The Associations between Food, Nutrition and Physical Activity and the Risk of Ovarian Cancer
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<tr>
<td>CUP</td>
<td>Continuous Update Project</td>
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<tr>
<td>WCRF/AICR</td>
<td>World Cancer Research Fund/American Institute for Cancer Research</td>
</tr>
<tr>
<td>SLR</td>
<td>Systematic Literature Review</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>LCI</td>
<td>Lower Limit Confidence Interval</td>
</tr>
<tr>
<td>UCI</td>
<td>Upper Limit Confidence Interval</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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## List of Abbreviations of cohort names

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

<table>
<thead>
<tr>
<th></th>
<th>DECREASES RISK</th>
<th>INCREASES RISK</th>
</tr>
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<tbody>
<tr>
<td><strong>Convincing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td></td>
<td>Adult attained height¹</td>
</tr>
<tr>
<td><strong>Limited — suggestive</strong></td>
<td>Non-starchy vegetables²</td>
<td>Lactation</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Limited — no conclusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Substantial effect on risk unlikely</strong></td>
<td></td>
<td>None identified</td>
</tr>
</tbody>
</table>

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

10,287 potentially relevant publications identified

10,014 papers excluded on the basis of title and abstract (including 486 papers not in English from which 13 papers excluded on the basis of title because no English abstract)

273 papers read and assessed in duplicate for inclusion

195 papers excluded for not fulfilling the inclusion criteria:
9 Commentary, editorial/did not contain original data
1 Conference report
31 Reviews
11 Meta-analyses
11 Pooled analyses
4 Exposure not relevant
42 Out of research topic
30 Studies on cancer patients
56 Case-control studies

2 papers on multiple cancers identified by CUP searches in other cancers

80 publications with inclusion criteria:
6 case cohorts
7 nested case-controls
64 prospective cohorts
1 historical cohort
2 RCTs

10,014 papers excluded on the basis of title and abstract (including 486 papers not in English from which 13 papers excluded on the basis of title because no English abstract)

195 papers excluded for not fulfilling the inclusion criteria:
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1 Conference report
31 Reviews
11 Meta-analyses
11 Pooled analyses
4 Exposure not relevant
42 Out of research topic
30 Studies on cancer patients
56 Case-control studies

2 papers on multiple cancers identified by CUP searches in other cancers

80 publications with inclusion criteria:
6 case cohorts
7 nested case-controls
64 prospective cohorts
1 historical cohort
2 RCTs
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.

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<td>3</td>
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<td>5.1.2.2</td>
<td>Soluble fibre</td>
<td>-</td>
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<tr>
<td>5.1.2.2</td>
<td>Cereal fibre</td>
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<tr>
<td>5.1.2.2</td>
<td>Vegetable fibre</td>
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<tr>
<td>5.1.2.2</td>
<td>Fruit fibre</td>
<td>-</td>
<td>1</td>
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<tr>
<td>5.1.4</td>
<td>Lactose</td>
<td>3</td>
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<td>Sucrose</td>
<td>-</td>
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<td>5.1.4</td>
<td>Mono/disaccharides</td>
<td>-</td>
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<td>5.2.1</td>
<td>Total fat</td>
<td>2</td>
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<tr>
<td>5.2.1</td>
<td>Animal fat</td>
<td>2</td>
<td>2</td>
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<td>5.2.1</td>
<td>Vegetable fat</td>
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<td>5.2.2</td>
<td>Saturated fatty acids</td>
<td>-</td>
<td>3</td>
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<tr>
<td>5.2.3</td>
<td>Monounsaturated fatty acids</td>
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<td>5.2.4</td>
<td>Polyunsaturated fatty acids</td>
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<td>5.2.5</td>
<td>Trans fatty acids</td>
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<td>2</td>
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<td>Total alcohol (as ethanol)</td>
<td>4</td>
<td>8</td>
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<tr>
<td>5.4.1.1</td>
<td>Alcohol (as ethanol) from beer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5.4.1.2</td>
<td>Alcohol (as ethanol) from wine</td>
<td>2</td>
<td>2</td>
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<td>5.5.1</td>
<td>Vitamin A, diet and supplements</td>
<td>1</td>
<td>2</td>
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<td>5.5.1</td>
<td>Dietary vitamin A</td>
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<td>Vitamin A supplement</td>
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<td>Retinol, diet</td>
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<td>Alpha-carotene</td>
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<td>2</td>
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<td>Total beta-carotene</td>
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<td>2</td>
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<tr>
<td>5.5.1.2</td>
<td>Dietary beta-carotene</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Code</td>
<td>Exposure heading</td>
<td>Publication date</td>
<td>Total</td>
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<td>----------</td>
<td>-----------------------------------</td>
<td>------------------</td>
<td>-------</td>
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<td>Beta-carotene supplements</td>
<td>-</td>
<td>1</td>
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<td>5.5.1.2</td>
<td>Dietary beta-cryptoxanthin</td>
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<td>3</td>
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<tr>
<td>5.5.2</td>
<td>Lutein</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5.5.2</td>
<td>Lutein and zeaxanthin</td>
<td>1</td>
<td>2</td>
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<tr>
<td>5.5.2</td>
<td>Dietary lycopene</td>
<td>1</td>
<td>3</td>
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<tr>
<td>5.5.3.1</td>
<td>Total folate</td>
<td>1</td>
<td>3</td>
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<tr>
<td>5.5.3.2</td>
<td>Dietary folate</td>
<td>3</td>
<td>6</td>
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<tr>
<td>5.5.3.4</td>
<td>Methionine</td>
<td>-</td>
<td>-</td>
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<tr>
<td>5.5.4</td>
<td>Riboflavin</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5.5.5</td>
<td>Thiamin (vitamin B1)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5.5.6</td>
<td>Niacin</td>
<td>-</td>
<td>1</td>
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<tr>
<td>5.5.7</td>
<td>Pyridoxine (vit B6)</td>
<td>-</td>
<td>1</td>
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<tr>
<td>5.5.9</td>
<td>Dietary vitamin C</td>
<td>2</td>
<td>5</td>
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<tr>
<td>5.5.9</td>
<td>Total vitamin C</td>
<td>1</td>
<td>4</td>
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<tr>
<td>5.5.10</td>
<td>Serum vitamin D</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>5.5.11</td>
<td>Dietary vitamin E</td>
<td>2</td>
<td>4</td>
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<tr>
<td>5.5.11</td>
<td>Total vitamin E</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>5.5.13</td>
<td>Antioxidant indices</td>
<td>-</td>
<td>2</td>
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<tr>
<td>5.5.13</td>
<td>Multivitamin/mineral supplements</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5.6.3</td>
<td>Calcium supplement</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5.6.3</td>
<td>Total calcium</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>5.6.3</td>
<td>Dietary calcium</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>5.6.4</td>
<td>Selenium, supplements</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5.6.6</td>
<td>Phosphorus</td>
<td>-</td>
<td>1</td>
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<tr>
<td>5.7.2</td>
<td>Isothiocyanates</td>
<td>-</td>
<td>1</td>
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<tr>
<td>5.7.5</td>
<td>Phytoestrogens</td>
<td>-</td>
<td>3</td>
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<tr>
<td>5.7.5</td>
<td>Total isoflavones</td>
<td>-</td>
<td>2</td>
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<tr>
<td>5.7.6</td>
<td>Caffeine</td>
<td>-</td>
<td>1</td>
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<tr>
<td>5.8</td>
<td>Flavonoids</td>
<td>-</td>
<td>2</td>
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<tr>
<td>6.1</td>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1</td>
<td>Energy Intake</td>
<td>1</td>
<td>3</td>
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<tr>
<td>8.1.1</td>
<td>BMI</td>
<td>14</td>
<td>32</td>
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<tr>
<td>8.1.2</td>
<td>Other weight adjusted for height measures</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8.1.3</td>
<td>Weight</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>8.1.5</td>
<td>Other body fatness indicators</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>8.1.6</td>
<td>Weight change</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>8.2.1</td>
<td>Waist circumference</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>8.2.2</td>
<td>Hips circumference</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>8.2.3</td>
<td>Waist to hip ratio</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>8.2.5</td>
<td>Somatotype in childhood</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>8.3.1</td>
<td>Height</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>8.4.1</td>
<td>Birthweight</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCl</th>
<th>UCl</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tworoger, 2006</td>
<td>USA</td>
<td>NHS</td>
<td>481 epithelial ovarian cancers</td>
<td>22</td>
<td>0.95</td>
<td>0.70</td>
<td>1.30</td>
<td>Low vs high (ref) methyl group score</td>
</tr>
<tr>
<td>Chang, 2008</td>
<td>USA</td>
<td>CTS</td>
<td>311 epithelial ovarian cancer</td>
<td>~ 9</td>
<td>1.65</td>
<td>1.06</td>
<td>2.54</td>
<td>Highest vs lowest score Plant based High protein/high fat High carbohydrate Ethnic Salad and wine</td>
</tr>
<tr>
<td>Key, 2009</td>
<td>UK</td>
<td>OVS, EPIC-Oxford</td>
<td>98 meat eater, 8 fish eater, 34 vegetarian</td>
<td>12.2</td>
<td>0.37</td>
<td>0.18</td>
<td>0.77</td>
<td>Fish eater vs meat eater Vegetarian vs meat eater</td>
</tr>
</tbody>
</table>

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 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 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 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

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

Table 4 Overall evidence on breastfeeding and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>One study was identified. No association was observed.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Two cohort studies identified. None of them reported significant associations.</td>
</tr>
</tbody>
</table>
Table 5 Summary of results of the highest versus lowest meta-analysis on breastfeeding and ovarian cancer

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>817</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>0.90 (0.75-1.08)</td>
</tr>
<tr>
<td>Contrast</td>
<td>Yes vs. No</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>I²: 0%, P=0.732</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Three cohort studies had reported on fruit and non-starchy vegetables and ovarian cancer. All of these reported no significant association.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
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</table>
Table 7 Summary of results of the dose-response meta-analysis of fruit and non-starchy vegetable intake and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Ovarian cancer</th>
<th>SLR</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Studies (n)</td>
<td></td>
<td>1134</td>
<td>1134</td>
</tr>
<tr>
<td>Cases (n)</td>
<td></td>
<td>1.06 (0.84-1.35)</td>
<td>1.01 (0.98-1.05)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td></td>
<td>Per 5 serv/d</td>
<td>Per 100 g/d</td>
</tr>
<tr>
<td>Increment</td>
<td></td>
<td>0%, p=not available</td>
<td>0%, p=0.91</td>
</tr>
<tr>
<td>Heterogeneity (I(^2), p-value)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPIC study and Pooling Project</td>
<td></td>
<td>13 studies</td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td></td>
<td>2711</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td></td>
<td>0.99 (0.97-1.01)</td>
<td></td>
</tr>
<tr>
<td>Increment</td>
<td></td>
<td>Per 100 g/d</td>
<td></td>
</tr>
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Table 8 Inclusion/exclusion table for meta-analysis of fruit and non-starchy vegetables and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>C U dose-response</th>
<th>C U H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11850</td>
<td>Mommers</td>
<td>2005</td>
<td>Case-cohort study</td>
<td>The Netherlands Cohort study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA09823</td>
<td>Schulz</td>
<td>2005</td>
<td>Prospective cohort study</td>
<td>EPIC study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Only continuous results presented</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Recalculated from servings to grams per day</td>
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</table>
Figure 3 Highest versus lowest forest plot of fruit and non-starchy vegetables and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mommers</td>
<td>2005</td>
<td>1.13 (0.70, 1.82)</td>
<td>OVA11850</td>
<td>NLCS</td>
<td>583 vs. 207 g/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.10 (0.64, 1.90)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>7.3 vs. &lt;3.3 servings</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 100 g per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mommers</td>
<td>2005</td>
<td>0.99 (0.88, 1.11)</td>
<td>8.52</td>
</tr>
<tr>
<td>Schulz</td>
<td>2005</td>
<td>1.01 (0.98, 1.05)</td>
<td>82.28</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.02 (0.91, 1.14)</td>
<td>9.20</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.906)</td>
<td></td>
<td>1.01 (0.98, 1.05)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Figure 5 Dose-response graph of fruit and non-starchy vegetables and ovarian cancer

Fruit and vegetables (g/day)
### 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, I²=28.8%, p_heterogeneity=0.22). Egger’s test for publication bias was not significant, p=0.22.

