2006	Prospective cohort study	Northern Sweden Health And Disease Cohort Study	Incidence	Yes	No	Yes		Overlap with Lukanova, 2002 OVA 03222, which was used in the dose-response analysis

										because it included 3 studies. For the high vs. low analysis results from the 2006 analysis of NSHDC study was used because it had a larger number of cases.
OVA11649	Lacey	2006	Prospective cohort study	Breast cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Midpoints	
OVA11690	Kuriyama	2005	Prospective cohort study	Miyagi Cohort Study	Incidence	No	Yes	Yes	Midpoints, person-years	
OVA11689	Rapp	2005	Prospective cohort study	VHM & PP	Incidence	No	Yes	Yes	Midpoints	
OVA09951	Niwa	2005	Prospective cohort study	Japan Collaborative Cohort Study	Incidence	Yes	Yes	Yes	Midpoints	
OVA09688	Anderson	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints	
OVA04756	Schouten	2003	Prospective cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Midpoints	
OVA01399	Engeland	2003	Prospective cohort study	Norwegian Tuberculosis Screening Study	Incidence	Yes	Yes	Yes	Midpoints	
OVA00733	Calle	2003	Prospective cohort study	Cancer Prevention Study II	Mortality	Yes	No	No		Overlap with Rodriguez et al, 2002, OVA04449, which was used because it had a slightly larger number of cases
OVA02429	Jonsson	2003	Prospective cohort study	Swedish Twin Cohort	Incidence	Yes	No	No		Overlap with Lundqvist et al, 2007, OVA11657
OVA04449	Rodriguez	2002	Prospective	Cancer	Mortality	Yes	Yes	Yes	Midpoints,	

			cohort study	Prevention Study II					recalculation of RRs using lowest category as reference	
OVA01439	Fairfield	2002	Prospective cohort study	Nurses' Health Study	Incidence	Yes	No	No		Overlap with Kotsopoulos et al, 2010, OVA11658
OVA03222	Lukanova	2002	Nested case-control study	New York University Women's Health Study, Northern Sweden Health and Disease Study & ORDET	Incidence	Yes	Yes	Yes		Results for the NSHDC study from Lukanova 2006 was used for the high vs. low analysis, but for the other two studies (ORDET, NYUWHS) Lukanova 2002 is used.
OVA03556	Mink	1996	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with Anderson et al, 2004, OVA09688
OVA05379	Tornberg	1994	Prospective cohort study	Central Sweden	Incidence	Yes	Yes	Yes	Midpoints, confidence intervals	
OVA02953	Lapidus	1988	Prospective cohort study	Gothenburg	Incidence	Yes	No	No		No risk estimate reported

Figure 182 Highest versus lowest forest plot of BMI and ovarian cancer

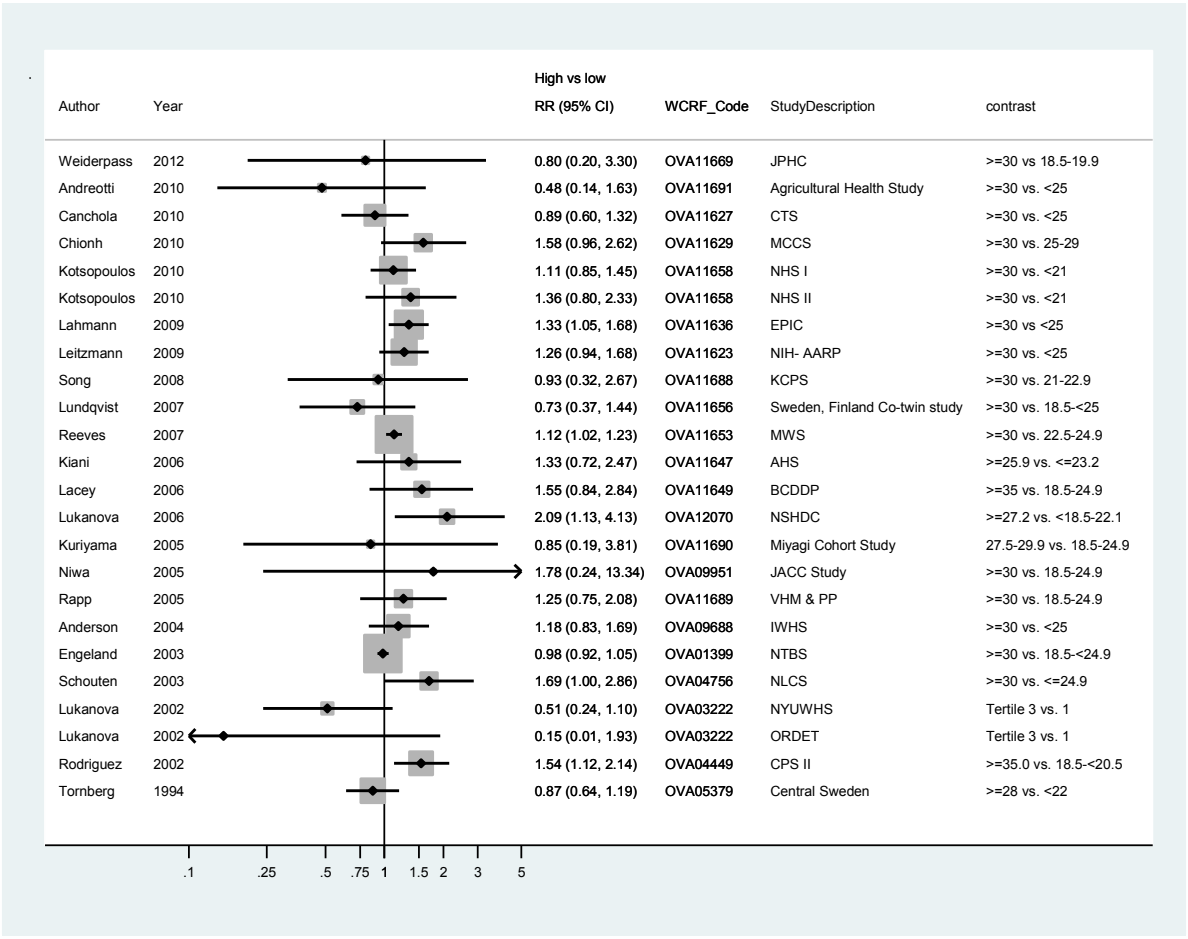


Figure 183 Dose-response meta-analysis of BMI and ovarian cancer, per 5 units

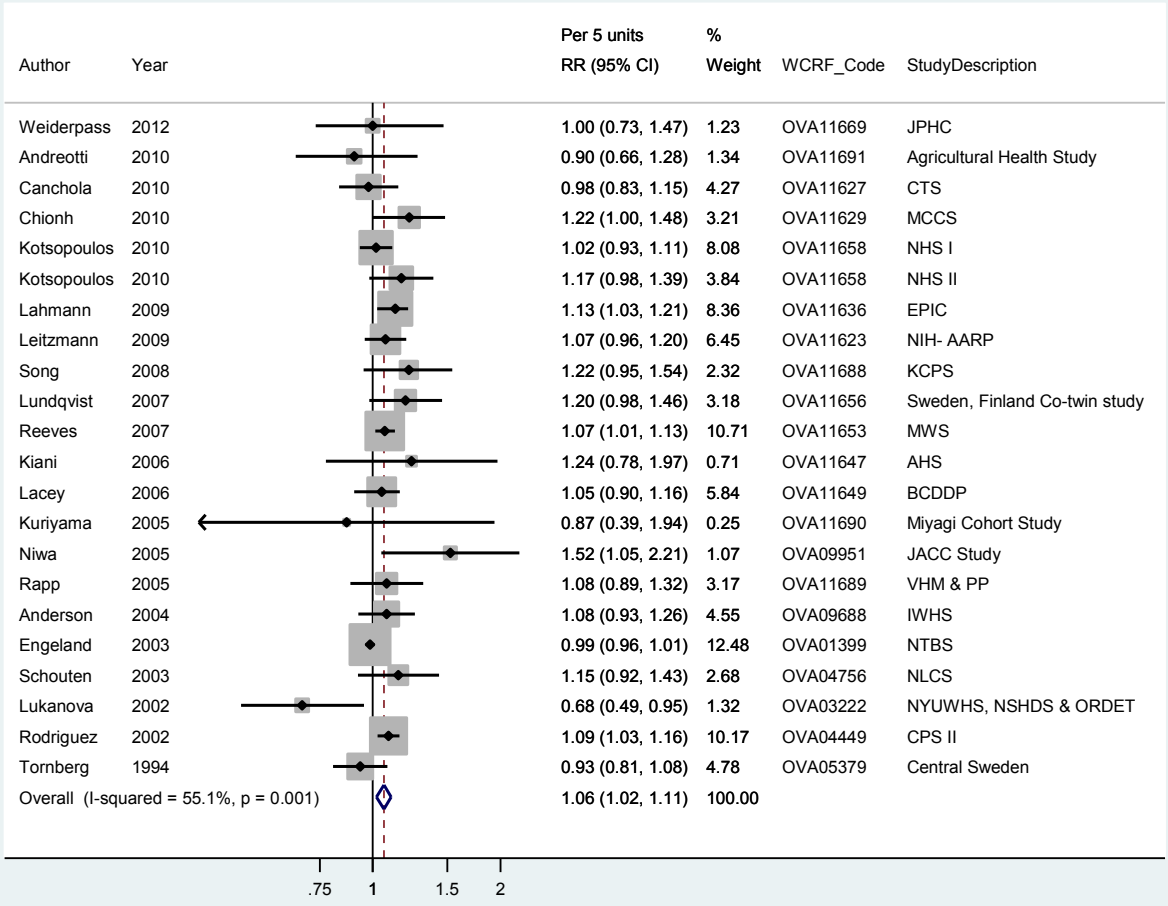


Figure 184 Figure Dose-response meta-analysis of BMI and ovarian cancer, per 5 units, by menopausal status