**Heterogeneity**
There was low heterogeneity, I²=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>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>George, 2009</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>514 cases</td>
<td>~8 years</td>
<td>1.04</td>
<td>0.79</td>
<td>1.37</td>
<td>1.8 vs. 0.4 cup equivalents/1000 kcal/d</td>
</tr>
</tbody>
</table>
Table 10 Overall evidence on non-starchy vegetables and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>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</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>1400</td>
<td>2053</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.92 (0.87-0.98)</td>
<td>0.94 (0.88-1.00)</td>
</tr>
<tr>
<td>Quantity</td>
<td>Per 1 serv/d</td>
<td>Per 100 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>0%, p=not available</td>
<td>28.8, p=0.22</td>
</tr>
<tr>
<td>EPIC, NIH-AARP study and Pooling Project</td>
<td>15 studies</td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>3225</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.98 (0.95-1.01)</td>
<td></td>
</tr>
<tr>
<td>Increment</td>
<td>100 g/d</td>
<td></td>
</tr>
<tr>
<td>WCRF code</td>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>OVA11685</td>
<td>George</td>
<td>2009</td>
</tr>
<tr>
<td>OVA11850</td>
<td>Mommers</td>
<td>2005</td>
</tr>
<tr>
<td>OVA09823</td>
<td>Schulz</td>
<td>2005</td>
</tr>
<tr>
<td>OVA09697</td>
<td>Larsson</td>
<td>2004</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
</tr>
</tbody>
</table>
Figure 6 Highest versus lowest forest plot of non-starchy vegetables and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>George</td>
<td>2009</td>
<td>1.04 (0.79, 1.37)</td>
<td>OVA11685</td>
<td>NIH-AARP</td>
<td>1.8 vs. 0.4 cup equiv/1000 kcal/d</td>
</tr>
<tr>
<td>Mommers</td>
<td>2005</td>
<td>0.96 (0.61, 1.58)</td>
<td>OVA11580</td>
<td>NLCS</td>
<td>291 vs. 115 g/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.81 (0.38, 1.87)</td>
<td>OVA09823</td>
<td>SMC</td>
<td>&gt;=3 vs. &lt;=1 serv/id</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.77 (0.48, 1.24)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>&gt;=4.4 vs. &lt;=1.6 serv/id</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.78 (0.42, 1.37)</td>
<td>OVA02880</td>
<td>MHS</td>
<td>&gt;31 vs. &lt;=16 serv/wk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 100 g per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>George</td>
<td>2009</td>
<td>1.00 (0.93, 1.07)</td>
<td>33.28</td>
</tr>
<tr>
<td>Mommers</td>
<td>2005</td>
<td>1.00 (0.79, 1.26)</td>
<td>5.99</td>
</tr>
<tr>
<td>Schultz</td>
<td>2005</td>
<td>0.94 (0.88, 1.03)</td>
<td>30.06</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.80 (0.67, 0.95)</td>
<td>10.14</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.91 (0.79, 1.06)</td>
<td>12.65</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.88 (0.72, 1.08)</td>
<td>7.89</td>
</tr>
<tr>
<td>Overall (I-squared = 28.8%, p = 0.219)</td>
<td></td>
<td>0.94 (0.88, 1.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
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, $I^2 = 21.3\%$, $P_{\text{heterogeneity}} = 0.28$) 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 ($I^2 = 21.3\%$, $P_{\text{heterogeneity}} = 0.28$). Egger’s tests suggested no evidence of publication bias ($p = 0.34$).

Table 13 Studies on cabbage identified in the CUP

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang, 2007</td>
<td>USA</td>
<td>California Teachers Study 1995</td>
<td>280</td>
<td>8.1</td>
<td>1.12</td>
<td>0.79</td>
<td>1.59</td>
<td>&gt;3.6 vs. 0 g/day</td>
</tr>
</tbody>
</table>

Table 14 Overall evidence on cabbage intake and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>Two studies were identified during the SLR; both studies found no association between cabbage consumption and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>One study was identified which reported no association. Overall, three studies were included in the meta-analysis.</td>
</tr>
</tbody>
</table>
Table 15 Summary of results of the dose response meta-analysis of cabbage intake and ovarian cancer

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1198</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 5g/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.00 (0.94 - 1.06)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>21.3 %, p=0.28</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
### Table 16: Inclusion/exclusion table for meta-analysis of cabbage intake and ovarian cancer

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

41
Figure 10 Highest versus lowest forest plot of cabbage intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.12 (0.79, 1.59)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>&gt;3.6g vs. 0 g/day</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.87 (0.58, 1.31)</td>
<td>OVA09697</td>
<td>SMC</td>
<td>&gt;=17.1 vs. 0 g/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 5 g</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.17 (0.95, 1.44)</td>
<td>7.86</td>
<td>OVA11654</td>
<td>52.99</td>
<td>CTS</td>
<td>EPIC</td>
</tr>
<tr>
<td>Schulz</td>
<td>2005</td>
<td>1.00 (0.94, 1.07)</td>
<td>52.99</td>
<td>OVA09823</td>
<td>52.99</td>
<td>EPIC</td>
<td>SMC</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.98 (0.90, 1.08)</td>
<td>39.15</td>
<td>OVA09697</td>
<td>39.15</td>
<td>SMC</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.00 (0.94, 1.06)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(i-squared = 21.3%, p = 0.281)
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, $I^2=35.5\%$, $p_{\text{heterogeneity}}=0.16$). Egger’s test for publication bias was not significant, $p=0.55$.

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

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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>George, 2009</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>514 cases</td>
<td>~8 years</td>
<td>1.04</td>
<td>0.79</td>
<td>1.37</td>
<td>1.8 vs. 0.4 cup equivalents/1000 kcal/d</td>
</tr>
<tr>
<td>Kiani, 2006</td>
<td>USA</td>
<td>Adventist Health Study</td>
<td>71 cases</td>
<td>Up to 16 years</td>
<td>0.46</td>
<td>0.20</td>
<td>1.04</td>
<td>&gt;1/d vs. ≤5/wk</td>
</tr>
</tbody>
</table>
Table 18 Overall evidence on fruits and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Five studies reported on fruit intake and ovarian cancer, none of which found a significant association.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>1400</td>
<td>2124</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.08 (1.02-1.14)</td>
<td>1.05 (0.98-1.12)</td>
</tr>
<tr>
<td>Quantity</td>
<td>Per 1 serv/d</td>
<td>Per 100 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I^2, p-value)</td>
<td>0%, p=not available</td>
<td>35.5, p=0.16</td>
</tr>
<tr>
<td>EPIC, NIH-AARP study and Pooling Project</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>3225</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.01 (0.98-1.05)</td>
<td></td>
</tr>
<tr>
<td>Increment</td>
<td>100 g/d</td>
<td></td>
</tr>
<tr>
<td>WCRF code</td>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>------</td>
</tr>
<tr>
<td>OVA11685</td>
<td>George</td>
<td>2009</td>
</tr>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
</tr>
<tr>
<td>OVA11850</td>
<td>Mommers</td>
<td>2005</td>
</tr>
<tr>
<td>OVA09823</td>
<td>Schulz</td>
<td>2005</td>
</tr>
<tr>
<td>OVA09697</td>
<td>Larsson</td>
<td>2004</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>George</td>
<td>2009</td>
<td>1.02 (0.74, 1.40)</td>
<td>OVA11685</td>
<td>NIH- AARP</td>
<td>2.4 vs. 0.4 cup equiv/1000 kcal/d</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>0.46 (0.20, 1.04)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>&gt;1/d vs. &lt;=5/wk</td>
</tr>
<tr>
<td>Mommers</td>
<td>2005</td>
<td>1.11 (0.70, 1.78)</td>
<td>OVA11850</td>
<td>NLCS</td>
<td>343 vs. 62 g/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.37 (0.90, 2.06)</td>
<td>OVA09697</td>
<td>SMC</td>
<td>&gt;=3.0 vs. &lt;=1 serv/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.27 (0.80, 2.02)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>&gt;=3.2 vs. &lt;=1 serv/d</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.13 (0.66, 1.93)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;23 vs. &lt;11 serv/wk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>Per 100 g/d</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>George</td>
<td>2009</td>
<td>0.97 (0.85, 1.11)</td>
<td>16.00</td>
<td>OVA11685</td>
<td>NIH- AARP</td>
<td></td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>0.16 (0.03, 0.96)</td>
<td>0.13</td>
<td>OVA11647</td>
<td>AHS</td>
<td></td>
</tr>
<tr>
<td>Mommers</td>
<td>2005</td>
<td>1.00 (0.89, 1.08)</td>
<td>21.62</td>
<td>OVA11850</td>
<td>NLCS</td>
<td></td>
</tr>
<tr>
<td>Schulz</td>
<td>2005</td>
<td>1.05 (1.00, 1.10)</td>
<td>36.53</td>
<td>OVA09823</td>
<td>EPIC</td>
<td></td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.16 (0.99, 1.37)</td>
<td>11.63</td>
<td>OVA09697</td>
<td>SMC</td>
<td></td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.19 (0.96, 1.48)</td>
<td>7.34</td>
<td>OVA01437</td>
<td>NHS</td>
<td></td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.08 (0.86, 1.36)</td>
<td>6.76</td>
<td>OVA02880</td>
<td>IWHS</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.05 (0.98, 1.12)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 16 Funnel plot of fruits and ovarian cancer

Funnel plot with pseudo 95% confidence limits

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

Dose-response graph of fruit intake and ovarian cancer

Kushi 1999
Fairfield 2001
Larsson 2004
Mommers 2005
George 2009

0 100 200 300 400
Fruits (g/day)
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, I²=0%, P heterogeneous =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, I²=0%, P heterogeneous =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 (I²=0%, P heterogeneous =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 heterogeneous=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 heterogeneous=0.88). The relative risks estimates were 1.26 (95% CI: 1.02-1.56; P heterogeneous=0.93) for the three cohort studies and 1.17 (95% CI: 1.03-1.34; P heterogeneous=0.58) for the four population-based case-control studies, respectively.
### Table 21 Studies on processed meat identified in the CUP

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>Netherlands</td>
<td>The Netherlands Cohort Study</td>
<td>340</td>
<td>16.3</td>
<td>0.83</td>
<td>0.59</td>
<td>1.20</td>
<td>High vs low quintile Per 25 g/day increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.75</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>Schulz, 2007</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>581</td>
<td>6.3</td>
<td>1.25</td>
<td>0.81</td>
<td>1.92</td>
<td>&gt;=42 g/day vs &lt;17g/day Per 15.6 g/day increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.05</td>
<td>0.91</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
<td>Cross, 2007</td>
<td>United States</td>
<td>National Institute of Health-American Association for Retired Persons</td>
<td>522</td>
<td>6.8</td>
<td>1.23</td>
<td>0.92</td>
<td>1.63</td>
<td>22.6 g/1000 kcal vs 1.6 g/1000 kcal</td>
</tr>
<tr>
<td>Sakauchi, 2007</td>
<td>Japan</td>
<td>Japan Collaborative Cohort study</td>
<td>57 deaths</td>
<td>13.3</td>
<td>0.91</td>
<td>0.30</td>
<td>2.76</td>
<td>&gt;=4 times/week vs &lt;=1.2 times/week</td>
</tr>
</tbody>
</table>

### Table 22 Overall evidence on processed meat and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>No study on processed meat (processed meat, processed pork and pork products) was identified.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Four prospective studies were identified. None of the studies reported a significant association of ovarian cancer and processed meat intake.</td>
</tr>
</tbody>
</table>
Table 23 Summary of results of the dose response meta-analysis on processed meat and ovarian cancer

<table>
<thead>
<tr>
<th>Ovarian cancer*</th>
<th></th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>SLR -</td>
<td>4</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1530</td>
</tr>
<tr>
<td>Increment unit</td>
<td>-</td>
<td>Per 50 g/d</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.13 (0.88-1.46)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ovarian cancer incidence*</th>
<th></th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>SLR -</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1473</td>
</tr>
<tr>
<td>Increment unit</td>
<td>-</td>
<td>Per 50 g/d</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.14 (0.88-1.47)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0% p=0.59</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 24 Inclusion/exclusion table for meta-analysis of processed meat and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort study</td>
<td>The Netherland Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Rescale of RR for continuous increase</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Rescale of RR for continuous increase</td>
</tr>
<tr>
<td>OVA11686</td>
<td>Cross</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>National Institute of Health-American Association for Retired Persons</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Reported median intake in g/1000 kcal was recalculated to g/energy intake by quintile</td>
</tr>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Japan Collaborative Cohort study</td>
<td>Mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Person/year per category g/day per quintile and mid-exposure values</td>
</tr>
</tbody>
</table>
Figure 18 Highest versus lowest forest plot of processed meat and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.83 (0.59, 1.20)</td>
<td>OVA11616</td>
<td>NCS</td>
<td></td>
</tr>
<tr>
<td>Cross</td>
<td>2007</td>
<td>1.23 (0.92, 1.63)</td>
<td>OVA11686</td>
<td>NIH-AARP</td>
<td></td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>0.91 (0.30, 2.76)</td>
<td>OVA11661</td>
<td>JACC</td>
<td></td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>1.25 (0.81, 1.92)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td></td>
</tr>
</tbody>
</table>

High vs low

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 50 g per</th>
<th>%</th>
<th>day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td></td>
<td></td>
<td>0.92 (0.56, 1.51)</td>
<td>25.95</td>
<td>OVA11616</td>
<td>NCS</td>
</tr>
<tr>
<td>Cross</td>
<td>2007</td>
<td></td>
<td></td>
<td>1.27 (0.87, 1.87)</td>
<td>43.15</td>
<td>OVA11686</td>
<td>NIH-AARP</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td></td>
<td></td>
<td>0.72 (0.06, 8.59)</td>
<td>1.04</td>
<td>OVA11661</td>
<td>JACC</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td></td>
<td></td>
<td>1.16 (0.73, 1.84)</td>
<td>29.87</td>
<td>OVA11639</td>
<td>EPIC</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td>1.13 (0.88, 1.46)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 20 Funnel plot of processed meat and ovarian cancer