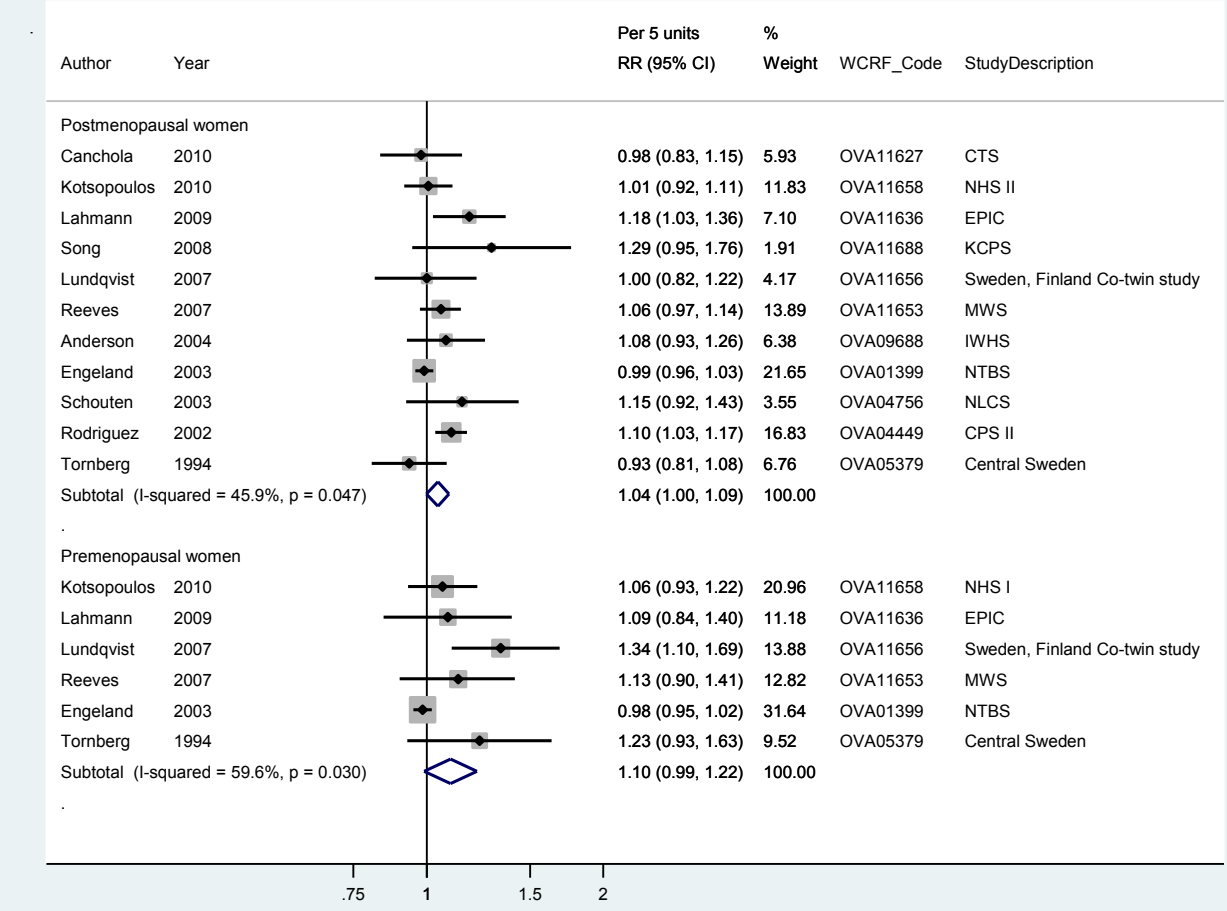


Figure 185 Funnel plot of BMI and ovarian cancer

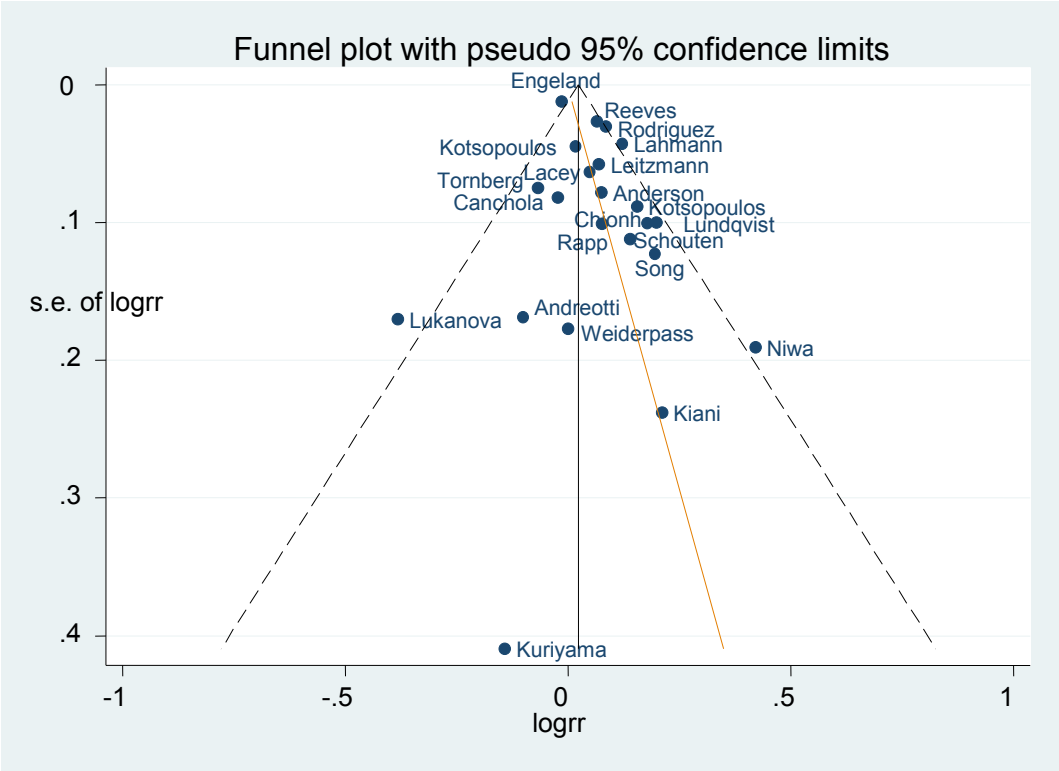


Figure 186 Dose-response graph of BMI and ovarian cancer

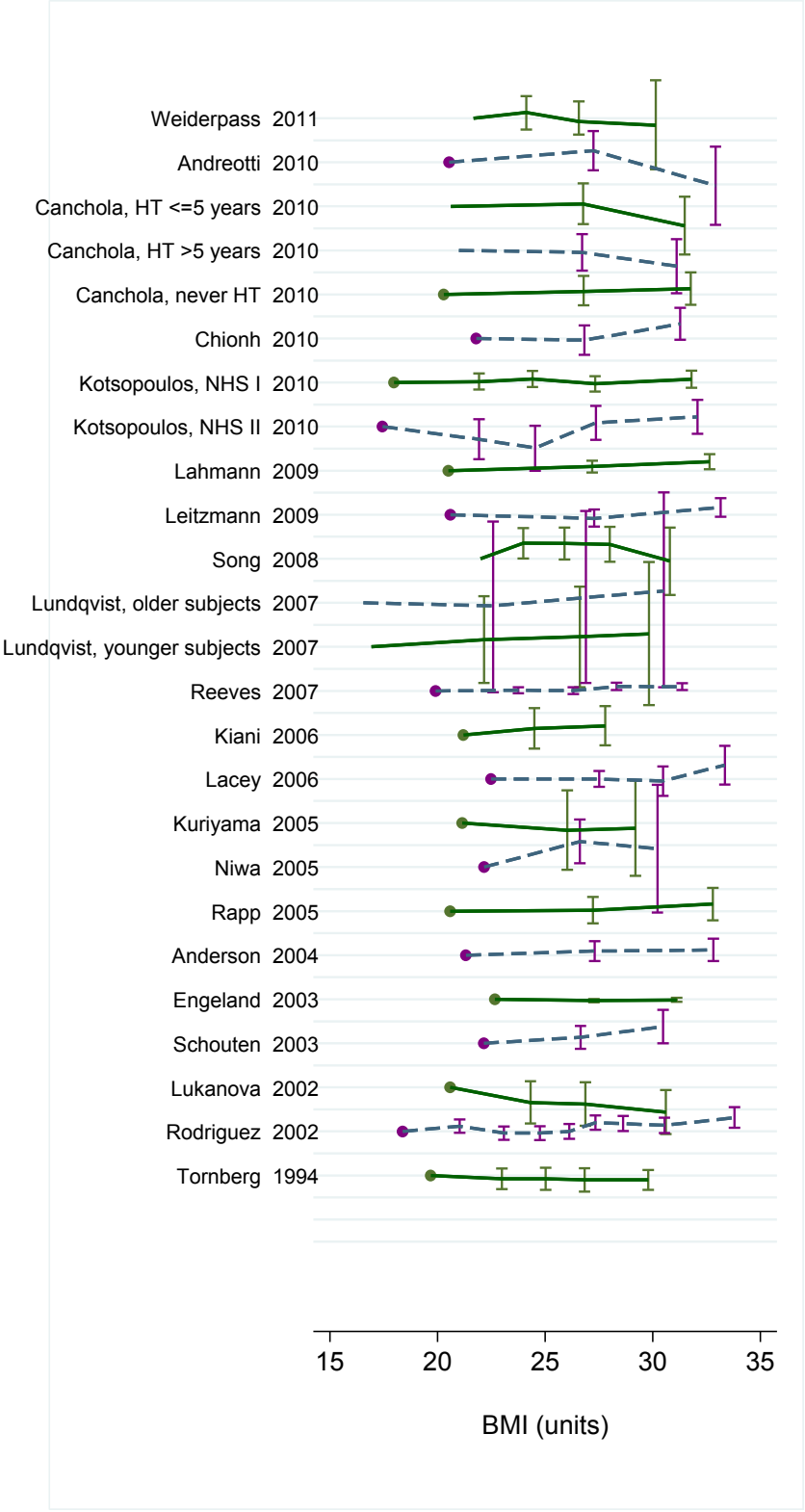


Figure 187 Non-linear dose-response graph of BMI and ovarian cancer
p<0.0001

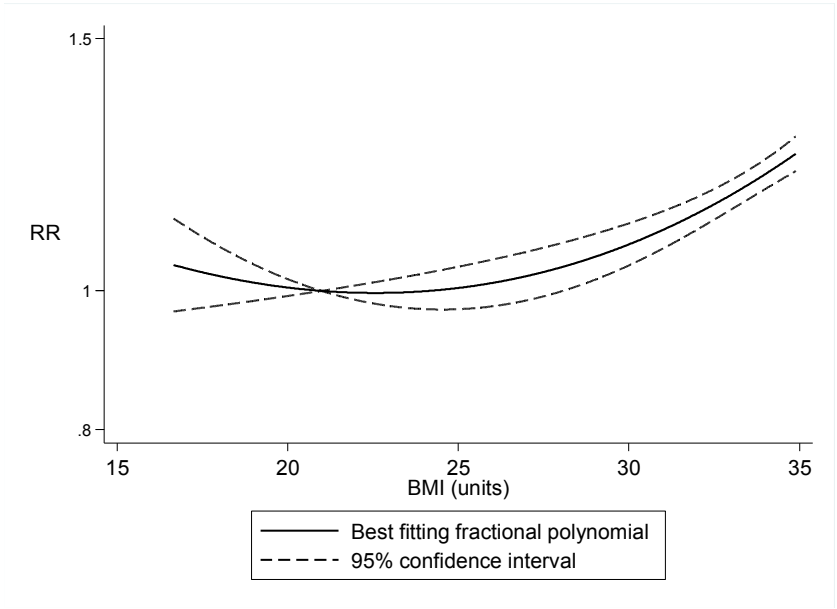
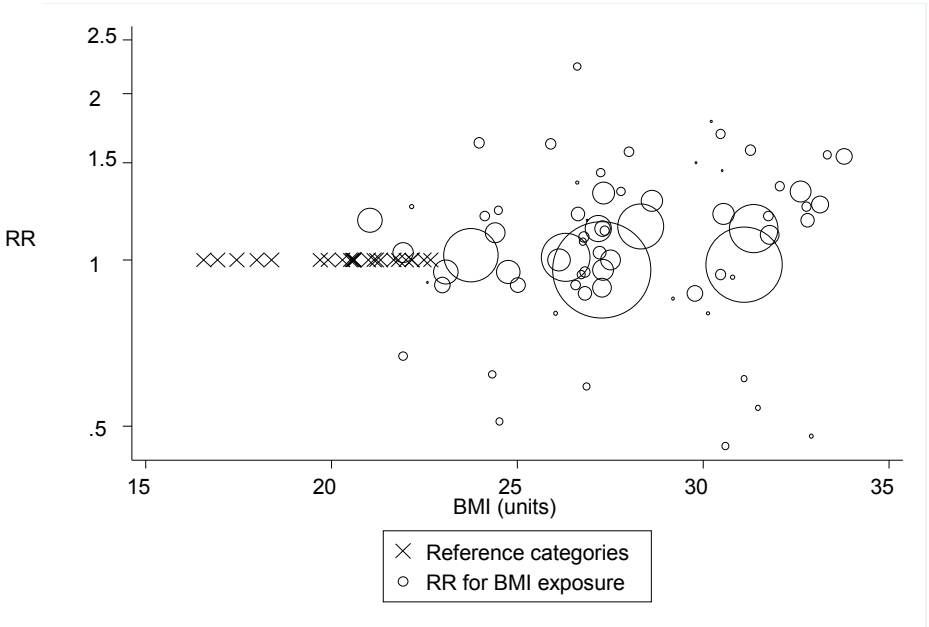


Table 193 Non-linear relative risks of BMI and ovarian cancer

BMI (kg/m2)	Estimated RR (95% CI)
21	1.00
22.5	1.00 (0.98-1.01)
25	1.00 (0.97-1.04)
27.5	1.03 (0.99-1.07)
30	1.08 (1.04-1.11)
32.5	1.15 (1.12-1.18)
35	1.25 (1.22-1.29)

Figure 188 Scatter plot of relative risks of ovarian cancer for BMI categories



8.1.3 Weight

Methods

A total of 5 cohort studies have been published on weight and ovarian cancer risk up to 2012, three of which were identified in the CUP. Dose-response analyses were conducted per 5 kg.