Funnel plot with pseudo 95% confidence limits

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

Processed meat (g/day)
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, I²=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 (I²=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\textsubscript{heterogeneity}=0.15 and RR= 1.39; 95% CI: 1.19-1.62; P\textsubscript{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

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

Table 26 Overall evidence on red meat and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
</tbody>
</table>
### Table 27 Summary of results of the dose response meta-analysis on red meat and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>2089</td>
</tr>
<tr>
<td>Increment unit</td>
<td>-</td>
<td>Per 100 g/d</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.03 (0.86-1.24)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.56</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 28 Inclusion/exclusion table for meta-analysis of red meat and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort study</td>
<td>The Netherland Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA11686</td>
<td>Cross</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>National Institute of Health-American Association for Retired Persons</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Reported median intake in g/1000 kcal was recalculated to g/energy intake by quintile</td>
<td>-</td>
</tr>
<tr>
<td>OVA10420</td>
<td>Larsson</td>
<td>2005</td>
<td>Prospective Cohort study</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective Cohort study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category, g/day per category and mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 22 Highest versus Lowest forest plot of red meat consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.93 (0.61, 1.42)</td>
<td>OVA11616</td>
<td>NCS</td>
<td>129.6 g/d vs 36.2 g/d</td>
</tr>
<tr>
<td>Cross</td>
<td>2007</td>
<td>1.19 (0.89, 1.59)</td>
<td>OVA11686</td>
<td>NIH-AARP</td>
<td>62.7 g/1000 kcal vs 9.8 g/1000 kcal</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>1.04 (0.70, 1.56)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td>&gt;=55 g/d vs &lt;25 g/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>1.01 (0.70, 1.46)</td>
<td>OVA10420</td>
<td>SMC</td>
<td>5.0 serving/wk vs 1.5 serving/wk</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.30 (0.93, 1.82)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>&gt;= 1 serv/day vs &lt;1 serv/month</td>
</tr>
</tbody>
</table>

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

| Author    | Year | Per 100 gr per | %
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.92 (0.71, 1.21)</td>
<td>44.64</td>
</tr>
<tr>
<td>Cross</td>
<td>2007</td>
<td>1.14 (0.84, 1.55)</td>
<td>33.76</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>0.79 (0.35, 1.68)</td>
<td>5.16</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>1.07 (0.58, 1.97)</td>
<td>8.50</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.51 (0.81, 2.85)</td>
<td>7.95</td>
</tr>
</tbody>
</table>
| Overall (I-squared = 0.0%, p = 0.561) |   | 1.03 (0.86, 1.24) | 100.00
Figure 24 Funnel plot of red meat consumption and ovarian cancer

Funnel plot with pseudo 95% confidence limits

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

Red meat (g/day)
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, $I^2=0\%$, $P_{\text{heterogeneity}}=0.94$) 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; $I^2= 0\%$, $P_{\text{heterogeneity}}=0.98$). 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 ($I^2=0\%$, $P_{\text{heterogeneity}}=0.94$). There was no indication of publication bias with Egger’s test ($p=0.46$).

Table 29 Studies on beef identified in the CUP

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>Netherlands</td>
<td>The Netherland Cohort Study</td>
<td>340</td>
<td>16.3</td>
<td>1.15</td>
<td>0.81</td>
<td>1.64</td>
<td>Highest vs low quintile Per 25 g/day increase</td>
</tr>
<tr>
<td>Sakauchi, 2007</td>
<td>Japan</td>
<td>Japan Collaborative Cohort study</td>
<td>77</td>
<td>13.3</td>
<td>1.24</td>
<td>0.50</td>
<td>3.05</td>
<td>$\geq$1-2 times/week vs Seldom</td>
</tr>
<tr>
<td>Kiani, 2006</td>
<td>USA</td>
<td>Adventist Health Study</td>
<td>71</td>
<td>16</td>
<td>1.09</td>
<td>0.50</td>
<td>2.38</td>
<td>$\geq$1 time/week vs Never</td>
</tr>
</tbody>
</table>
Table 30 Overall evidence on beef and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>No studies were found on beef intake and ovarian cancer risk.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Three prospective studies were identified. None of the studies reported a significant association of ovarian cancer and beef intake.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>488</td>
</tr>
<tr>
<td>Increment unit</td>
<td>-</td>
<td>Per 50 g/d</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.15 (0.91-1.44)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>411</td>
</tr>
<tr>
<td>Increment unit</td>
<td>-</td>
<td>Per 50 g/d</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.14 (0.90-1.44)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td></td>
<td>0%, p=0.98</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort study</td>
<td>The Netherlands Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Japan Collaborative Cohort study</td>
<td>Mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category g/day per category and mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Adventist Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases and person/ years per category g/day per category and mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 26 Highest versus lowest forest plot of beef consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>Study Description</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilising</td>
<td>2011</td>
<td>1.15 (0.81, 1.64)</td>
<td>OVA11616</td>
<td>NCS</td>
<td>50.4 g/d vs 2.2 g/d</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>1.24 (0.50, 3.05)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>&gt;=1-2 times/wk vs seldom</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.09 (0.50, 2.38)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>&gt;=1 time/wk vs never</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 50 gr per day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilising</td>
<td>2011</td>
<td>1.14 (0.90, 1.44)</td>
<td>95.61</td>
<td>OVA11616</td>
<td>NCS</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>1.49 (0.30, 7.29)</td>
<td>2.09</td>
<td>OVA11661</td>
<td>JACC</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.16 (0.25, 5.28)</td>
<td>2.30</td>
<td>OVA11647</td>
<td>AHS</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.948)</td>
<td></td>
<td>1.15 (0.91, 1.44)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

64
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, I²=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; I²= 0%, P_heterogeneity=0.85). In influence analysis the summary RR ranged from 0.99 (95% CI: 0.89-1.09) 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 (I²=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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UC1</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>Netherlands</td>
<td>The Netherlands Cohort Study</td>
<td>340</td>
<td>16.3</td>
<td>1.06</td>
<td>0.96</td>
<td>1.48</td>
<td>1.14 Highest vs low quintile Per 25 g/day increase</td>
</tr>
<tr>
<td>Sakauchi, 2007</td>
<td>Japan</td>
<td>Japan Collaborative Cohort study</td>
<td>77</td>
<td>13.3</td>
<td>1.13</td>
<td>0.40</td>
<td>3.17</td>
<td>1.2 times/week vs &lt;= 1-2 times/month</td>
</tr>
<tr>
<td>Schulz, 2007</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition Study</td>
<td>581</td>
<td>6.3</td>
<td>1.05</td>
<td>0.88</td>
<td>1.47</td>
<td>1.21 &gt;=23 g/da vs &lt;8 g/d Per 9.3 g/day intake</td>
</tr>
<tr>
<td>Kiani, 2006</td>
<td>USA</td>
<td>Adventist Health Study</td>
<td>71</td>
<td>16</td>
<td>1.23</td>
<td>0.66</td>
<td>2.32</td>
<td>1 time/week vs Never</td>
</tr>
</tbody>
</table>

Table 34 Overall evidence on poultry and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
Table 35 Summary of results of the dose response meta-analysis on poultry and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1427</td>
</tr>
<tr>
<td>Increment unit</td>
<td>-</td>
<td>Per 25 g/d</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.00 (0.91-1.10)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.93</td>
</tr>
<tr>
<td><strong>Ovarian cancer incidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1350</td>
</tr>
<tr>
<td>Increment unit</td>
<td>-</td>
<td>Per 25 g/d</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.00 (0.90-1.10)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td></td>
<td>0%, p=0.85</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 36 Inclusion/exclusion table for meta-analysis of poultry and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort study</td>
<td>The Netherland Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Rescale of RR for continuous increase</td>
</tr>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Japan Collaborative Cohort study</td>
<td>Mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Person/ years per category g/day per category and mid-exposure values</td>
</tr>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Adventist Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Cases and person/ years per category g/day per category and mid-exposure values</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective Cohort study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Person/ years per category g/day per category and mid-exposure values</td>
</tr>
</tbody>
</table>
Figure 30 Highest versus lowest forest plot of poultry consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI) WCRF_Code</th>
<th>StudyDescription contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilging</td>
<td>2011</td>
<td>1.06 (0.76, 1.48) OVA11616</td>
<td>NCS 22.8 g/d vs 0 g/day</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>1.13 (0.40, 3.17) OVA11661</td>
<td>JACC &gt;=3-4 times/wk vs &lt;=1-2 times/wk</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>1.05 (0.75, 1.47) OVA11639</td>
<td>EPIC &gt;=23 g/d vs &lt; 8 g/day</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.23 (0.66, 2.32) OVA11647</td>
<td>AHS &gt;=1 time/wk vs never</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>0.98 (0.73, 1.32) OVA00454</td>
<td>NHS &gt;=1 time/day vs &lt; 1 time/month</td>
</tr>
</tbody>
</table>

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

| Author  | Year | Per 25 g per % day RR (95% CI) Weight WCRF_Code StudyDescription |
|---------|------|---------------------------------------------------------------|--------------------------------|
| Gilsing | 2011 | 0.96 (0.80, 1.14) 29.67 OVA11616 NCS                         |
| Sakauchi| 2007 | 1.05 (0.65, 1.69) 4.07 OVA11661 JACC                         |
| Schulz  | 2007 | 1.11 (0.70, 1.66) 4.99 OVA11639 EPIC                         |
| Kiani   | 2006 | 1.20 (0.66, 2.15) 2.69 OVA11647 AHS                          |
| Bertone | 2002 | 1.00 (0.88, 1.13) 58.58 OVA00454 NHS                         |
| Overall (I-squared = 0.0%, p = 0.935) | | 1.00 (0.91, 1.10) 100.00                                      |
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; I²= 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; I²= 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 (I²= 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>Netherlands</td>
<td>The Netherlands Cohort Study</td>
<td>340</td>
<td>16.3</td>
<td>1.01</td>
<td>0.91</td>
<td>0.71</td>
<td>1.43 1.12 &gt;=20 g/day vs 0 Per 25 g/day increase</td>
</tr>
<tr>
<td>Schulz, 2007</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>581</td>
<td>6.3</td>
<td>0.90</td>
<td>1.01</td>
<td>0.56</td>
<td>1.43 1.20 &gt;=44 g/day vs &lt;17 per g/day Per 17 g/day increase</td>
</tr>
<tr>
<td>Sakauchi, 2007</td>
<td>Japan</td>
<td>Japan Collaborative Cohort study</td>
<td>77</td>
<td>13.3</td>
<td>1.33</td>
<td>1.29</td>
<td>0.59</td>
<td>2.98 Almost every day vs &lt;=1-2 times/week</td>
</tr>
<tr>
<td>Kiani, 2006</td>
<td>USA</td>
<td>Adventist Health Study</td>
<td>71</td>
<td>16</td>
<td>1.39</td>
<td>1.28</td>
<td>0.73</td>
<td>2.62 &gt;=1 times/week vs never</td>
</tr>
</tbody>
</table>

Table 38 Overall evidence on fish intake and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>One study was identified. There was no association of fish consumption and risk of ovarian cancer in this study.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Four cohort studies were identified. None reported significant associations between fish consumption and ovarian cancer. Overall, the CUP meta-analysis included five studies.</td>
</tr>
</tbody>
</table>
Table 39 Summary of results of the dose response meta-analysis on fish intake and ovarian cancer

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1357</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 25 g/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.01 (0.91-1.13)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>0%, p=0.66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1280</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 25 g/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.00 (0.88-1.12)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>0%, p=0.59</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
### Table 40 Inclusion/exclusion table for meta-analysis on fish intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF_Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort study</td>
<td>The Netherland Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>-----------------</td>
<td>Rescale of RR for continuous increase</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td></td>
</tr>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Japan Collaborative Cohort study</td>
<td>Mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category g/day per quintile and mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Adventist Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases and person/ years per category g/day per quintile and mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA10420</td>
<td>Larsson</td>
<td>2005</td>
<td>Prospective Cohort study</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>------</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 34 Highest versus lowest forest plot of fish and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>CRF_Code</th>
<th>StudyDescription</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>1.01 (0.71, 1.43)</td>
<td>OVA11616</td>
<td>NLCS</td>
<td>28.2 g/d vs 0 g/d</td>
</tr>
<tr>
<td>Sakauchi2007</td>
<td>1.33 (0.59, 2.98)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>Almost every day vs &lt;=1-times/wk</td>
<td></td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>0.90 (0.56, 1.43)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td>&gt;=44 g/d vs &lt;17 g/d</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.39 (0.73, 2.62)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>&gt;=1 times/wk vs Never</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>1.08 (0.75, 1.55)</td>
<td>OVA10420</td>
<td>SMC</td>
<td>3 vs 0.5 serv/wk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 25 g per day</th>
<th>RR (95% CI)</th>
<th>Weight (%</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.91 (0.74, 1.12)</td>
<td>28.86</td>
<td>OVA11616</td>
<td>NLCS</td>
<td></td>
</tr>
<tr>
<td>Sakauchi2007</td>
<td>1.11 (0.83, 1.49)</td>
<td>14.56</td>
<td>OVA11661</td>
<td>JACC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>1.01 (0.79, 1.29)</td>
<td>20.62</td>
<td>OVA11639</td>
<td>EPIC</td>
<td></td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.40 (0.72, 2.72)</td>
<td>2.80</td>
<td>OVA11647</td>
<td>AHS</td>
<td></td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>1.04 (0.85, 1.26)</td>
<td>33.15</td>
<td>OVA10420</td>
<td>SMC</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.01 (0.91, 1.13)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall (I-squared = 0.0%, p = 0.665)
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; I² = 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; I² = 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 (I² = 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