Main results

The summary RR per 5 kg of weight was 1.05 (95% CI: 1.02-1.07, I^2=0%, $p_{heterogeneity}$=0.55).

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.55.

Published pooled analysis

A pooled analysis of 47 studies (17 of which were prospective studies) with 25157 cases and 81311 controls studies reported a pooled RR of 1.18 (95% CI: 1.10-1.26) for a body weight ≥80 versus <60 kg (mean: 90.3 versus 54.1) (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). Because this pooled analysis did not present results for weight only for cohort studies, but for cohort and population-based case-control studies we have not conducted further analyses adding the non-overlapping studies from the CUP analysis.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating body fatness to ovarian cancer was limited and no conclusion was possible.

Table 194 Studies on weight identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Brändstedt, 2011	Sweden	Malmo Diet and Cancer Cohort	93	13.1 years	0.96	0.57	1.59	≥71 vs. <62 kg
Lahmann, 2009	10 European Countries	European Prospective Investigation into Cancer and Nutrition	611	8.9 years	1.27 1.05	1.00 1.01	1.61 1.08	>72.6 vs. <58.1 kg Per 5 kg
Lacey, 2006	USA	Breast Cancer Detection Demonstration Project Follow-Up Study	346	14.5 years	1.09 1.01	0.77 0.98	1.55 1.03	≥161 vs. ≤120 lbs Per 5 lbs

Table 195 Overall evidence on weight and ovarian cancer

SLR	Summary of evidence
2005 SLR	Two cohort studies reported on weight and ovarian cancer. Both studies showed non-significant positive associations between weight and ovarian cancer risk.
Continuous Update Project	Three additional studies reported on weight and ovarian cancer risk, with the largest study showing a significant increase in risk and the two remaining studies showing no association.

Table 196 Summary of results of the dose-response meta-analysis of weight and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1129
RR (95% CI)	-	1.05 (1.02-1.07)
Quantity	-	Per 5 kg
Heterogeneity (I^2, p-value)	-	0%, p=0.55

*No meta-analysis was conducted in the 2nd report

Table 197 Inclusion/exclusion table for meta-analysis of weight and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11644	Brändstedt	2011	Prospective cohort study	Malmo Diet and Cancer Cohort study	Incidence	No	No	No		Overlap with Lahmann et al OVA11636
OVA11636	Lahmann	2009	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA11649	Lacey	2006	Prospective cohort study	Breast cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Midpoints	
OVA04756	Schouten	2003	Prospective cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Midpoints	
OVA02953	Lapidus	1987	Prospective cohort study	Gothenburg	Incidence	Yes	No	No		No risk estimate reported

Figure 189 Highest versus lowest forest plot of weight and ovarian cancer

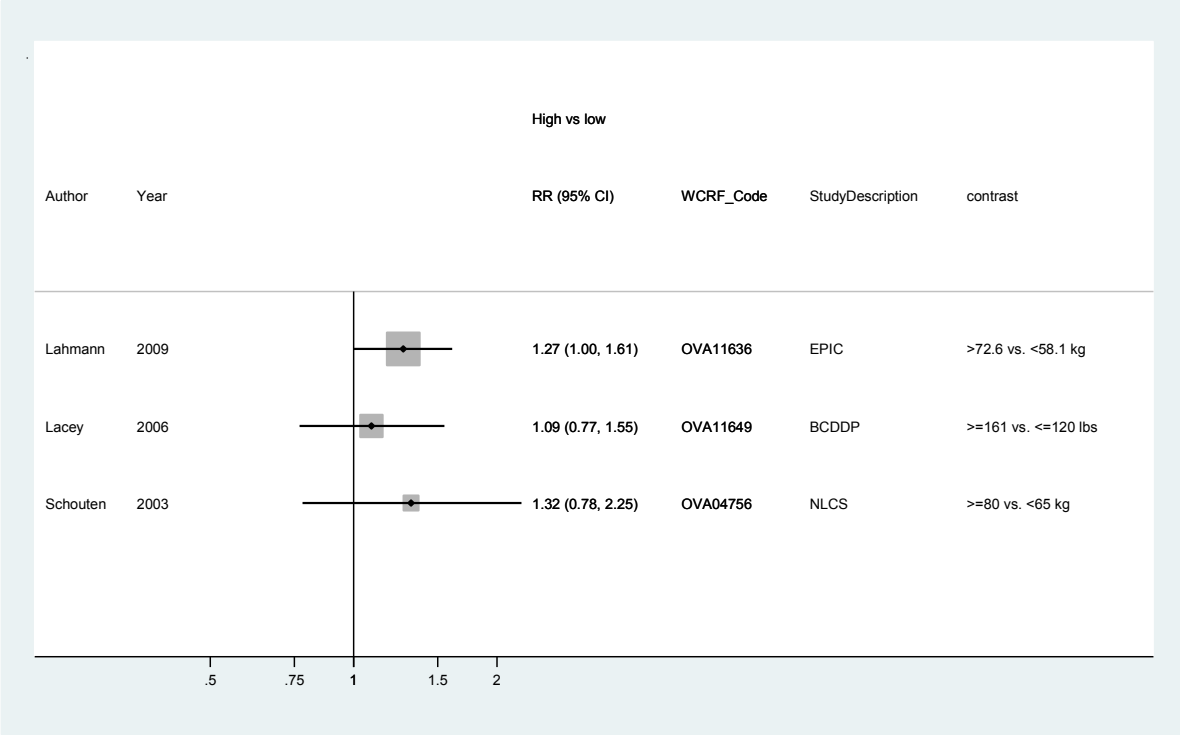
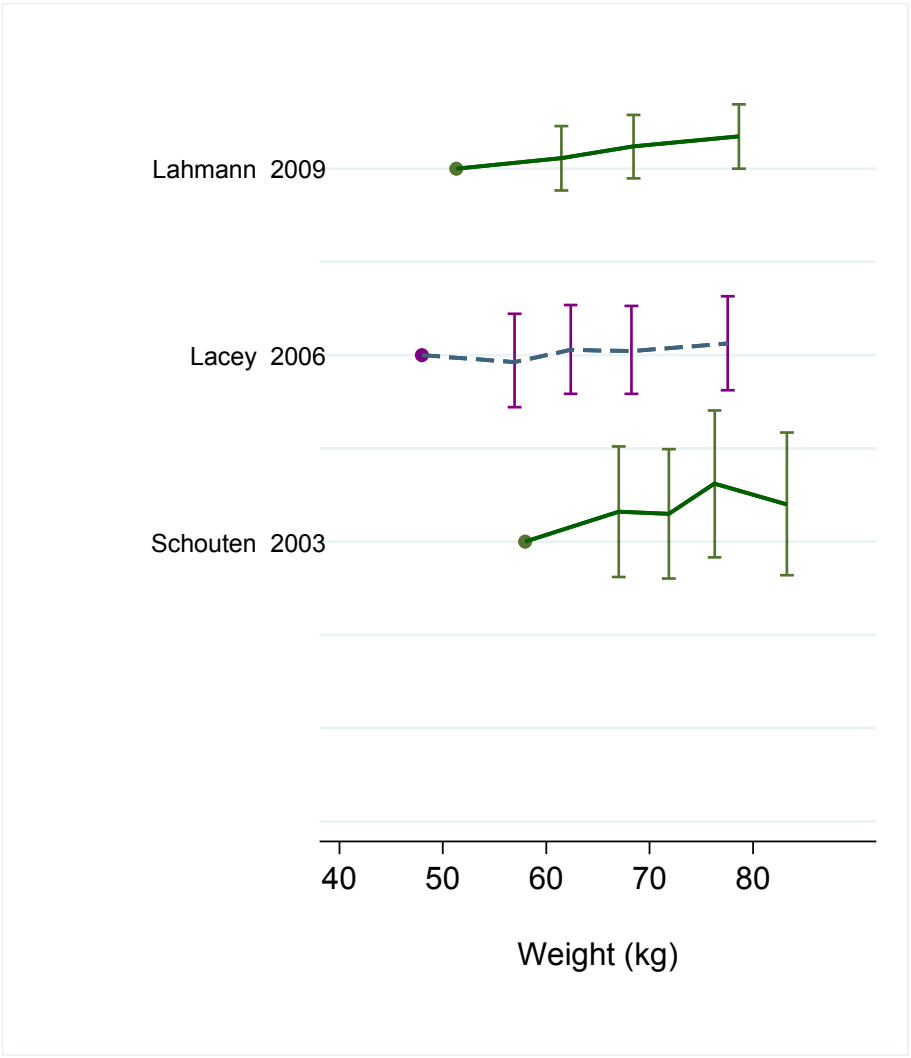


Figure 190 Dose-response meta-analysis of weight and ovarian cancer, per 5kg

Figure 191 Dose-response graph of weight and ovarian cancer, per 5 kg



8.2.1 Waist circumference

Methods

A total of 6 cohort studies (6 publications) have been published on waist circumference and ovarian cancer risk up to 2012, of which 6 studies were identified in the CUP. One publication (Kotsopoulos et al, 2010) contained results from two studies (NHS1 and NHS2). Dose-response analyses were conducted per 10 cm.

Main results

The summary RR per 10 cm of waist circumference was 1.03 (95% CI: 0.97-1.10, I^2=0%, $p_{heterogeneity}$=0.69).

Heterogeneity

There was no heterogeneity, I^2=0.0%, $p_{heterogeneity}$=0.69.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating abdominal fatness (including waist circumference) to ovarian cancer risk was considered limited and no conclusion was possible.

Table 198 Studies on waist circumference identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Brändstedt, 2011	Sweden	Malmo Diet and Cancer Cohort	93	13.1 years	0.67	0.40	1.11	≥80 vs. <72 cm
Chionh, 2010	Australia	Melbourne Collaborative Cohort Study	113	10.2 years	0.96 1.03	0.54 0.87	1.69 1.23	≥87 vs. <71.2 cm Per 10 cm
Canchola, 2010	USA	California Teachers Study	277	12.1 years	1.8 1.00 1.09	1.1 0.44 0.51	3.0 2.28 2.33	≥35 vs. <35 inches, never used HT ≥35 vs. <35 inches, HT ≤5 years* ≥35 vs. <35 inches, HT >5 years*
Kotsopoulos, 2010	USA	Nurses' Health Study I	273	20 years	0.99	0.59	1.64	≥35 vs. <28 inches
Kotsopoulos, 2010	USA	Nurses' Health Study II	52	12 years	1.12	0.35	3.57	≥35 vs. <28 inches
Lahmann, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	611	8.9 years	1.12 1.02	0.86 0.98	1.45 1.06	>87.0 vs. <71.7 cm Per 5 cm

*The original publication presented results with the joint effect of waist circumference and HT use. These results have been recalculated using the Hamling method (Hamling et al, 2008) so that there is a reference category within each stratum of HT use.

Table 199 Overall evidence on waist circumference and ovarian cancer

SLR	Summary of evidence
2005 SLR	One study reported a positive correlation between waist circumference and ovarian cancer.
Continuous Update Project	Six cohort studies reported on waist circumference and ovarian cancer. Only one of these studies found a significant association which was restricted to a subgroup of non-users of HT.

Table 200 Summary of results of the dose-response meta-analysis of waist circumference and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1049
RR (95% CI)	-	1.03 (0.97-1.10)
Quantity	-	Per 10 cm
Heterogeneity (I^2, p-value)	-	0%, p=0.69

*No meta-analysis was conducted in the 2nd report

Table 201 Inclusion/exclusion table for meta-analysis of waist circumference and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11644	Brändstedt	2011	Prospective cohort study	Malmo Diet and Cancer Cohort study	Incidence	No	No	No		Overlap with Lahmann et al OVA11636
OVA11629	Chionh	2010	Prospective cohort study	Melbourne Collaborative Cohort Study	Incidence	No	Yes	Yes	Midpoints	
OVA11627	Canchola	2010	Prospective cohort study	California Teachers Study	Incidence	No	No	Yes		Only two categories of exposure
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 1	Incidence	No	Yes	Yes		
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 2	Incidence	No	Yes	Yes		
OVA11636	Lahmann	2009	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA02953	Lapidus	1988	Prospective cohort study	Gothenburg	Incidence	Yes	No	No		No risk estimate reported

Figure 192 Highest versus lowest forest plot of waist circumference and ovarian cancer

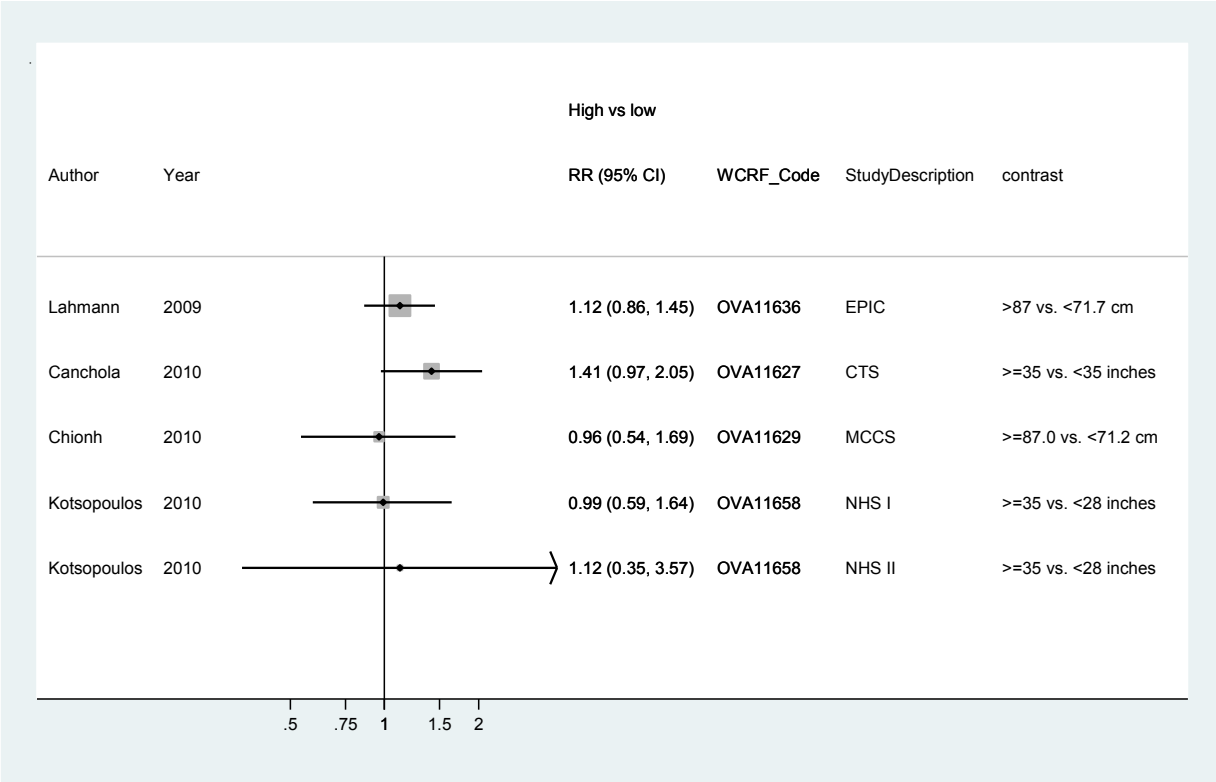


Figure 193 Dose-response meta-analysis of waist circumference and ovarian cancer, per 10 cm

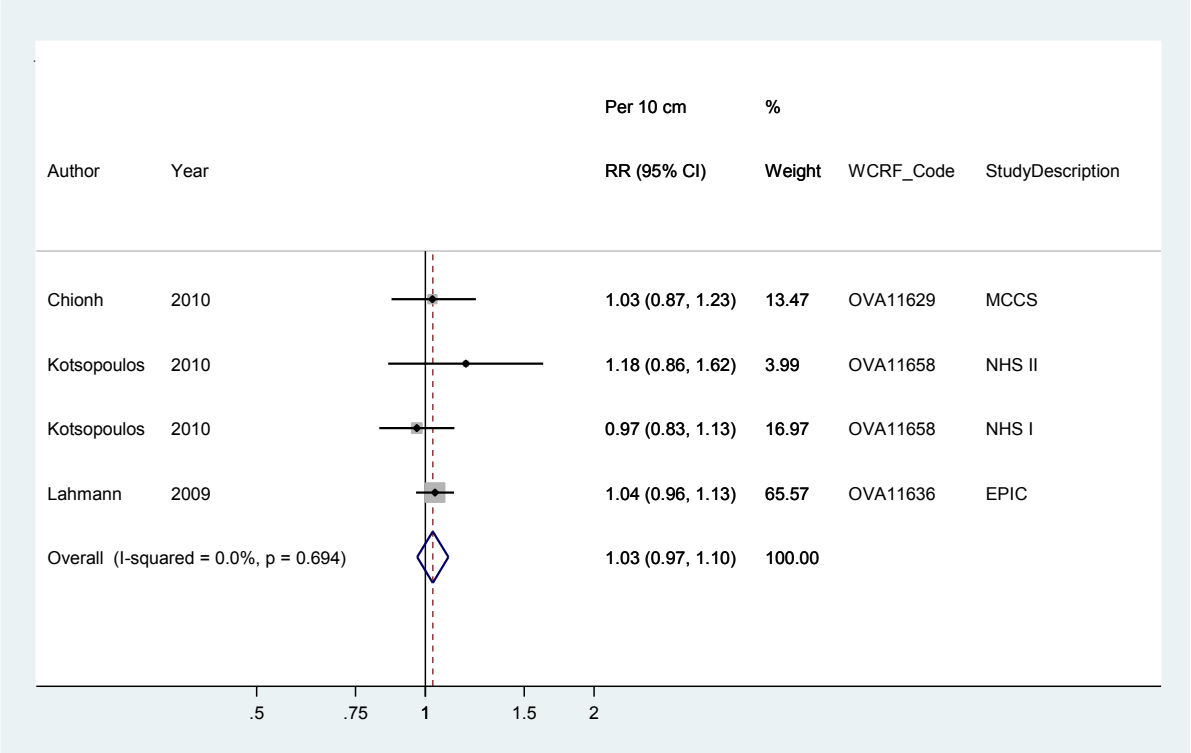
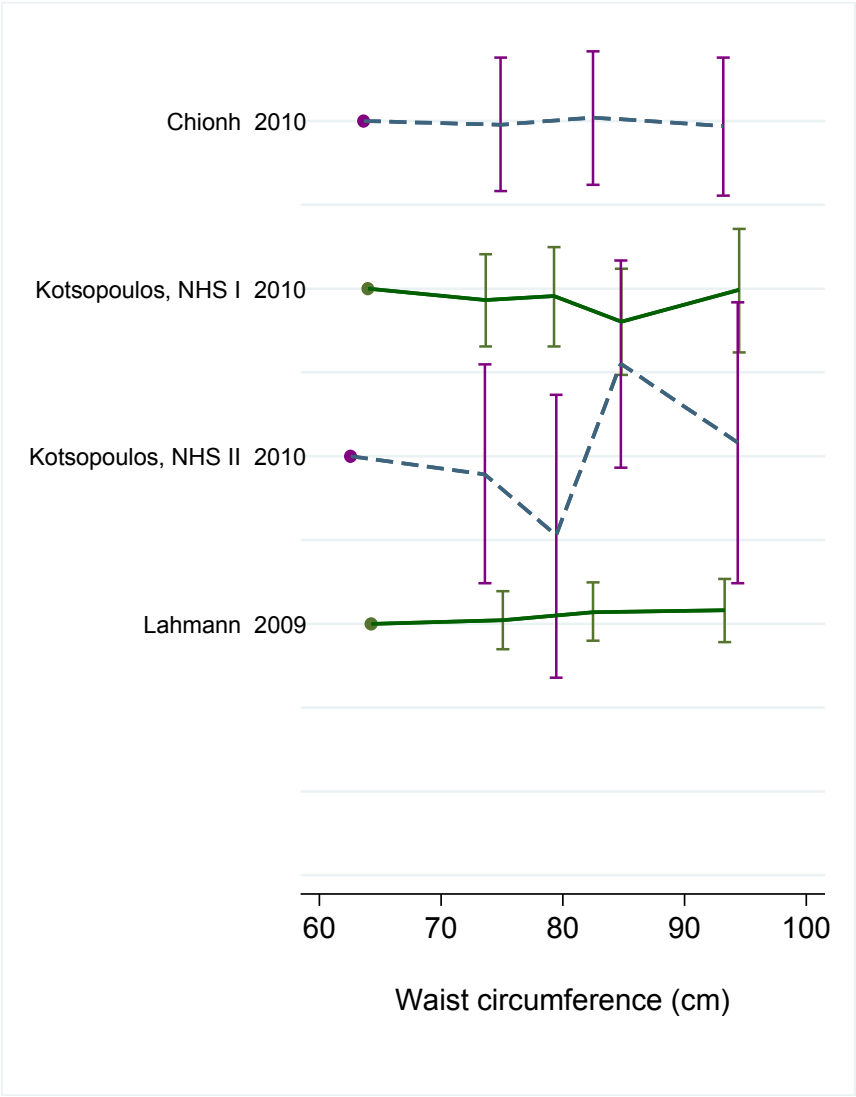


Figure 194 Dose-response graph of waist circumference and ovarian cancer



8.2.2 Hip circumference

Methods

A total of 4 cohort studies (4 publications) have been published on hip circumference and ovarian cancer risk up to 2012. Three of these studies were identified in the CUP. One publication (Kotsopoulos et al, 2010) contained results from two studies (NHSI and NHSII). Dose-response analyses were conducted per 10 cm.

Main results

The summary RR per 10 cm of hip circumference was 1.01 (95% CI: 0.75-1.36, I^2=81.1%, $p_{heterogeneity}$=0.005).

Heterogeneity

There was high heterogeneity, I^2=81.1%, $p_{heterogeneity}$=0.005.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was no judgement of the association between hip circumference and ovarian because there was only one study published.

Table 202 Studies on hip circumference identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Brändstedt, 2011	Sweden	Malmo Diet and Cancer Cohort	93	13.1 years	0.77	0.45	1.29	≥101 vs. <93 cm
Kotsopoulos, 2010	USA	Nurses' Health Study I	273	20 years	0.67	0.39	1.17	43-65 vs. <37 inches
Kotsopoulos, 2010	USA	Nurses' Health Study II	52	12 years	1.12	0.35	3.57	43-65 vs. <37 inches
Lahmann, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	611	8.9 years	1.33 1.06	1.04 1.01	1.70 1.10	>106.0 vs <94.7 cm Per 5 cm

Table 203 Overall evidence on hip circumference and ovarian cancer

SLR	Summary of evidence
2005 SLR	One study reported a non-significant positive correlation between hip circumference and ovarian cancer.
Continuous Update Project	Three cohort studies reported on hip circumference and ovarian cancer. The largest of these studies found a positive association.