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

Table 42 Overall evidence on eggs consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>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).</td>
</tr>
</tbody>
</table>
Table 43 Summary of results of the dose response meta-analysis of eggs consumption and ovarian cancer

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

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

*No meta-analysis was conducted in the Second Expert Report
### Table 44 Inclusion/exclusion table for meta-analysis of eggs consumption and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Japan Collaborative Cohort study</td>
<td>Mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category g/day per category and mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>......</td>
<td>Only high versus low reported</td>
</tr>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Adventist Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases and person/ years per category g/day per category and mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA10420</td>
<td>Larsson</td>
<td>2005</td>
<td>Prospective Cohort study</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>......</td>
<td>-</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective Cohort study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category g/day per category and mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category g/day per category and mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA05024</td>
<td>Snowdon</td>
<td>1985</td>
<td>Prospective Cohort study</td>
<td>Seventh-Day Adventist- 1960</td>
<td>Mortality</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Two categories of exposure (high vs. low).</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 38 Highest versus lowest forest plot of egg consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>Study Description</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.78 (0.53, 1.15)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>High vs low quintile</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>0.65 (0.30, 1.41)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>Almost every day vs &lt;=1-2 times/wk</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>1.19 (0.85, 1.67)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td>&gt;=16 g/d vs &lt; 9g/d</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.02 (0.50, 2.10)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>&gt;2 times/wk vs never to &lt;1 time/wk</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>0.93 (0.55, 1.57)</td>
<td>OVA10420</td>
<td>SMC</td>
<td>5 serv/wk vs 0.5 serv/wk</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.62 (1.04, 2.53)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>&gt;=1 serv/day vs &lt;1 serv/month</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.61 (0.89, 3.69)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;4 serv/wk vs &lt;1 serv/wk</td>
</tr>
<tr>
<td>Snowdon</td>
<td>1985</td>
<td>3.00 (1.20, 7.30)</td>
<td>OVA05024</td>
<td>AHS, 1960</td>
<td>&gt;=3 times/wk vs &lt;1 time/wk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>Study Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>0.71 (0.39, 1.31)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>10.94</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>0.89 (0.59, 1.33)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td>17.73</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.04 (0.36, 2.99)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>4.56</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>1.02 (0.74, 1.40)</td>
<td>OVA10420</td>
<td>SMC</td>
<td>21.92</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.31 (1.04, 1.64)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>27.18</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.80 (1.19, 2.70)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>17.66</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.13 (0.89, 1.44)</td>
<td></td>
<td></td>
<td>100.00</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park, 2009</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>515</td>
<td>~6.3 years</td>
<td>1.03</td>
<td>0.77</td>
<td>1.37</td>
<td>1.6 vs. 0.2 serv/1000 kcal</td>
</tr>
<tr>
<td>Schulz, 2007</td>
<td>Europe</td>
<td>EPIC Study</td>
<td>581</td>
<td>8.1 years</td>
<td>0.84</td>
<td>0.56</td>
<td>1.26</td>
<td>≥209 vs. &lt;131 g/d Per 39.4 g/d</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>USA</td>
<td>California Teachers Study</td>
<td>280</td>
<td>8.3 years</td>
<td>0.42</td>
<td>0.20</td>
<td>0.89</td>
<td>Q5 vs. Q1</td>
</tr>
<tr>
<td>Koralek, 2006</td>
<td>USA</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>146</td>
<td>8.3 years</td>
<td>0.42</td>
<td>0.20</td>
<td>0.89</td>
<td>≥7 vs. 0 serv/d</td>
</tr>
</tbody>
</table>
Table 46 Overall evidence on dairy products and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>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.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1647</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.06 (0.92-1.23)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 200 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>66.1%, p=0.02</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
**Table 48 Inclusion/exclusion table for meta-analysis of dairy products and ovarian cancer**

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11694</td>
<td>Park</td>
<td>2009</td>
<td>Prospective</td>
<td>NIH-AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Distribution of cases/person-years</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective</td>
<td>EPIC study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Midpoints</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Only high vs. low comparison reported</td>
</tr>
<tr>
<td>OVA11662</td>
<td>Koralek</td>
<td>2006</td>
<td>Prospective</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Distribution of person-years</td>
</tr>
<tr>
<td>OVA10870</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Distribution of person-years, midpoints</td>
</tr>
</tbody>
</table>
Figure 42 Highest versus lowest forest plot of dairy products and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park</td>
<td>2009</td>
<td>1.03 (0.77, 1.37)</td>
<td>NIH-AARP</td>
<td>1.6 vs. 0.2 serv/1000 kcal/d</td>
<td></td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.84 (0.56, 1.26)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>Quintile 5 vs. 1</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>0.58 (0.26, 1.29)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td>&gt;=209 vs. &lt;131 g/d</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.42 (0.20, 0.89)</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td>5.1 vs. 0.5 serv/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.60 (1.10, 2.50)</td>
<td>OVA10870</td>
<td>SMC</td>
<td>&gt;=4 vs. &lt;2 serv/d</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.76 (0.99, 3.13)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;23 vs. &lt;9 serv/wk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park</td>
<td>2009</td>
<td>1.06 (0.92, 1.23)</td>
<td>100.00</td>
<td>OVA11694</td>
<td>NIH-AARP</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>0.55 (0.10, 2.98)</td>
<td>0.72</td>
<td>OVA11639</td>
<td>EPIC</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.86 (0.73, 1.01)</td>
<td>24.60</td>
<td>OVA11662</td>
<td>BCDDP</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.19 (1.03, 1.38)</td>
<td>25.54</td>
<td>OVA10870</td>
<td>SMC</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.22 (1.01, 1.47)</td>
<td>22.28</td>
<td>OVA02880</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.06 (0.92, 1.23)</td>
<td>100.00</td>
<td>OVA11694</td>
<td>NIH-AARP</td>
</tr>
</tbody>
</table>
Figure 44 Funnel plot of dairy products and ovarian cancer

![Funnel plot with pseudo 95% confidence limits](image)

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

![Dose-response graph](image)
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, I²=0%, p heterogeneity=0.47). There was no evidence of publication bias with Egger’s test, p=0.68.

Heterogeneity
There was no heterogeneity, I²=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, I²=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

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

Table 50 Overall evidence on milk and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>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.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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).</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1647</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.01 (0.93-1.09)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 200 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.47</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 52 Inclusion/exclusion table for meta-analysis of milk and ovarian cancer

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

*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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.97 (0.67, 1.42)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>Quintile 5 vs. 1</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>1.67 (0.66, 4.23)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>Almost every day vs. &lt;=1-2/mo</td>
</tr>
<tr>
<td>Schultz</td>
<td>2007</td>
<td>0.93 (0.70, 1.25)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td>&gt;=264 vs. &lt;66 g/d</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>1.21 (0.61, 2.44)</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td>14 vs. 0 servings</td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>0.98 (0.65, 1.48)</td>
<td>OVA09788</td>
<td>NLCS</td>
<td>343 vs. 0 g/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.55 (1.00, 2.40)</td>
<td>OVA11491</td>
<td>NHS</td>
<td>&gt;=1/d vs. almost never-1-3/mo</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.30 (0.90, 1.90)</td>
<td>OVA10870</td>
<td>SMC</td>
<td>&gt;=2 serv/d vs. &lt;=1/wk</td>
</tr>
<tr>
<td>Ursin</td>
<td>1990</td>
<td>5.95 (0.72, 49.32)</td>
<td>OVA11697</td>
<td></td>
<td>&gt;&gt;2 vs. &lt;1 glass/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 200 g per day RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>1.58 (0.67, 3.72) 0.83</td>
<td>OVA11661</td>
<td>JACC</td>
</tr>
<tr>
<td>Schultz</td>
<td>2007</td>
<td>0.97 (0.81, 1.15) 20.24</td>
<td>OVA11639</td>
<td>EPIC</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.93 (0.79, 1.08) 24.50</td>
<td>OVA11662</td>
<td>BCDDP</td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>1.01 (0.80, 1.27) 11.30</td>
<td>OVA09788</td>
<td>NLCS</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.07 (0.96, 1.21) 43.13</td>
<td>OVA10870</td>
<td>SMC</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.472)</td>
<td></td>
<td>1.01 (0.93, 1.09) 100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, I²=0%, p_{heterogeneity}=0.60).

Heterogeneity
There was no evidence of heterogeneity, I²=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, I²=51.7%, p_{heterogeneity}=0.04) for all studies, and 1.17 (95% CI: 0.81-1.68, I²=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) p_{trend}= 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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiani, 2006</td>
<td>USA</td>
<td>Adventist Health Study</td>
<td>71</td>
<td>~16 years</td>
<td>1.48</td>
<td>0.74</td>
<td>2.98</td>
<td>≥1/day vs. never</td>
</tr>
<tr>
<td>Koralek, 2006</td>
<td>USA</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>146</td>
<td>8.3 years</td>
<td>0.80</td>
<td>0.39</td>
<td>1.63</td>
<td>12.7 vs. 0 serv/wk</td>
</tr>
</tbody>
</table>
### Table 54 Overall evidence on whole milk and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Two cohort studies reported on whole milk and ovarian cancer. Both studies showed no significant association between whole milk and ovarian cancer risk.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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).</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>518</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.04 (0.88-1.23)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 200 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.60</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 56 Inclusion/exclusion table for meta-analysis of whole milk and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective</td>
<td>Adventist Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, distribution of person-years</td>
</tr>
<tr>
<td>OVA11662</td>
<td>Koralek</td>
<td>2006</td>
<td>Prospective</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years</td>
</tr>
<tr>
<td>OVA10870</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>OVA11491</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, distribution of person-years</td>
<td></td>
</tr>
</tbody>
</table>
Figure 50 Highest versus lowest forest plot of whole milk and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.48 (0.74, 2.98)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>&gt;=1/d vs. never</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.80 (0.39, 1.63)</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td>12.7 vs. 0 serv/wk</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.18 (0.68, 2.03)</td>
<td>OVA11481</td>
<td>NHS</td>
<td>&gt;=1/d vs. never-3/mo</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.13 (0.86, 1.49)</td>
<td>38.60</td>
<td>OVA11647</td>
<td>AHS</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.91 (0.67, 1.25)</td>
<td>29.00</td>
<td>OVA11662</td>
<td>BCDDP</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.05 (0.78, 1.42)</td>
<td>32.41</td>
<td>OVA11491</td>
<td>NHS</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.603)</td>
<td></td>
<td>1.04 (0.88, 1.23)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 52 Dose-response graph of whole milk and ovarian cancer

Kiani 2006

Koralek 2006

Fairfield 2004

Whole milk (g/day)
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, $I^2=24.1\%$, $p_{\text{heterogeneity}}=0.24$). There was no evidence of publication bias with Egger’s test, $p=0.64$.