Table 204 Summary of results of the dose-response meta-analysis of hip circumference and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	936
RR (95% CI)	-	1.01 (0.75-1.36)
Quantity	-	Per 10 cm
Heterogeneity (I^2, p-value)	-	81.1%, p=0.005

*No meta-analysis was conducted in the 2nd report

Table 205 Inclusion/exclusion table for meta-analysis of hip circumference and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11644	Brändstedt	2011	Prospective cohort study	Malmo Diet and Cancer Cohort study	Incidence	No	No	No		Overlap with Lahmann et al OVA11636
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 1	Incidence	No	Yes	Yes		
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 2	Incidence	No	Yes	Yes		
OVA11636	Lahmann	2009	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA02953	Lapidus	1988	Prospective cohort study	Gothenburg	Incidence	Yes	No	No		No risk estimate reported

Figure 195 Highest versus lowest forest plot of hip circumference and ovarian cancer

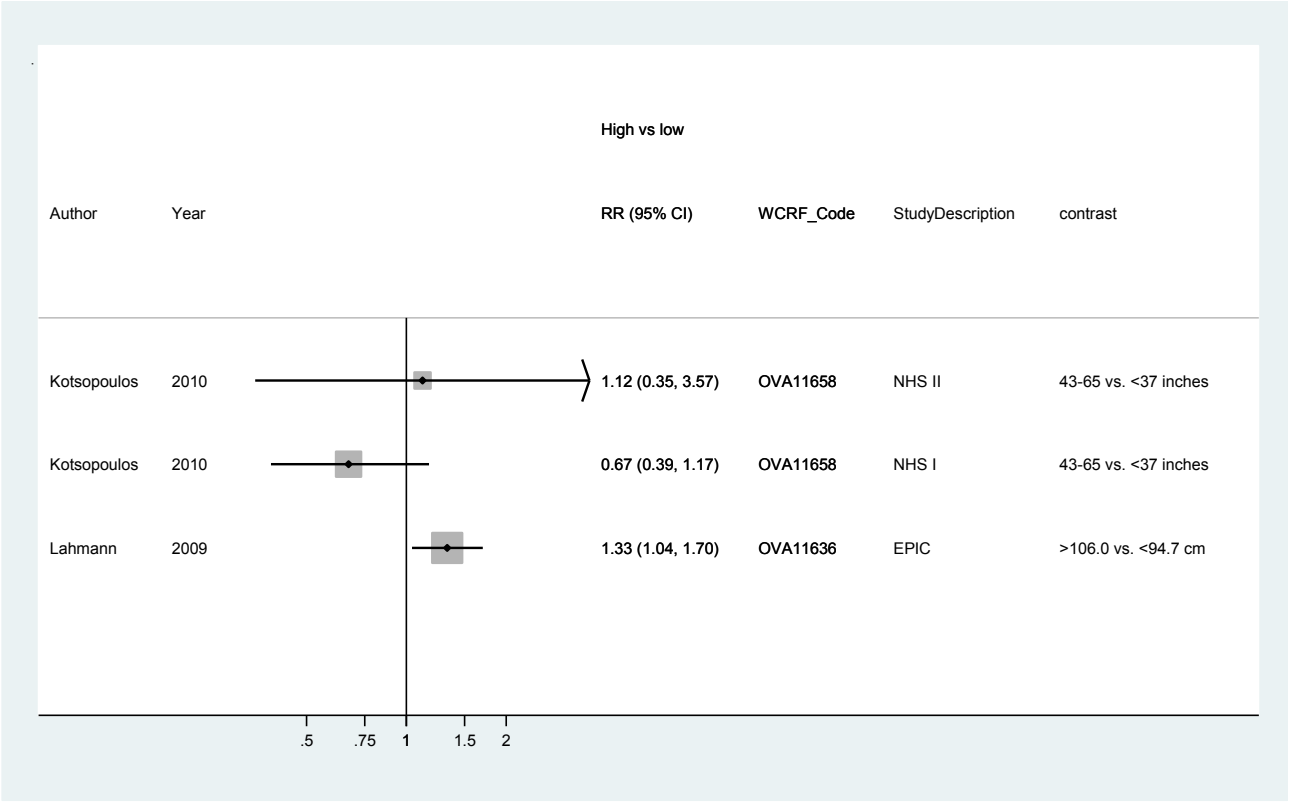


Figure 196 Dose-response meta-analysis of hip circumference and ovarian cancer, per 10 cm

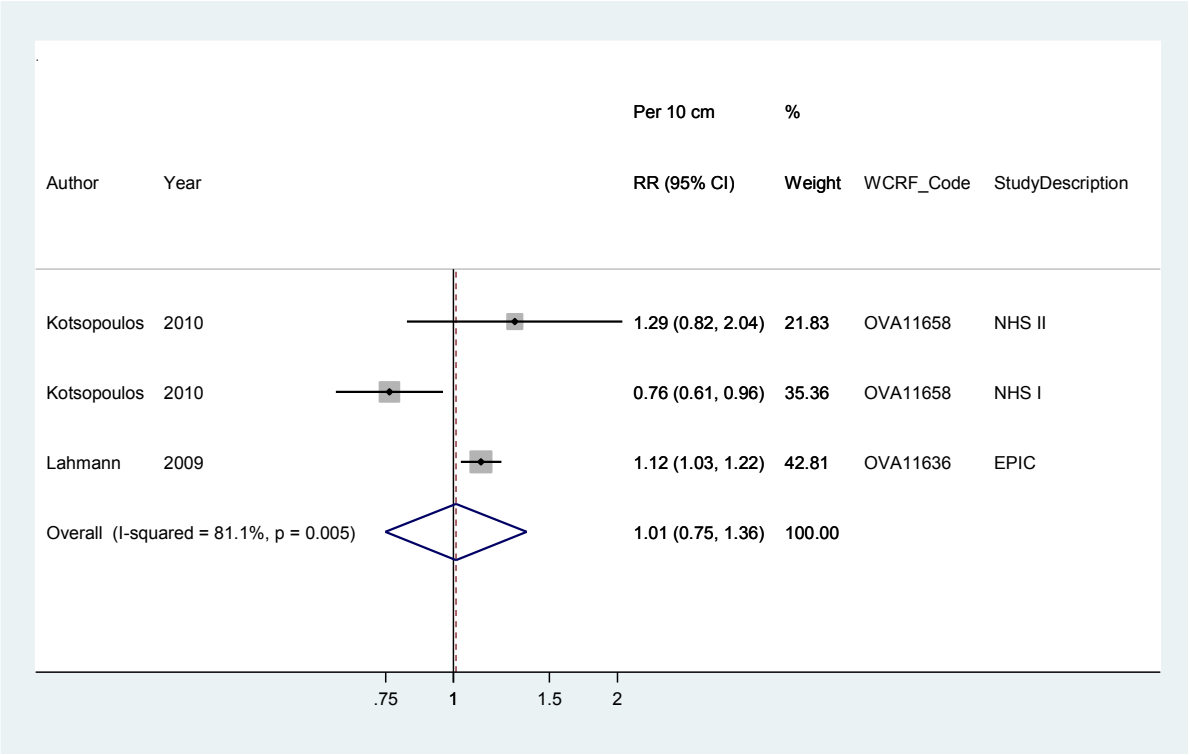
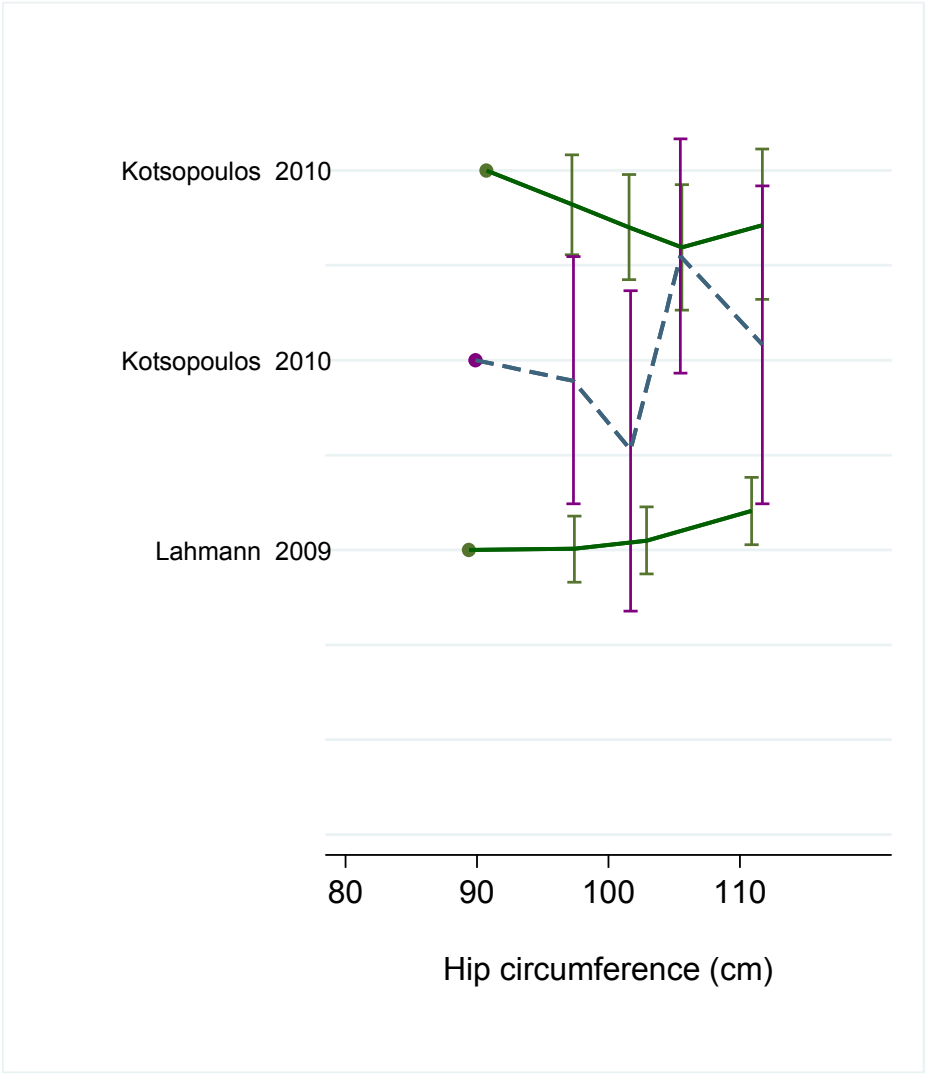


Figure 197 Dose-response graph of hip circumference and ovarian cancer



8.2.3 Waist-to-hip ratio

Methods

A total of 7 cohort studies (8 publications) have been published on waist-to-hip ratio and ovarian cancer risk up to 2012, five studies (4 publications) of which were identified in the CUP. One publication (Kotsopoulos et al, 2010) contained results from two studies (NHS1 and NHS2). Dose-response analyses were conducted per 0.1 units.

Main results

The summary RR per 0.1 waist-to-hip ratio units was 0.99 (95% CI: 0.92-1.06, I^2=0%, $p_{heterogeneity}$=0.45).

Heterogeneity

There was no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.45.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating abdominal fatness (including waist-to-hip ratio) to ovarian cancer risk was considered limited and no conclusion was possible.

Table 206 Studies on waist-to-hip ratio identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Brändstedt, 2011	Sweden	Malmo Diet and Cancer Cohort	93	13.1 years	0.60	0.36	1.00	≥0.81 vs. <0.77 units
Canchola, 2010	USA	California Teachers Study	277	12.1 years	0.95 0.79 1.06	0.56 0.36 0.48	1.60 1.68 2.33	≥0.80 vs. <0.80 units, never used HT ≥0.80 vs. <0.80 units, used HT ≤5 years ≥0.80 vs. <0.80 units, used HT >5 years
Kotsopoulos, 2010	USA	Nurses' Health Study I	273	20 years	0.78	0.52	1.16	≥0.84 vs. <0.73 units
Kotsopoulos, 2010	USA	Nurses' Health Study II	52	12 years	1.08	0.46	2.56	≥0.84 vs. <0.73 units
Lahmann, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	611	8.9 years	0.91 0.98	0.72 0.92	1.17 1.05	>0.83 vs. <0.74 units Per 0.05 units

*The original publication presented results with the joint effect of waist-to-hip ratio and HT use. These results have been recalculated using the Hamling method (Hamling et al, 2008) so that there is a reference category within each stratum of HT use.

Table 207 Overall evidence on waist-to-hip ratio and ovarian cancer

SLR	Summary of evidence
2005 SLR	One study reported a positive correlation between waist-to-hip ratio and ovarian cancer.
Continuous Update Project	Seven cohort studies reported on waist-to-hip ratio and ovarian cancer. None of these studies found a significant association.

Table 208 Summary of results of the dose-response meta-analysis of waist-to-hip ratio and ovarian cancer

Ovarian cancer		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1166
RR (95% CI)	-	0.99 (0.92-1.06)
Quantity	-	Per 10 cm
Heterogeneity (I^2, p-value)	-	0%, p=0.45

*No meta-analysis was conducted in the 2nd report

Table 209 Inclusion/exclusion table for meta-analysis of waist-to-hip ratio and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11644	Brändstedt	2011	Prospective cohort study	Malmo Diet and Cancer Cohort study	Incidence	No	No	No		Overlap with Lahmann et al OVA11636
OVA11627	Canchola	2010	Prospective cohort study	California Teachers Study	Incidence	No	No	Yes		Only two categories of exposure
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 1	Incidence	No	Yes	Yes	Midpoints	
OVA11658	Kotsopoulos	2010	Prospective cohort study	Nurses' Health Study 2	Incidence	No	Yes	Yes	Midpoints	
OVA11636	Lahmann	2009	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA09688	Andersson	2004	Prospective cohort study	Iowa Women's Health Initiative	Incidence	Yes	Yes	Yes		
OVA03222	Lukanova	2002	Nested case-control study	New York University Women's Health Study & the ORDET Study	Incidence	Yes	No	Yes		Exposure level not available
OVA03556	Mink	1996	Prospective cohort study	Iowa Women's Health Initiative	Incidence	Yes	No	No		Overlap with Andersson et al, 2004, OVA09688
OVA02953	Lapidus	1988	Prospective cohort study	Gothenburg	Incidence	Yes	No	No		No risk estimate reported

Figure 198 Highest versus lowest forest plot of waist-to-hip ratio and ovarian cancer

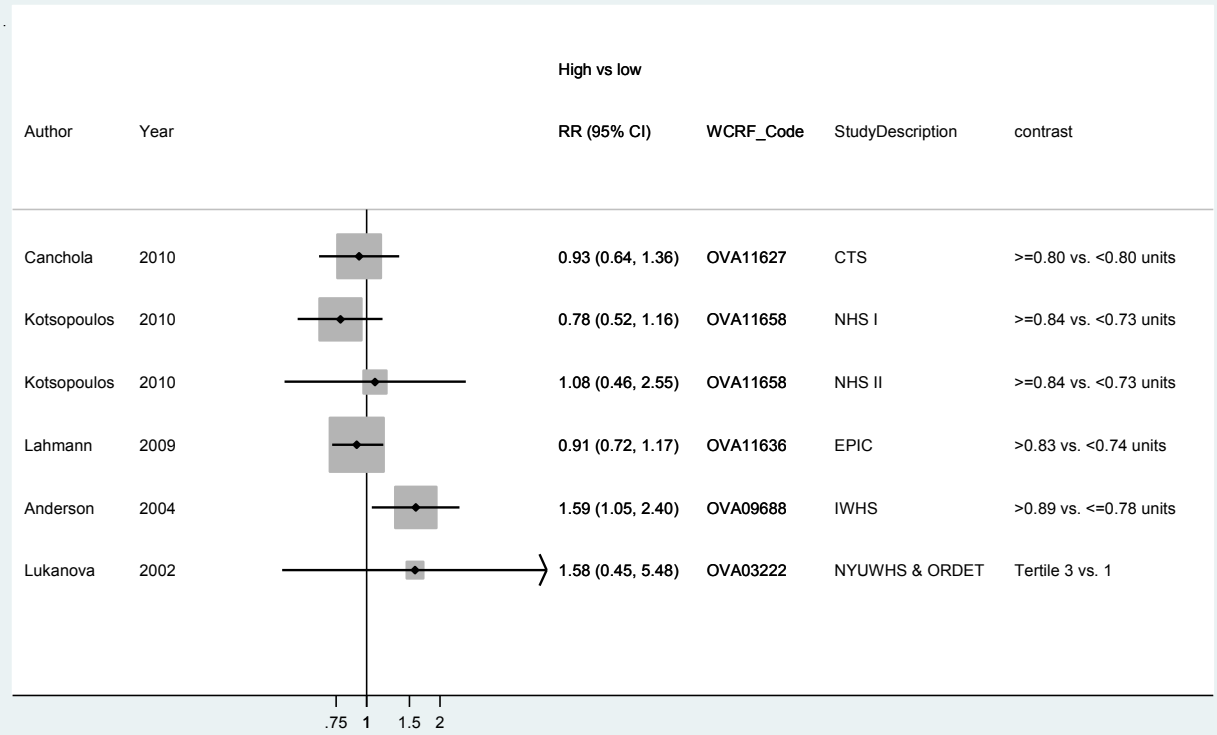


Figure 199 Dose-response meta-analysis of waist-to-hip ratio and ovarian cancer, per 0.1 units

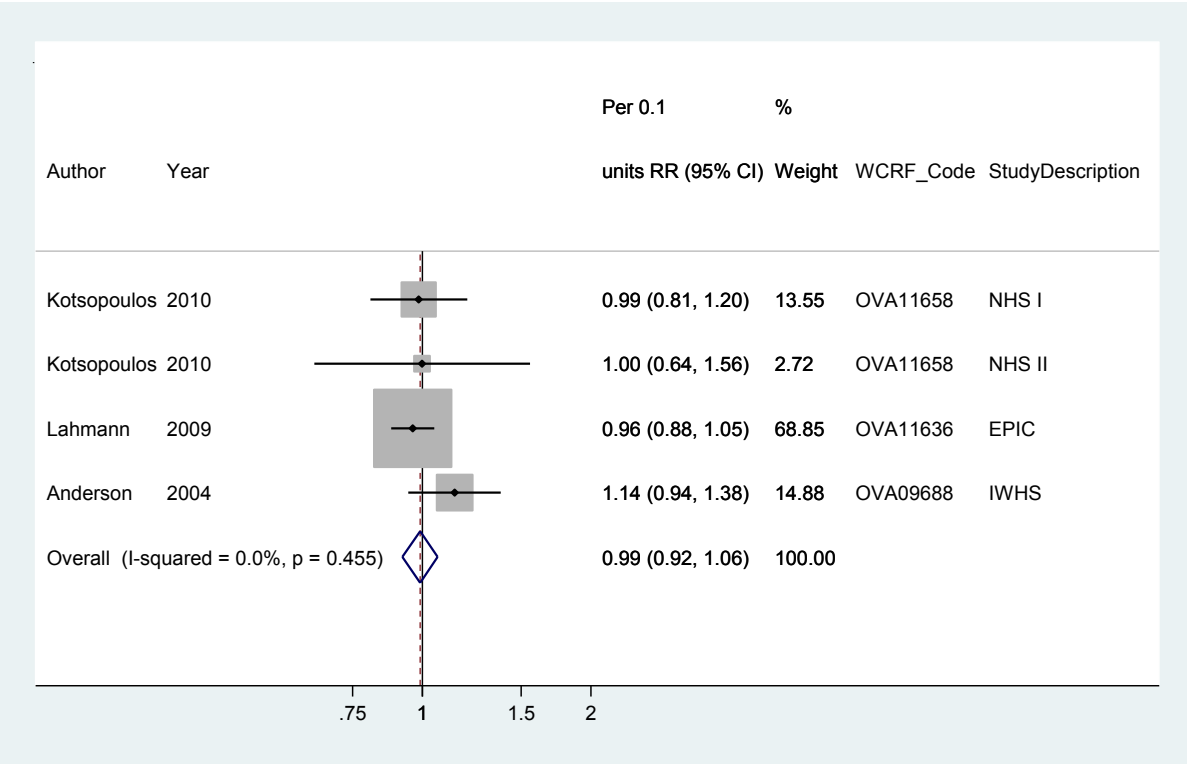
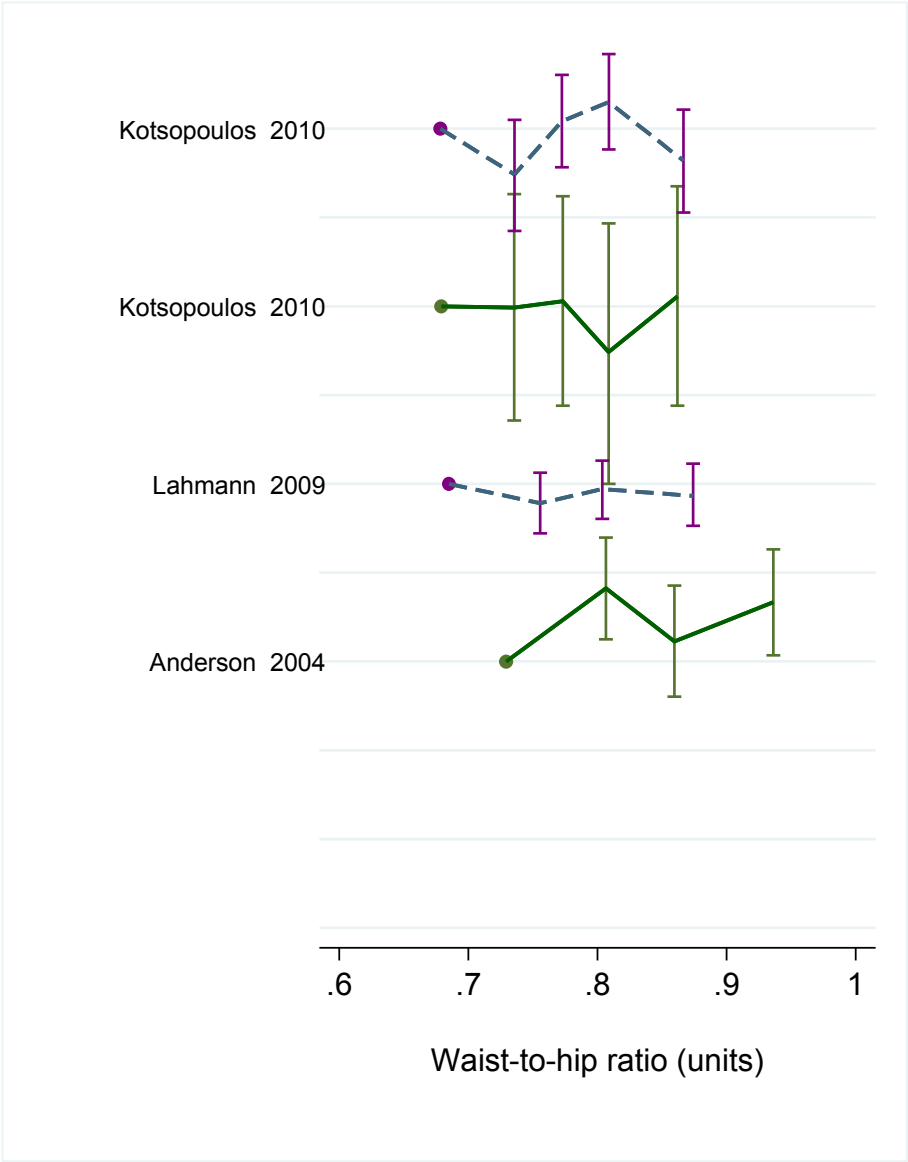


Figure 200 Dose-response graph of waist-to-hip ratio and ovarian cancer



8.3.1 Height

Methods

A total of 18 cohort studies (17 publications) have been published on adult attained height and ovarian cancer risk up to 2012, ten (11 publications) of which were identified in the CUP. Two publications contained results from two studies (Baer et al, 2008 and Lundqvist et al, 2007) and another study contained results from three studies (Lukanova, 2002). Dose-response analyses were conducted per 5 cm. For studies that did not use the lowest category as the reference (Engeland, 2003 and Rodriguez 2002), we transformed the RRs so that the category with the lowest exposure was the reference category using the method by Hamling et al, 2008.