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

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, $I^2=33.1\%$, $p_{\text{heterogeneity}}=0.14$) for all studies (Larsson et al, 2006) and summary RR=1.04 (95% CI: 0.60-1.81, $I^2=70.6\%$, $p_{\text{heterogeneity}}=0.03$) 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, $p_{\text{heterogeneity}}=0.74$) for $\geq$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

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

Table 58 Overall evidence on cheese and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Four cohort studies reported on cheese and ovarian cancer and found no significant associations between cheese intake and ovarian cancer risk.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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).</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1833</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.03 (0.83-1.28)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 50 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>24.1%, p=0.24</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 60 Inclusion/exclusion table for meta-analysis of cheese and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective study</td>
<td>Japan Collaborative Cohort Study</td>
<td>Mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective study</td>
<td>EPIC study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
</tr>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective study</td>
<td>Adventist Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA11662</td>
<td>Koralek</td>
<td>2006</td>
<td>Prospective study</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years</td>
</tr>
<tr>
<td>OVA09788</td>
<td>Mommers</td>
<td>2006</td>
<td>Prospective study</td>
<td>Netherlands Cohort Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA11491</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA10870</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective study</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Overlap with Fairfield et al, 2004 (OVA11491)</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
</tr>
</tbody>
</table>
Figure 53 Highest versus lowest forest plot of cheese and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>1.66 (0.65, 4.25)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>&gt;=1-2/wk vs. seldom</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>1.18 (0.77, 1.60)</td>
<td>OVA11639</td>
<td>EPIC</td>
<td>&gt;=44 vs. &lt;19 g/d</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>1.68 (0.82, 3.44)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>&gt;2/wk vs. 0-&lt;1/wk</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.87 (0.50, 1.53)</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td>5 vs. 0 serv/wk</td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>1.06 (0.54, 2.08)</td>
<td>OVA09768</td>
<td>NLCS</td>
<td>50 vs. 0 g/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>0.65 (0.43, 0.97)</td>
<td>OVA11491</td>
<td>NHS</td>
<td>&gt;=5-7/wk vs. never-3/mo</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.20 (0.90, 1.70)</td>
<td>OVA10870</td>
<td>SMC</td>
<td>&gt;=2 vs. &lt;1 serv/d</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.56 (0.85, 2.86)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;4/wk vs. &lt;1/wk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 50 g per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>day RR (95% CI)</td>
<td>Weight</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>9.52 (0.09, 998.70)</td>
<td>0.21</td>
</tr>
<tr>
<td>Schulz</td>
<td>2007</td>
<td>1.13 (0.74, 1.70)</td>
<td>18.00</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>2.82 (0.46, 17.28)</td>
<td>1.36</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.79 (0.33, 1.89)</td>
<td>5.48</td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>0.98 (0.64, 1.52)</td>
<td>16.94</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>0.61 (0.37, 1.00)</td>
<td>13.74</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.12 (0.93, 1.34)</td>
<td>39.61</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.95 (0.75, 5.04)</td>
<td>4.65</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.03 (0.83, 1.28)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
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, I²=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, I²=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, I²=11.6%, p heterogeneity=0.34) for all studies, and 0.95 (95% CI: 0.69-1.30, I²=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 (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 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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakauchi, 2007</td>
<td>Japan</td>
<td>Japan Collaborative Cohort Study</td>
<td>77</td>
<td>13.3 years</td>
<td>1.66</td>
<td>0.71</td>
<td>3.91</td>
<td>≥1-2/wk vs. seldom</td>
</tr>
<tr>
<td>Schulz, 2007</td>
<td>Europe</td>
<td>EPIC Study</td>
<td>581</td>
<td>~6.3 years</td>
<td>0.90</td>
<td>0.69</td>
<td>1.19</td>
<td>≥83 vs. &lt;6 g/d</td>
</tr>
</tbody>
</table>

Table 62 Overall evidence on yogurt and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Three cohort studies reported on yogurt and ovarian cancer and found no significant associations between yogurt intake and ovarian cancer risk.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1477</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.06 (0.91-1.24)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 200 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.55</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 64 Inclusion/exclusion table for meta-analysis of yogurt and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective</td>
<td>Japan Collaborative Cohort Study</td>
<td>Mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA11639</td>
<td>Schulz</td>
<td>2007</td>
<td>Prospective</td>
<td>EPIC study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Midpoints</td>
</tr>
<tr>
<td>OVA09788</td>
<td>Mommers</td>
<td>2006</td>
<td>Prospective</td>
<td>Netherlands Cohort Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>OVA10870</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Distribution of person-years, midpoints</td>
</tr>
<tr>
<td>OVA11491</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 57 Highest versus lowest forest plot of yogurt and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>1.66 (0.71, 3.91) OVA11661</td>
<td>JACC</td>
<td>&gt;1-2/wk vs. seldom</td>
</tr>
<tr>
<td>Schultz</td>
<td>2007</td>
<td>0.90 (0.69, 1.19) OVA11639</td>
<td>EPIC</td>
<td>&gt;=63 vs. &lt;6 g/d</td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>0.87 (0.59, 1.28) OVA09788</td>
<td>NLCS</td>
<td>139 vs. 0 g/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.26 (0.59, 2.67) OVA11491</td>
<td>NHS</td>
<td>&gt;=5-7/wk vs. never-3/mo</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.10 (0.80, 1.50) OVA10870</td>
<td>SMC</td>
<td>&gt;=2 serv/d vs. &lt;=1/wk</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 200 g per day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>4.04 (0.22, 73.62)</td>
<td>0.29</td>
<td>OVA11661</td>
<td>JACC</td>
</tr>
<tr>
<td>Schultz</td>
<td>2007</td>
<td>1.30 (0.83, 2.02)</td>
<td>12.54</td>
<td>OVA11639</td>
<td>EPIC</td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>0.78 (0.47, 1.30)</td>
<td>9.66</td>
<td>OVA09788</td>
<td>NLCS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.10 (0.85, 1.86)</td>
<td>9.01</td>
<td>OVA11491</td>
<td>NHS</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.06 (0.88, 1.28)</td>
<td>68.50</td>
<td>OVA10870</td>
<td>SMC</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.06 (0.91, 1.24)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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; $\hat{I}^2=28.8\%$, $P_{\text{heterogeneity}}=0.188$) 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 ($\hat{I}^2=28.8\%$, $p=0.188$). 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 ($\hat{I}^2=50.9\%$; $p=0.057$) (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

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

### Table 66 Overall evidence on coffee consumption and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>Two studies addressed the relationship between coffee intake and ovarian cancer risk. None of them reported significant associations</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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</td>
</tr>
</tbody>
</table>
Table 67 Summary of results of the dose response meta-analysis of coffee consumption and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Ovarian cancer</th>
<th>Ovarian cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLR*</td>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>3208</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 200ml/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.02 (0.98-1.06)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>28.8%, p=0.188</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>3159</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 200ml/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.02 (0.98-1.06)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>36.8%, p=0.135</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HV/L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11676</td>
<td>Braem</td>
<td>2012</td>
<td>Prospective Cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence EOC (borderline and invasive)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Average median intake per quintile in each participating country</td>
<td>-</td>
</tr>
<tr>
<td>OVA11693</td>
<td>Nilsson</td>
<td>2010</td>
<td>Prospective Cohort study</td>
<td>Västerbotten Intervention Project</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category and mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11633</td>
<td>Tworoger</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Nurse’s Health Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11650</td>
<td>Lueth</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Two categories of exposure (high vs. low)</td>
<td>-</td>
</tr>
<tr>
<td>OVA11659</td>
<td>Silvera,</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11648</td>
<td>Steevens,</td>
<td>2007</td>
<td>Case-cohort study</td>
<td>The Netherlands Cohort Study on Diet and Cancer</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA09965</td>
<td>Larsson</td>
<td>2005</td>
<td>Prospective Cohort study</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence invasive EOC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA09682</td>
<td>Stensvold</td>
<td>1994</td>
<td>Prospective Cohort study</td>
<td>Norway, 1977</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA11692</td>
<td>Snowdon</td>
<td>1984</td>
<td>Prospective Cohort study</td>
<td>Adventist Health Study, 1960</td>
<td>Mortality</td>
<td>New</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category and mid-exposure values. Sample size was obtained from article OVA05024</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 61 Highest versus lowest forest plot of coffee consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braem</td>
<td>2012</td>
<td>1.05 (0.75, 1.46)</td>
<td>OVA11676</td>
<td>EPIC</td>
<td>Quintile 5 vs quintile 1</td>
</tr>
<tr>
<td>Nilsson</td>
<td>2010</td>
<td>1.41 (0.53, 3.74)</td>
<td>OVA11693</td>
<td>VIP</td>
<td>&gt;=4 occ/d vs &lt;1 occ/d</td>
</tr>
<tr>
<td>Lueth</td>
<td>2008</td>
<td>1.28 (0.76, 2.16)</td>
<td>OVA11650</td>
<td>IWHS</td>
<td>&gt;=5 cups/d vs. 0 cups/d</td>
</tr>
<tr>
<td>Tworoger</td>
<td>2008</td>
<td>0.75 (0.55, 1.02)</td>
<td>OVA11633</td>
<td>NHS</td>
<td>&gt;=3 cups/d vs. None</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.02 (0.55, 1.90)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>Highest vs lowest quintile</td>
</tr>
<tr>
<td>Silvera</td>
<td>2007</td>
<td>1.62 (0.95, 2.75)</td>
<td>OVA11659</td>
<td>CNBSS</td>
<td>&gt;= 4 cups/d vs. None</td>
</tr>
<tr>
<td>Steevens</td>
<td>2007</td>
<td>1.08 (0.75, 1.57)</td>
<td>OVA11648</td>
<td>NLCS</td>
<td>&gt;=5 cups/d vs. 0&lt;1 cup/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>1.02 (0.62, 1.69)</td>
<td>OVA09965</td>
<td>SMC</td>
<td>&gt;=4 cups/d vs &lt;1 cup/d</td>
</tr>
<tr>
<td>Stensvold</td>
<td>1994</td>
<td>1.12 (0.92, 1.35)</td>
<td>OVA09682</td>
<td>Norway</td>
<td>9 cups/day vs &lt;1 cup/d</td>
</tr>
<tr>
<td>Snowdon</td>
<td>1984</td>
<td>1.20 (0.60, 2.50)</td>
<td>OVA11692</td>
<td>AHS, 1962</td>
<td>&gt;=2 cups/d vs &lt;1 cup/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 200ml per %</th>
<th>day RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braem</td>
<td>2012</td>
<td></td>
<td>1.03 (0.96, 1.10)</td>
<td>17.75</td>
<td>OVA11676</td>
</tr>
<tr>
<td>Nilsson</td>
<td>2010</td>
<td></td>
<td>1.06 (0.87, 1.30)</td>
<td>3.57</td>
<td>OVA11693</td>
</tr>
<tr>
<td>Lueth</td>
<td>2008</td>
<td></td>
<td>1.03 (0.96, 1.11)</td>
<td>17.06</td>
<td>OVA11650</td>
</tr>
<tr>
<td>Tworoger</td>
<td>2008</td>
<td></td>
<td>0.92 (0.85, 0.99)</td>
<td>16.72</td>
<td>OVA11633</td>
</tr>
<tr>
<td>Silvera</td>
<td>2007</td>
<td></td>
<td>1.09 (1.00, 1.19)</td>
<td>13.23</td>
<td>OVA11659</td>
</tr>
<tr>
<td>Steevens</td>
<td>2007</td>
<td></td>
<td>1.04 (0.97, 1.12)</td>
<td>17.41</td>
<td>OVA11648</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td></td>
<td>0.99 (0.88, 1.11)</td>
<td>9.03</td>
<td>OVA09965</td>
</tr>
<tr>
<td>Stensvold</td>
<td>1994</td>
<td></td>
<td>1.11 (0.92, 1.34)</td>
<td>3.98</td>
<td>OVA09682</td>
</tr>
<tr>
<td>Snowdon</td>
<td>1984</td>
<td></td>
<td>1.10 (0.77, 1.55)</td>
<td>1.25</td>
<td>OVA11692</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.02 (0.98, 1.06)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>
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