A potential non-linear dose-response meta-analysis was explored using fractional polynomial models (Royston, 2000).

Main results

The summary RR per 5 cm of height was 1.08 (95% CI: 1.05-1.10, I^2=34.8%, $p_{heterogeneity}$=0.10). There was no evidence of publication bias with Egger's test, p=0.29. The non-linear model showed a linear-dose response in most of the exposure range, p=0.09.

Heterogeneity

There was moderate heterogeneity, I^2=34.8%, $p_{heterogeneity}$=0.10.

Published pooled analysis

A pooled analysis of 47 studies with 25157 cases and 81311 controls (17 of which were prospective studies) studies reported a pooled RR of 1.07 (95% CI: 1.05-1.09) per 5 cm increase in height (excluding results from 6 hospital-based case-control studies) (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012). Restricting the analysis to the 17 prospective studies (10858 cases and 44731 controls) showed a pooled RR of 1.08 (95% CI: 1.06-1.10) per 5 cm increase in height. In categorical analyses the pooled RR was 1.27 (95% CI: 1.20-1.35) for a height of ≥170 cm compared with <160 cm (mean: 172.7 vs. 154.8 cm).

A pooled analysis including 1428 ovarian cancer deaths reported a pooled RR of 1.07 (95% CI: 1.01-1.13) for each 6.5 cm increase in height (The Emerging Risk Factors Collaboration, 2012).

A pooled analysis of 12 prospective studies found a pooled RR of 1.38 (95% CI: 1.16-1.65) for a height of ≥170 cm compared with <160 cm and a RR of 1.10 (95% CI: 1.05-1.15) for each 5 cm increase in height (Schouten et al, 2008). When we added the results from the non-overlapping studies in the CUP analysis to the results of the pooled analysis the summary RR per 5 cm increase in height was 1.08 (95% CI: 1.06-1.11).

Table 210 Table of results of new studies

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Weiderpass, 2012	Japan	Japan Public Health Center-based Prospective Study	86	16 years	1.03	0.68	1.55	Per 10 cm
Green, 2011	United Kingdom	Million Women's Study	4830	9.4 years	1.17	1.09	1.25	Per 10 cm
Brändstedt, 2011	Sweden	Malmo Diet and Cancer Cohort	93	13.1 years	1.15	0.69	1.91	≥166 vs. <160 cm
Chionh, 2010	Australia	Melbourne Collaborative Cohort Study	113	10.2 years	1.13 0.97	0.82 0.54	1.55 1.76	Per 10 cm ≥164.3 vs. <155.2 cm
Lahmann, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	611	8.9 years	1.12 1.05	0.87 0.98	1.45 1.12	>166.2 vs. <157.0 cm Per 5 cm
Sung, 2009	Korea	Korean Cancer Prevention Study	398	8.72 years	1.68 1.24	1.14 1.08	2.48 1.41	>158 vs. <151.1 cm Per 5 cm
Song, 2008	Korea	Korean Cancer Prevention Study	143 deaths	9.86 years	2.73 1.29	1.31 1.09	5.70 1.53	≥161 vs. <149 cm Per 5 cm
Baer, 2008	USA	Nurses' Health Study 1	735	28 years	1.27	0.88	1.82	≥1.75 vs. <1.6 m
Baer, 2008	USA	Nurses' Health Study 2	137	16 years	2.35	1.19	4.63	≥1.75 vs. <1.6 m
Lundqvist, 2007	Sweden	Swedish and Finnish Twin Cohort Studies	268	26.3 years	1.7	0.8	3.5	Quartile 4 vs. 1
Lacey, 2006	USA	Breast Cancer Detection Demonstration Project Follow-Up Study	346	14.5 years	0.90 1.00	0.64 0.95	1.26 1.04	≥66 vs. <62 inches Per 1 inch

Table 211 Table of overall evidence

SLR	Summary of evidence
2005 SLR	Six cohort studies reported on height and ovarian cancer.
Continuous Update Project	Ten additional cohort studies reported on height and ovarian cancer, of which three found statistically significant positive associations and the remaining studies were null.

Table 212 Summary of results of the dose-response meta-analysis of height and ovarian cancer in the 2nd Report and in the Continuous Update Project.

Ovarian cancer		
	SLR	Continuous Update Project
Studies (n)	3	14*
Cases (n)	8277	17312
RR (95% CI)	1.15 (1.08-1.21)	1.08 (1.05-1.10)
Quantity	Per 10 cm	Per 5 cm
Heterogeneity (I^2, p-value)	32.5%, p=not available	34.8%, p=0.10

* One study reported a risk estimate for two studies combined (Lundqvist et al, 2007). Thirteen risk estimates are included in the analysis.

Table 213 Inclusion/exclusion table of height and ovarian cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
OVA11669	Weiderpass	2012	Prospective cohort study	Japan Public Health-Center Based Prospective Study	Incidence	No	Yes	No		Only continuous result
OVA11677	Green	2011	Prospective cohort study	Million Women's Study	Incidence	No	Yes	No		Only continuous result
OVA11644	Brändstedt	2011	Prospective cohort study	Malmo Diet and Cancer Cohort study	Incidence	No	No	No		Overlap with Lahmann et al 2009
OVA11629	Chionh	2010	Prospective cohort study	Melbourne Collaborative Cohort Study	Incidence	No	Yes	Yes	Midpoints	
OVA11636	Lahmann	2009	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA11687	Sung	2009	Prospective cohort study	Korean Cancer Prevention Study	Incidence	No	Yes	Yes	Midpoints	
OVA11688	Song	2008	Prospective cohort study	Korean Cancer Prevention Study	Mortality	No	No	No		Overlap with Sung et al, 2009
OVA11632	Baer	2008	Prospective cohort study	Nurses' Health Study I	Incidence	No	Yes	Yes	Midpoints	
OVA11632	Baer	2008	Prospective cohort study	Nurses' Health Study II	Incidence	No	Yes	Yes	Midpoints	
OVA11656	Lundqvist	2007	Prospective cohort study	Sweden, Finland Co-twin study	Incidence	No	Yes	Yes	Midpoints, distribution of person-years	
OVA11649	Lacey	2006	Prospective cohort study	Breast cancer Detection Demonstration Project	Incidence	No	Yes	Yes	Midpoints	
OVA09688	Anderson	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints	

OVA02429	Jonsson	2003	Prospective cohort study	Swedish Twin Cohort	Incidence	No	No	No		Overlap with Lundqvist et al OVA11656
OVA04756	Schouten	2003	Prospective cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Midpoints	
OVA01399	Engeland	2003	Prospective cohort study	Norwegian Tuberculosis Screening Programme	Incidence	Yes	Yes	Yes	Midpoints	
OVA03222	Lukanova	2002	Nested case-control study	New York University Women's Health Study, Northern Sweden Health and Disease Study, ORDET Study	Incidence	Yes	No	No		Results reported in text only, cut-points and results for the overall sample not available, only subgroup below age 55 years
OVA04449	Rodriguez	2002	Prospective cohort study	Cancer Prevention Study II	Mortality	Yes	Yes	Yes	Midpoints	
OVA02953	Lapidus	1987	Prospective cohort study	Gothenburg	Incidence	Yes	No	No		No risk estimate reported