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

Table 70 Overall evidence on tea consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
</tbody>
</table>
Table 71 Summary of results of the dose response meta-analysis of tea consumption and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>2703</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 200 ml/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>0.96 (0.91-1.00)</td>
</tr>
<tr>
<td>Heterogeneity ($I^2$,p-value)</td>
<td>-</td>
<td>17.6%, p=0.30</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the second report
<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11676</td>
<td>Braem</td>
<td>2012</td>
<td>Prospective Cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence EOC (borderline and invasive)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Average median intake per quintile in each participating country</td>
<td></td>
</tr>
<tr>
<td>OVA11633</td>
<td>Tworoger</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Nurse’s Health Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>California Teachers Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>OVA11659</td>
<td>Silvera</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA11638</td>
<td>Gates</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Nurse’s Health Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>OVA11648</td>
<td>Steevens</td>
<td>2007</td>
<td>Case-cohort study</td>
<td>The Netherlands Cohort Study on Diet and Cancer</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td></td>
</tr>
<tr>
<td>OVA09751</td>
<td>Larsson</td>
<td>2005</td>
<td>Prospective Cohort study</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence invasive EOC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA06053</td>
<td>Zheng</td>
<td>1996</td>
<td>Prospective Cohort study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence EOC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category ml/day per category and mid-exposure values</td>
<td></td>
</tr>
</tbody>
</table>
Figure 65 Highest versus lowest forest plot of tea consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braem</td>
<td>2012</td>
<td>1.07 (0.78, 1.46)</td>
<td>OVA11676</td>
<td>EPIC</td>
<td>Quintile 5 vs quintile 1</td>
</tr>
<tr>
<td>Two Roger</td>
<td>2008</td>
<td>0.96 (0.70, 1.30)</td>
<td>OVA11633</td>
<td>NHS</td>
<td>&gt;=2 cups/d vs. &lt;=1 cup/d</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.27 (0.79, 2.06)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>Highest vs. lowest quintile</td>
</tr>
<tr>
<td>Silvera</td>
<td>2007</td>
<td>1.07 (0.64, 1.79)</td>
<td>OVA11659</td>
<td>CNBSS</td>
<td>&gt;=4 cups/d vs. none</td>
</tr>
<tr>
<td>Steeves</td>
<td>2007</td>
<td>0.65 (0.41, 1.03)</td>
<td>OVA11648</td>
<td>NLCS</td>
<td>&gt;=5 cups/d vs. 0-1 cups/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td>0.54 (0.31, 0.91)</td>
<td>OVA09751</td>
<td>SMC</td>
<td>&gt;=2 cups/d vs. never/seldom</td>
</tr>
<tr>
<td>Zheng</td>
<td>1996</td>
<td>0.98 (0.50, 1.90)</td>
<td>OVA06053</td>
<td>IWHS</td>
<td>&gt;=2 cups/d vs. never/monthly</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 200 ml/day</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braem</td>
<td>2012</td>
<td></td>
<td>15.35</td>
<td>0.99 (0.89, 1.11)</td>
<td>15.35</td>
<td>OVA11676</td>
<td>EPIC</td>
</tr>
<tr>
<td>Two Roger</td>
<td>2008</td>
<td></td>
<td>13.43</td>
<td>0.97 (0.85, 1.10)</td>
<td>13.43</td>
<td>OVA11633</td>
<td>NHS</td>
</tr>
<tr>
<td>Silvera</td>
<td>2007</td>
<td></td>
<td>19.94</td>
<td>1.01 (0.91, 1.11)</td>
<td>19.94</td>
<td>OVA11659</td>
<td>CNBSS</td>
</tr>
<tr>
<td>Steeves</td>
<td>2007</td>
<td></td>
<td>40.45</td>
<td>0.94 (0.89, 1.00)</td>
<td>40.45</td>
<td>OVA11648</td>
<td>NLCS</td>
</tr>
<tr>
<td>Larsson</td>
<td>2005</td>
<td></td>
<td>6.10</td>
<td>0.78 (0.64, 0.95)</td>
<td>6.10</td>
<td>OVA09751</td>
<td>SMC</td>
</tr>
<tr>
<td>Zheng</td>
<td>1996</td>
<td></td>
<td>4.73</td>
<td>0.98 (0.78, 1.22)</td>
<td>4.73</td>
<td>OVA06053</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.96 (0.91, 1.00)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1-squared = 17.8%, p = 0.300)
Figure 67 Funnel plot of tea consumption and ovarian cancer

Figure 68 Dose-response graph of tea and ovarian cancer
4 Food production, preservation, processing and preparation

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, $I^2=43\%$, $p_{\text{heterogeneity}}=0.18$). When the analysis was restricted to never smokers the summary RR was 1.14 (95% CI: 1.00-1.30, $I^2=0\%$, $p_{\text{heterogeneity}}=0.64$).

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

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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson, 2010</td>
<td>USA</td>
<td>Nurses’ Health Study</td>
<td>416</td>
<td>26 years</td>
<td>1.25</td>
<td>1.19</td>
<td>1.77</td>
<td>25.1 vs. 8.7 µg/d, all 25.1 vs. 8.7 µg/d, never smokers</td>
</tr>
<tr>
<td>Larsson, 2009</td>
<td>Sweden</td>
<td>Swedish Mammography Cohort study</td>
<td>368</td>
<td>17.5 years</td>
<td>0.86</td>
<td>0.63</td>
<td>1.16</td>
<td>32.5 vs. 16.9 µg/d, long-term intake ≥29.2 vs. &lt;20.5 µg/d, 10-year follow-up ≥29.2 vs. &lt;20.5 µg/d, never smokers, 10-year follow-up</td>
</tr>
<tr>
<td>Hogervorst, 2007</td>
<td>Nether-</td>
<td>Netherlands Cohort study</td>
<td>300</td>
<td>11.3 years</td>
<td>1.78</td>
<td>1.22</td>
<td>2.88</td>
<td>36.8 vs. 9.5 µg/d, all 36.8 vs. 9.5 µg/d, never smokers</td>
</tr>
</tbody>
</table>

### Table 74 Overall evidence on acrylamide and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>No cohort studies reported on dietary acrylamide and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SlR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1084</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.07 (0.94-1.21)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 10 µg/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>43%, p=0.18</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th></th>
<th>Continuous Update Project in never smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>360</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.14 (1.00-1.30)</td>
</tr>
<tr>
<td>Quantity</td>
<td>Per 10 µg/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>0%, p=0.64</td>
</tr>
</tbody>
</table>
Table 77 Inclusion/exclusion table for meta-analysis of dietary acrylamide and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11619</td>
<td>Wilson</td>
<td>2010</td>
<td>Prospective cohort</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OVA11617</td>
<td>Larsson</td>
<td>2009</td>
<td>Prospective cohort</td>
<td>Swedish Mammography Cohort</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OVA11622</td>
<td>Hogervorst</td>
<td>2007</td>
<td>Case cohort</td>
<td>Netherlands Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 69 Highest versus lowest forest plot of dietary acrylamide and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson</td>
<td>2010</td>
<td>1.25 (0.88, 1.77)</td>
<td>OVA11619</td>
<td>NHS</td>
<td>25.1 vs. 8.7 µg/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2009</td>
<td>0.86 (0.63, 1.16)</td>
<td>OVA11617</td>
<td>SMC</td>
<td>32.5 vs. 16.9 µg/d</td>
</tr>
<tr>
<td>Hogervorst</td>
<td>2007</td>
<td>1.78 (1.10, 2.88)</td>
<td>OVA11622</td>
<td>NLCS</td>
<td>36.8 vs. 9.5 µg/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 µg per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson</td>
<td>2010</td>
<td>1.17 (0.96, 1.43)</td>
<td>26.06</td>
</tr>
<tr>
<td>Larsson</td>
<td>2009</td>
<td>0.92 (0.77, 1.12)</td>
<td>27.95</td>
</tr>
<tr>
<td>Hogervorst</td>
<td>2007</td>
<td>1.11 (0.99, 1.25)</td>
<td>45.99</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.07 (0.94, 1.21)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Figure 71 Dose-response graph of acrylamide and ovarian cancer

![Graph showing dose-response relationship between dietary acrylamide and ovarian cancer.](image)

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 µg</th>
<th>RR never</th>
<th>% smokers (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson</td>
<td>2010</td>
<td>1.08</td>
<td>1.14</td>
<td>15.22</td>
<td>OVA11619</td>
<td>NHS</td>
<td></td>
</tr>
<tr>
<td>Larsson</td>
<td>2009</td>
<td>0.93</td>
<td>0.93</td>
<td>7.11</td>
<td>OVA11617</td>
<td>SMC</td>
<td></td>
</tr>
<tr>
<td>Hogervorst</td>
<td>2007</td>
<td>1.17</td>
<td>1.14</td>
<td>77.67</td>
<td>OVA11622</td>
<td>NLCS</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.14</td>
<td>1.14</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Dietary acrylamide (ug/day) range from 0 to 40)
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, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.81$) 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 ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.81$). Egger’s tests suggested no evidence of publication bias ($p = 0.94$).

Table 78 Studies on dietary fibre identified in the CUP

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LC</th>
<th>UC</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedelin, 2010</td>
<td>Sweden</td>
<td>Women’s Lifestyle and Health Study</td>
<td>163</td>
<td>16</td>
<td>0.82</td>
<td>0.50</td>
<td>1.35</td>
<td>69.3 vs. 0 g/day</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>USA</td>
<td>California Teachers Study 1995</td>
<td>280</td>
<td>8.1</td>
<td>1.24</td>
<td>0.84</td>
<td>1.84</td>
<td>Q5 vs. Q1</td>
</tr>
<tr>
<td>Silvera, 2007</td>
<td>Canada</td>
<td>Canadian National Breast Screening Study</td>
<td>264</td>
<td>16.4</td>
<td>0.77</td>
<td>0.52</td>
<td>1.14</td>
<td>&gt;24 vs. &lt;15.6 g/day</td>
</tr>
</tbody>
</table>
Table 79 Overall evidence on dietary fibre and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>One study which was identified during the SLR and found no association with ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>566</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 5g/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>0.94 (0.84 - 1.05)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>0 %, p=0.81</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 81 Inclusion/exclusion table for meta-analysis of dietary fibre intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11620</td>
<td>Hedelin</td>
<td>2010</td>
<td>Prospective Cohort study</td>
<td>Women's Lifestyle and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mean intake in g/d/MJ rescaled to g/d, mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>California Teachers Study, 1995</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Only high vs. low data</td>
</tr>
<tr>
<td>OVA11640</td>
<td>Silvera</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category and mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 73 Highest versus lowest forest plot dietary fibre intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedelin</td>
<td>2010</td>
<td>0.82 (0.50, 1.35)</td>
<td>OVA11620</td>
<td>WLHS</td>
<td>69.3 vs. 0 g/day</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.24 (0.84, 1.84)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>Q5 vs. Q1</td>
</tr>
<tr>
<td>Silvera</td>
<td>2007</td>
<td>0.77 (0.52, 1.14)</td>
<td>OVA11640</td>
<td>CNBSS</td>
<td>&gt;24 vs. &lt;15.6 g/day</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.01 (0.61, 1.68)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;23.6 vs. &lt;16.3 g/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 5 g</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedelin</td>
<td>2010</td>
<td>0.90 (0.70, 1.15)</td>
<td>18.34</td>
<td>OVA11620</td>
<td>WLHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silvera</td>
<td>2007</td>
<td>0.93 (0.81, 1.07)</td>
<td>56.91</td>
<td>OVA11640</td>
<td>CNBSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.00 (0.80, 1.24)</td>
<td>24.75</td>
<td>OVA02880</td>
<td>IWHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.94 (0.84, 1.05)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, $I^2=40.0\%$, $p_{\text{heterogeneity}}=0.14$). There was no evidence of publication bias with Egger’s test, $p=0.40$.

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

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, $I^2=54.6\%$, $p_{\text{heterogeneity}}=0.01$), however, there was a positive association among the three cohort studies, summary RR=1.47 (95% CI: 1.17-1.84, $I^2=0\%$, $p_{\text{heterogeneity}}=0.92$) (Larsson et al, 2006).

A pooled analysis of 12 cohort studies found a pooled RR=1.19 (95% CI: 1.01-1.40, $p_{\text{heterogeneity}}=0.58$) for $\geq 30$ 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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiani, 2006</td>
<td>USA</td>
<td>Adventist Health Study</td>
<td>71</td>
<td>~16 years</td>
<td>0.78</td>
<td>0.61</td>
<td>1.04</td>
<td>Per 83.7 g/wk</td>
</tr>
<tr>
<td>Koralek, 2006</td>
<td>USA</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>146</td>
<td>8.3 years</td>
<td>0.88</td>
<td>0.47</td>
<td>1.65</td>
<td>22.5 vs. 4.4 g/d</td>
</tr>
</tbody>
</table>
Table 83 Table of the overall evidence

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>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).</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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).</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1175</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.03 (0.94-1.13)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 10 g/d</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>40.0%, p=0.14</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 85 Inclusion/exclusion table of lactose and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective</td>
<td>Adventist</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>Only continuous estimates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>study</td>
<td>Health Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11662</td>
<td>Koralek</td>
<td>2006</td>
<td>Prospective</td>
<td>Breast Cancer</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>study</td>
<td>Detection Demonstration Project</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA09788</td>
<td>Mommers</td>
<td>2006</td>
<td>Prospective</td>
<td>Netherlands</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>Distribution of person-years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>study</td>
<td>Cohort Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11491</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA10870</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective</td>
<td>Swedish Mammmography Cohort</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>Continuous estimates, high vs. low comparison only for serous ovarian cancer (not total ovarian cancer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Distribution of person-years, midpoints</td>
<td></td>
</tr>
</tbody>
</table>
Figure 77 Lactose and ovarian cancer, cancer, highest vs. lowest

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.88 (0.47, 1.65)</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td>22.5 vs. 44 mg/d</td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>0.93 (0.60, 1.45)</td>
<td>OVA09788</td>
<td>NLCS</td>
<td>40 vs. 5 g/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.40 (0.98, 2.01)</td>
<td>OVA11491</td>
<td>NHS</td>
<td>26 vs. 3.2 g/d</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.60 (0.95, 2.70)</td>
<td>OVA02880</td>
<td>MHS</td>
<td>33.85 vs. 6.1 g/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 g/day</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiani</td>
<td>2006</td>
<td>0.81 (0.66, 1.03)</td>
<td>12.18</td>
<td>OVA11647</td>
<td>AHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.89 (0.64, 1.24)</td>
<td>6.48</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mommers</td>
<td>2006</td>
<td>1.00 (0.90, 1.13)</td>
<td>25.84</td>
<td>OVA09788</td>
<td>NLCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.12 (0.97, 1.28)</td>
<td>22.00</td>
<td>OVA11491</td>
<td>NHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.10 (0.90, 1.30)</td>
<td>15.84</td>
<td>OVA10870</td>
<td>SMC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.14 (0.96, 1.34)</td>
<td>17.66</td>
<td>OVA02880</td>
<td>IWHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.03 (0.94, 1.13)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(i-squared = 40.0%, p = 0.139)
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, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.44$) 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 ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.44$). 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UC1</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang, 2007</td>
<td>USA</td>
<td>California Teachers Study 1995</td>
<td>280</td>
<td>8.1</td>
<td>0.85</td>
<td>0.58</td>
<td>1.24</td>
<td>Q5 vs. Q1</td>
</tr>
<tr>
<td>Gilsing, 2011</td>
<td>The Netherlands</td>
<td>The Netherlands Cohort study</td>
<td>340</td>
<td>16.3</td>
<td>1.06</td>
<td>1.01</td>
<td>1.49</td>
<td>86.5g/day vs. &lt;61.0 g/day Per 10.3g/day intake</td>
</tr>
<tr>
<td>Blank, 2012</td>
<td>USA</td>
<td>NIH- AARP Diet and Health Study</td>
<td>695</td>
<td>9</td>
<td>1.28</td>
<td>1.01</td>
<td>1.63</td>
<td>75.7 g/day vs. 32.4g/day</td>
</tr>
</tbody>
</table>