Figure 201 Height and ovarian cancer, cancer, highest vs. lowest

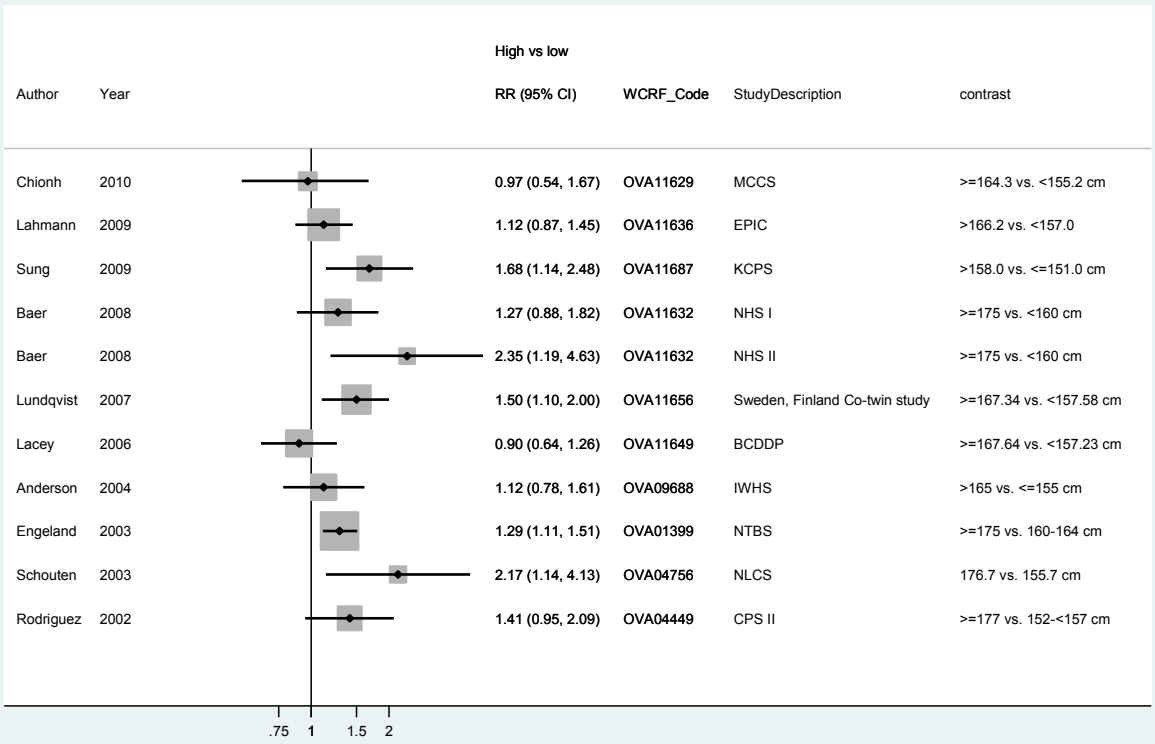


Figure 202 Dose-response meta-analysis of height and ovarian cancer, per 5 cm

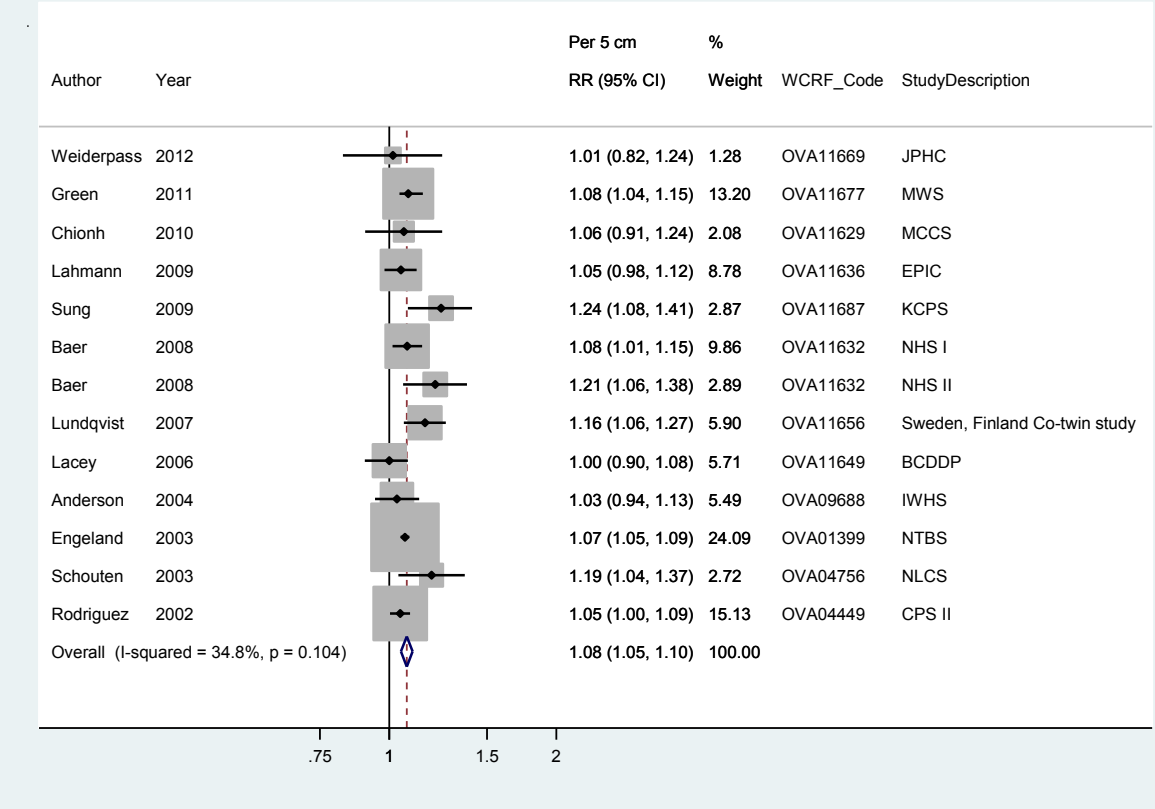


Figure 203 Funnel plot of height and ovarian cancer

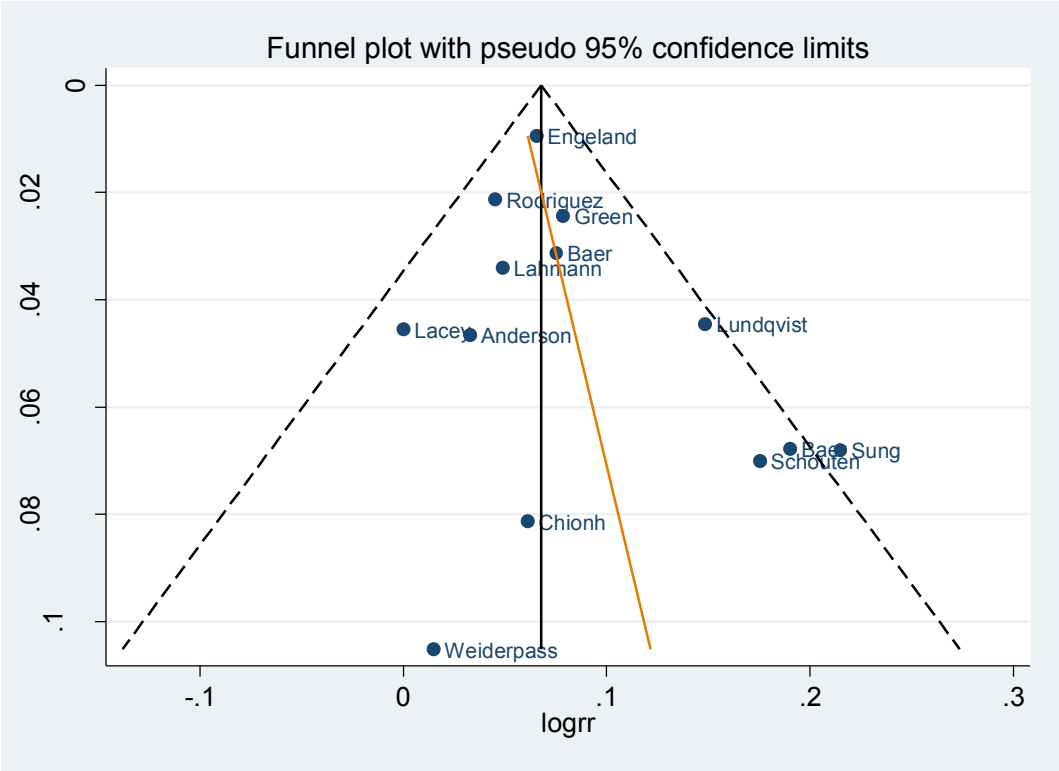


Figure 204 Dose-response graph of height and ovarian cancer

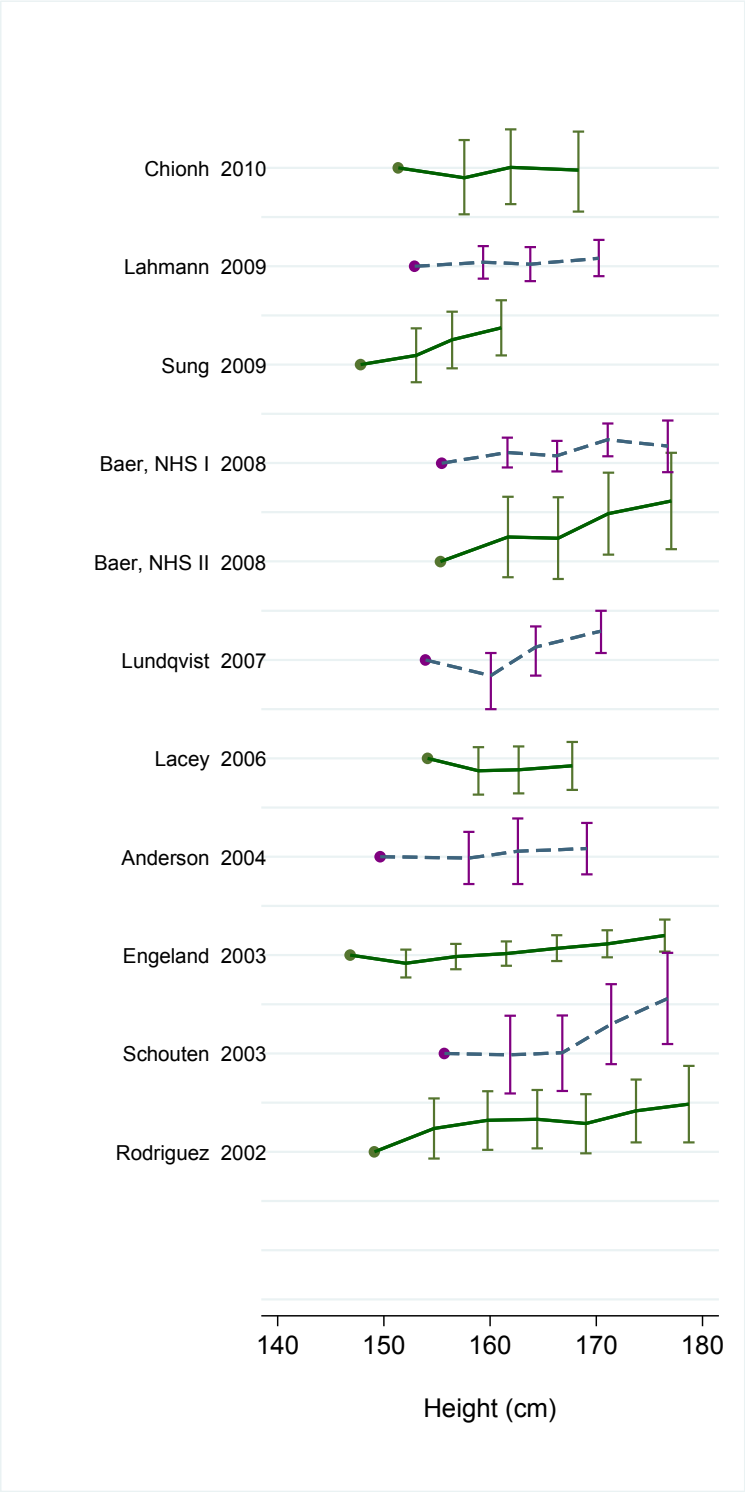


Figure 205 Non-linear dose-response graph of height and ovarian cancer

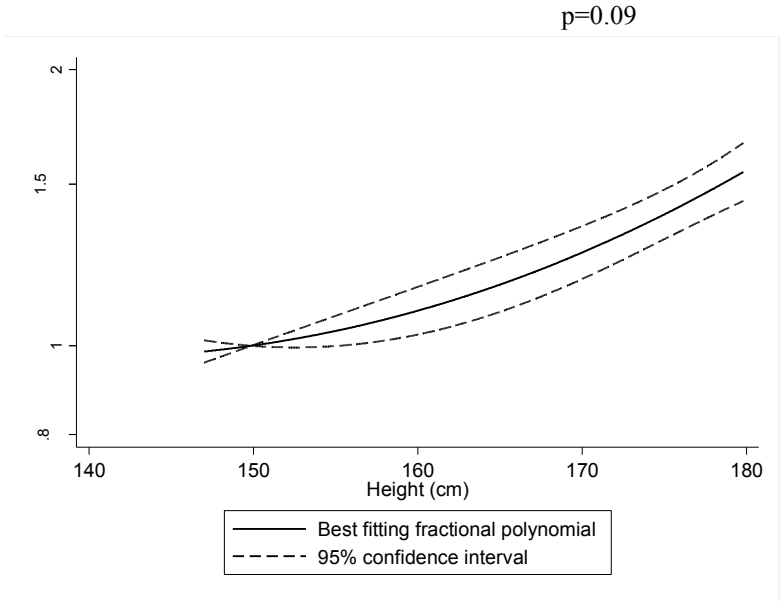
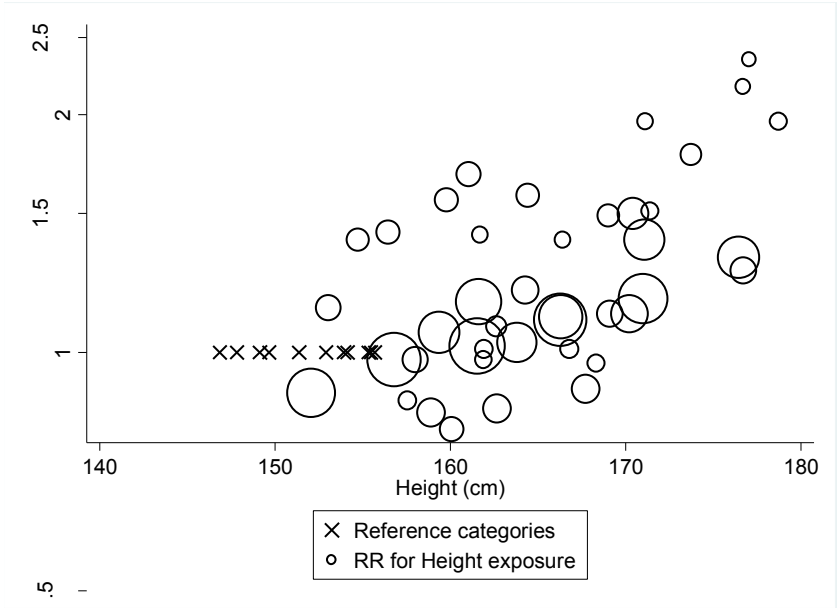


Table 214 Non-linear relative risks of height and ovarian cancer

Height (cm)	RR (95% CI)
150	1.00
155	1.04 (1.00-1.08)
160	1.09 (1.03-1.16)
165	1.17 (1.09-1.25)
170	1.27 (1.18-1.35)
175	1.39 (1.31-1.48)
180	1.56 (1.45-1.68)

Figure 206 Scatter plot of relative risks of ovarian cancer for height categories



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