Table 87 Overall evidence on total fat and ovarian cancer

<table>
<thead>
<tr>
<th>Study name</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>Two studies were identified during the SLR. Both studies found no association between total fat intake and ovarian cancer risk.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study name</th>
<th>Ovarian cancer meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Studies (n)</td>
<td>-</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
</tr>
<tr>
<td>NIH-AARP and pooled analysis</td>
<td>-</td>
</tr>
<tr>
<td>Studies (n)</td>
<td>-</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
**Table 89 Inclusion/exclusion table for meta-analysis of total fat intake and ovarian cancer**

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11675</td>
<td>Blank</td>
<td>2012</td>
<td>Prospective Cohort study</td>
<td>NIH- AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Percentage of kcal from fat rescaled to g/day using calorie intake per category; mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort</td>
<td>The Netherlands Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td></td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>California Teachers Study 1995</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>No intake amounts per category</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective Cohort study</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category</td>
<td></td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category and mid-exposure values</td>
<td></td>
</tr>
</tbody>
</table>
Figure 81 Highest versus lowest forest plot of total fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.28 (1.01, 1.63)</td>
<td>OVA11675</td>
<td>NIH- AARP</td>
<td>75.7 vs 32.4 g/day</td>
</tr>
<tr>
<td>Gilising</td>
<td>2011</td>
<td>1.06 (0.73, 1.49)</td>
<td>OVA11616</td>
<td>NLCS</td>
<td>86.5 vs &lt;61.0 g/day</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.85 (0.58, 1.24)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>Q5 vs Q1</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.03 (0.72, 1.45)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>83.5 vs 48.5 g/day</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.80 (0.47, 1.36)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;75.9 vs &lt;62.4 g/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 g</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR (95% CI)</td>
<td>Weight</td>
</tr>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.05 (1.00, 1.11)</td>
<td>64.63</td>
</tr>
<tr>
<td>Gilising</td>
<td>2011</td>
<td>1.01 (0.90, 1.13)</td>
<td>12.72</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.00 (0.91, 1.08)</td>
<td>19.91</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.89 (0.70, 1.14)</td>
<td>2.74</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.441)</td>
<td></td>
<td>1.03 (0.99, 1.07)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
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, \( \hat{I}^2 = 41.7 \% \), \( P_{\text{heterogeneity}} = 0.18 \)) 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 (\( \hat{I}^2 = 41.7\% \), \( P_{\text{heterogeneity}} = 0.18 \)). 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

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

### Table 91: Overall evidence on saturated fat and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1174</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 5g/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.07 (0.95 - 1.20)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>41.7 %, p=0.180</td>
</tr>
<tr>
<td>NIH-AARP and pooled analysis</td>
<td>12 cohorts</td>
<td></td>
</tr>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>2827</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 5 % energy</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.07 (0.99-1.15)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 93 Inclusion/exclusion table for meta-analysis of saturated fat intake and ovarian cancer

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

144
Figure 85 Highest versus lowest forest plot saturated fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.03 (0.71, 1.50)</td>
<td>OVA111675</td>
<td>NIH- AARP</td>
<td>25 vs 9.3 g/day</td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>1.48 (0.94, 2.34)</td>
<td>OVA111616</td>
<td>NLCS</td>
<td>37.5 vs 23.1 g/day</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.72 (0.48, 1.08)</td>
<td>OVA111654</td>
<td>CTS</td>
<td>Q5 vs Q1</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>0.91 (0.62, 1.32)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>Q5 vs Q1</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.17 (0.69, 1.97)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;27.4 vs &lt;21.6 g/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.01 (0.90, 1.12)</td>
<td>46.64</td>
<td>OVA111675</td>
<td>NIH- AARP</td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>1.18 (1.03, 1.34)</td>
<td>39.28</td>
<td>OVA111616</td>
<td>NLCS</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.00 (0.76, 1.33)</td>
<td>14.07</td>
<td>OVA02880</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.07 (0.95, 1.20)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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: 0.87-1.0) 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>The Netherlands</td>
<td>The Netherlands Cohort study</td>
<td>340</td>
<td>16.3</td>
<td>0.90</td>
<td>0.85</td>
<td>0.80</td>
<td>1.46 1.12</td>
</tr>
<tr>
<td>Blank, 2012</td>
<td>USA</td>
<td>NIH- AARP Diet and Health Study</td>
<td>695</td>
<td>9</td>
<td>1.01</td>
<td>0.63</td>
<td>1.6</td>
<td>28.6 vs. 11.6 g/day</td>
</tr>
</tbody>
</table>

Table 95 Overall evidence on monounsaturated fat and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Two studies were identified during the SLR; Kushi et al, 1999 reported a not significant protective association between monounsaturated fat intake and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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

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

*No meta-analysis was conducted in the 2nd report*
### Table 97 Inclusion/exclusion table for meta-analysis of monounsaturated fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11675</td>
<td>Blank</td>
<td>2012</td>
<td>Prospective Cohort study</td>
<td>NIH- AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Percentage of kcal from fat rescaled to g/day using calorie intake per category; mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort</td>
<td>The Netherlands Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective Cohort study</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>No intake amounts per category</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category and mid-exposure values</td>
<td></td>
</tr>
</tbody>
</table>
Figure 89 Highest versus lowest forest plot monounsaturated fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.01 (0.63, 1.60)</td>
<td>OVA11675</td>
<td>NIH- AARP</td>
<td>28.6 vs 11.6 g/day</td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.90 (0.55, 1.46)</td>
<td>OVA11616</td>
<td>NLCS</td>
<td>33.5 vs 21.7 g/day</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.07 (0.75, 1.52)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>Q5 vs Q1</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.65 (0.38, 1.13)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;28.6 vs &lt;22.7 g/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 5 g</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.00 (0.88, 1.13)</td>
<td>56.65</td>
<td>OVA11675</td>
<td>NIH- AARP</td>
<td></td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.94 (0.80, 1.12)</td>
<td>31.78</td>
<td>OVA11616</td>
<td>NLCS</td>
<td></td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.88 (0.67, 1.17)</td>
<td>11.57</td>
<td>OVA02880</td>
<td>IWHS</td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.694)</td>
<td></td>
<td>0.97 (0.88, 1.06)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, $I^2 = 73.2 \%$, $P_{\text{heterogeneity}} = 0.02$) 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 ($I^2 = 73.2\%$, $P_{\text{heterogeneity}}= 0.02$). 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LC1</th>
<th>UC1</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>The Netherlands</td>
<td>The Netherlands Cohort study</td>
<td>340</td>
<td>16.3</td>
<td>0.89</td>
<td>0.47</td>
<td>1.01</td>
<td>23.2g/day vs. 8 g/day Per 6.1g/day intake</td>
</tr>
<tr>
<td>Blank, 2012</td>
<td>USA</td>
<td>NIH- AARP Diet and Health Study</td>
<td>695</td>
<td>9</td>
<td>1.28</td>
<td>0.92</td>
<td>1.77</td>
<td>19.3 g/day vs. 7.3 g/day</td>
</tr>
</tbody>
</table>

Table 99 Overall evidence on polyunsaturated fat and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Two studies were identified during the SLR; none of them reported significant associations</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Two cohort studies were identified. No study reported significant associations. Overall, three studies were included in the meta-analysis.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
<tr>
<td>NIH-AARP and pooled analysis</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 101 Inclusion/exclusion table for meta-analysis of polyunsaturated fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11675</td>
<td>Blank</td>
<td>2012</td>
<td>Prospective Cohort study</td>
<td>NIH- AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Percentage of kcal from fat rescaled to g/day using calorie intake per category; mid-exposure values</td>
</tr>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort study</td>
<td>The Netherlands Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective Cohort study</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category and mid-exposure values</td>
<td></td>
</tr>
</tbody>
</table>
Figure 93 Highest versus lowest forest plot polyunsaturated fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.28 (0.92, 1.77)</td>
<td>OVA11675</td>
<td>NIH-AARP</td>
<td>19.3g vs 7.3g</td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.69 (0.47, 1.01)</td>
<td>OVA11616</td>
<td>NLCS</td>
<td>23.2g vs 8g</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>1.14 (0.79, 1.63)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>Q5 vs Q1</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.63 (0.38, 1.03)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>15.3g vs 9.6g</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.11 (0.98, 1.26)</td>
<td>41.72</td>
<td>OVA11675</td>
<td>NIH-AARP</td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.92 (0.82, 1.02)</td>
<td>43.73</td>
<td>OVA11616</td>
<td>NLCS</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.73 (0.48, 1.10)</td>
<td>14.54</td>
<td>OVA02880</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall (I-squared = 73.2%, p = 0.024)</td>
<td></td>
<td>0.96 (0.80, 1.16)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 95 Funnel plot of polyunsaturated fat intake and ovarian cancer

![Funnel plot with pseudo 95% confidence limits](image)

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

![Dose-response graph](image)
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, 2012) were combined with the results of a pooled analysis of 4 cohorts (Genkinger et 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>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank, 2012</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>695</td>
<td>9</td>
<td>1.19</td>
<td>0.94</td>
<td>1.50</td>
<td>Q4 vs Q1 (% kcal from total energy)</td>
</tr>
<tr>
<td>Gilsing, 2011</td>
<td>The Netherlands</td>
<td>The Netherlands Cohort study</td>
<td>340</td>
<td>16.3</td>
<td>1.51</td>
<td>1.04</td>
<td>2.20</td>
<td>3.5 vs 1.5 g/day Per 0.1 g/day intake</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>One cohort study reported no association.</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11675</td>
<td>Blank</td>
<td>2012</td>
<td>Prospective Cohort study</td>
<td>NIH- AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Only highest vs lowest comparison</td>
</tr>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort</td>
<td>The Netherlands Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective Cohort study</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
<td>No exposure level reported</td>
</tr>
</tbody>
</table>
Figure 97 Highest versus lowest forest plot of trans-unsaturated fatty acids intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>High vs. low RR (95% CI)</th>
<th>Study</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genkinger, 2006</td>
<td>1.04 (0.84, 1.28)</td>
<td>Pooled analysis, 4 cohorts</td>
<td>Q4 vs Q1 % energy</td>
</tr>
<tr>
<td>Gilsing, 2011</td>
<td>1.51 (1.04, 2.20)</td>
<td>NLCS</td>
<td>Q5 vs Q1 g/day</td>
</tr>
<tr>
<td>Blank, 2012</td>
<td>1.19 (0.94, 1.50)</td>
<td>NIH-AARP</td>
<td>Q5 vs Q1 % energy</td>
</tr>
</tbody>
</table>
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, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.88$) 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 ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.88$). 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>The Netherlands</td>
<td>The Netherlands Cohort study</td>
<td>340</td>
<td>16.3</td>
<td>1.301.01</td>
<td>0.93</td>
<td>1.83</td>
<td>56.6/day vs. &lt;23.9 g/day Per 10.3g/day intake</td>
</tr>
<tr>
<td>Blank, 2012</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>695</td>
<td>9</td>
<td>1.30</td>
<td>1.02</td>
<td>1.66</td>
<td>22 vs. 7.9 % of energy from fat</td>
</tr>
</tbody>
</table>
### Table 106 Overall evidence on animal fat and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLR</strong> Two large US Cohort studies (Bertone et al, 2002 –NHS-, Kushi et al, 1999 –IOWA-) did not find any association</td>
</tr>
<tr>
<td><strong>Continuous Update Project</strong> 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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1174</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 5 g/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.03 (1.01 - 1.05)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>0 %, p=0.69</td>
</tr>
<tr>
<td>NIH-AARP and published pooled analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies (n)</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Cases (n)</td>
<td></td>
<td>2120</td>
</tr>
<tr>
<td>Increment unit used</td>
<td></td>
<td>Per 5 % energy</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td></td>
<td>1.04 (1.03-1.06)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 108 Inclusion/exclusion table for meta-analysis of animal fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11675</td>
<td>Blank</td>
<td>2012</td>
<td>Prospective</td>
<td>NIH- AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Percentage of kcal from animal fat rescaled to g/day using calorie intake per category; mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort</td>
<td>The Netherlands Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td></td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>No intake levels</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category and mid-exposure values</td>
<td></td>
</tr>
</tbody>
</table>
Figure 98 Highest versus lowest forest plot of animal fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.30 (1.02, 1.66)</td>
<td>OVA11675</td>
<td>NIH-AARP</td>
<td>22 vs 7.9 kcal from energy</td>
</tr>
<tr>
<td>Gilson</td>
<td>2011</td>
<td>1.30 (0.94, 1.83)</td>
<td>OVA11616</td>
<td>NLCS</td>
<td>56.6 vs 23.9 g/day</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>0.95 (0.66, 1.38)</td>
<td>OVA00454</td>
<td>NHS</td>
<td>Q4 vs Q1</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.98 (0.57, 1.69)</td>
<td>OVA02880</td>
<td>IOWA</td>
<td>&gt;45.8 vs &lt;32.6 g/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 5 g</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.03 (1.00, 1.06)</td>
<td>55.25</td>
<td>OVA11675</td>
<td>NIH-AARP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilson</td>
<td>2011</td>
<td>1.04 (1.00, 1.09)</td>
<td>25.26</td>
<td>OVA11616</td>
<td>NLCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.02 (0.97, 1.07)</td>
<td>19.49</td>
<td>OVA02880</td>
<td>IWHS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall (I-squared = 0.0%, p = 0.843) | 1.03 (1.01, 1.05) | 100.00 |
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, I² = 0%, $P_{\text{heterogeneity}} = 0.49$) 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 ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.51$). 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Studies</th>
<th>Follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilsing, 2011</td>
<td>The Netherlands</td>
<td>The Netherlands Cohort study</td>
<td>340</td>
<td>16.3</td>
<td>0.64</td>
<td>0.93</td>
<td>0.45</td>
<td>1.07</td>
<td>15.9/day vs. &lt;2.8 g/day Per 6.8 g/day intake</td>
</tr>
<tr>
<td>Blank, 2012</td>
<td>USA</td>
<td>NIH- AARP Diet and Health Study</td>
<td>695</td>
<td>9</td>
<td>1.00</td>
<td>1.02</td>
<td>0.79</td>
<td>1.27</td>
<td>&gt;19.4 vs. &lt;6.4 of energy from fat Per 5% energy increase</td>
</tr>
</tbody>
</table>

Table 110 Overall evidence on vegetable fat and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>None of the two large US cohort studies identified (Bertone et al, 2002 – NHS-, Kushi et al, 1999 –IOWA-) found any association</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
</tr>
<tr>
<td>NIH-AARP and published pooled analysis</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 112 Inclusion/exclusion table for meta-analysis of vegetable fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11675</td>
<td>Blank</td>
<td>2012</td>
<td>Prospective</td>
<td>NIH- AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Percentage of kcal from vegetable fat rescaled to g/day using calorie intake per category; mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11616</td>
<td>Gilsing</td>
<td>2011</td>
<td>Case-Cohort</td>
<td>The Netherlands Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
<tr>
<td>OVA00454</td>
<td>Bertone</td>
<td>2002</td>
<td>Prospective</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>No intake levels</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category and mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 102 Highest versus lowest forest plot of vegetable fat intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.00 (0.79, 1.27)</td>
<td>OVA11675</td>
<td>NIH- AARP</td>
<td>&gt;19.5 vs &lt;6.4 % energy</td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.64 (0.45, 0.91)</td>
<td>OVA11616</td>
<td>NLCS</td>
<td>&gt;15.6 vs &lt;2.8 g/d</td>
</tr>
<tr>
<td>Bertone</td>
<td>2002</td>
<td>0.98 (0.68, 1.43)</td>
<td>OVA0454</td>
<td>NHS</td>
<td>QS vs Q1</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.75 (0.44, 1.27)</td>
<td>OVA02880</td>
<td>IOWA</td>
<td>&gt;37.6 vs &lt;23.2 g/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blank</td>
<td>2012</td>
<td>1.00 (0.79, 1.27)</td>
<td>77.59</td>
<td>OVA11675</td>
<td>NIH- AARP</td>
</tr>
<tr>
<td>Gilsing</td>
<td>2011</td>
<td>0.93 (0.81, 1.07)</td>
<td>3.80</td>
<td>OVA11616</td>
<td>NLCS</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.98 (0.92, 1.04)</td>
<td>18.61</td>
<td>OVA02880</td>
<td>IOWA</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.00 (0.97, 1.02)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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; \( I^2 = 7.0 \%), P_{\text{heterogeneity}}=0.37 \) 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass, 2011</td>
<td>Japan</td>
<td>Japan Public Health Center-based Prospective Study</td>
<td>86</td>
<td>7.6</td>
<td>1.0</td>
<td>1.0</td>
<td>0.50</td>
<td>Yes vs. No Per grams per week</td>
</tr>
<tr>
<td>Yang, 2011</td>
<td>United States</td>
<td>National Health Institute-American Association of Retired Persons</td>
<td>849</td>
<td>9.8</td>
<td>0.93</td>
<td>0.67</td>
<td>1.30</td>
<td>&gt;=24 g/d vs 0 g/d</td>
</tr>
<tr>
<td>Allen, 2009</td>
<td>United Kingdom</td>
<td>Million Women Study</td>
<td>846</td>
<td>7.2</td>
<td>0.94</td>
<td>0.81</td>
<td>1.09</td>
<td>&gt;=15 drinks/week vs. never and former drinkers</td>
</tr>
<tr>
<td>Kabat, 2008</td>
<td>Canada</td>
<td>Canadian National Breast Cancer Screening Study</td>
<td>264</td>
<td>16.4</td>
<td>1.23</td>
<td>0.74</td>
<td>2.04</td>
<td>&gt;=30 g/d vs. 0 g/d</td>
</tr>
<tr>
<td>Tworoger, 2008</td>
<td>United States</td>
<td>Nurses’ Health Study</td>
<td>507</td>
<td>24</td>
<td>0.99</td>
<td>0.72</td>
<td>1.36</td>
<td>&gt;=15 g/d vs. &lt;0.1 g/d</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>United States</td>
<td>California Teacher Study</td>
<td>253</td>
<td>8.1</td>
<td>1.15</td>
<td>0.71</td>
<td>1.84</td>
<td>&gt;=20 g/d vs. 0 g/d</td>
</tr>
<tr>
<td>Sakauchi, 2007</td>
<td>Japan</td>
<td>Japan Collaborative Cohort (JACC) Study</td>
<td>77</td>
<td>~14</td>
<td>0.65</td>
<td>0.35</td>
<td>1.23</td>
<td>Yes vs. No</td>
</tr>
<tr>
<td>Navarro-Silveira, 2006</td>
<td>Canada</td>
<td>Canadian National Breast Cancer Screening Study</td>
<td>264</td>
<td>16.4</td>
<td>1.10</td>
<td>0.74</td>
<td>1.65</td>
<td>&gt;10 g/day versus non-drinkers</td>
</tr>
</tbody>
</table>
Table 114 Overall evidence on alcohol consumption and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>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).</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>413</td>
<td>2954</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>Per 30 g/day</td>
<td>Per 10g/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>0.95 (0.87-1.03)</td>
<td>1.01 (0.96-1.06)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>45.9%</td>
<td>7.0%, p=0.37</td>
</tr>
<tr>
<td>Pooling project and 4 cohorts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCRF_Code</td>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>OVA11669</td>
<td>Weiderpass</td>
<td>2011</td>
</tr>
<tr>
<td>OVA11672</td>
<td>Yang</td>
<td>2011</td>
</tr>
<tr>
<td>OVA11667</td>
<td>Allen</td>
<td>2009</td>
</tr>
<tr>
<td>OVA11681</td>
<td>Kabat</td>
<td>2008</td>
</tr>
<tr>
<td>OVA11633</td>
<td>Tworoger</td>
<td>2008</td>
</tr>
<tr>
<td>OVA11626</td>
<td>Chang</td>
<td>2007</td>
</tr>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
</tr>
<tr>
<td>OVA11624</td>
<td>Navarro-Silva</td>
<td>2006</td>
</tr>
<tr>
<td>OVA10451</td>
<td>Kelemen</td>
<td>2004</td>
</tr>
<tr>
<td>OVA09696</td>
<td>Larsson</td>
<td>2004</td>
</tr>
<tr>
<td>OVA09692</td>
<td>Schouten</td>
<td>2004</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
</tr>
</tbody>
</table>
### Figure 106 Highest versus lowest forest plot of alcohol consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twohoger</td>
<td>2008</td>
<td>0.99 (0.72, 1.36)</td>
<td>OVA11633</td>
<td>NHS</td>
<td>&gt;=15 g/d vs. &lt;0.1 g/d</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>0.65 (0.35, 1.23)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>Yes vs. No</td>
</tr>
<tr>
<td>Weiderpass</td>
<td>2011</td>
<td>1.00 (0.50, 1.80)</td>
<td>OVA11669</td>
<td>JPHC</td>
<td>Yes vs. No</td>
</tr>
<tr>
<td>Yang</td>
<td>2011</td>
<td>0.93 (0.67, 1.30)</td>
<td>OVA11672</td>
<td>NIH- AARP</td>
<td>&gt;=24 g/d vs 0 g/d</td>
</tr>
<tr>
<td>Allen</td>
<td>2009</td>
<td>0.94 (0.81, 1.09)</td>
<td>OVA11667</td>
<td>MWS</td>
<td>&gt;=15 g/week vs. &lt;0 g/week</td>
</tr>
<tr>
<td>Kabat</td>
<td>2008</td>
<td>1.23 (0.74, 2.04)</td>
<td>OVA11681</td>
<td>CNBSS</td>
<td>&gt;=30 g/d vs 0 g/d</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.15 (0.71, 1.84)</td>
<td>OVA11626</td>
<td>CTS</td>
<td>&gt;=20 g/d vs 0 g/d</td>
</tr>
<tr>
<td>Schouten</td>
<td>2004</td>
<td>0.92 (0.55, 1.54)</td>
<td>OVA09692</td>
<td>NCS</td>
<td>&gt;= 15 vs. 0 g/d</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.24 (0.84, 1.81)</td>
<td>OVA09696</td>
<td>SMC</td>
<td>&gt;=27.3 g/week vs 0-7 g/week</td>
</tr>
<tr>
<td>Kelemen</td>
<td>2004</td>
<td>0.58 (0.30, 1.11)</td>
<td>OVA10451</td>
<td>JPHC</td>
<td>&gt;=10 g/d vs &lt;0.01 g/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 g per day RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass</td>
<td>2011</td>
<td>1.00 (0.49, 1.00)</td>
<td>1.87</td>
</tr>
<tr>
<td>Yang</td>
<td>2011</td>
<td>1.03 (0.93, 1.13)</td>
<td>23.45</td>
</tr>
<tr>
<td>Allen</td>
<td>2009</td>
<td>0.99 (0.93, 1.05)</td>
<td>46.08</td>
</tr>
<tr>
<td>Twohoger</td>
<td>2008</td>
<td>0.98 (0.85, 1.13)</td>
<td>11.10</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.12 (0.96, 1.31)</td>
<td>9.18</td>
</tr>
<tr>
<td>Kelemen</td>
<td>2004</td>
<td>0.69 (0.43, 1.10)</td>
<td>1.09</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>2.05 (0.86, 4.86)</td>
<td>0.32</td>
</tr>
<tr>
<td>Schouten</td>
<td>2004</td>
<td>1.01 (0.84, 1.21)</td>
<td>6.90</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.01 (0.96, 1.06)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Author</th>
<th>g/day RR (95% CI)</th>
<th>Weight</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass, 2011</td>
<td>1.00 (0.49, 1.78)</td>
<td>0.34</td>
<td>JPHC</td>
</tr>
<tr>
<td>Yang, 2011</td>
<td>1.03 (0.93, 1.13)</td>
<td>14.99</td>
<td>NIH-AARP</td>
</tr>
<tr>
<td>Allen, 2009</td>
<td>0.99 (0.93, 1.05)</td>
<td>38.60</td>
<td>MHS</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>1.12 (0.96, 1.31)</td>
<td>5.88</td>
<td>CTS</td>
</tr>
<tr>
<td>Genginker, 2006</td>
<td>1.00 (0.95, 1.07)</td>
<td>40.18</td>
<td>Pooling 10 cohorts</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.670)</td>
<td>1.01 (0.97, 1.05)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>
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; $I^2=63.0\%$, $P_{\text{heterogeneity}}=0.06$) 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tworoger, 2008</td>
<td>United States</td>
<td>Nurses’ Health Study</td>
<td>507</td>
<td>24</td>
<td>0.86</td>
<td>0.44</td>
<td>1.68</td>
<td>&gt;=1 drink/d vs. non drinkers</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>United States</td>
<td>California Teacher Study</td>
<td>253</td>
<td>8.1</td>
<td>0.54</td>
<td>0.17</td>
<td>1.70</td>
<td>&gt;=13.1 g/d vs. non drinkers</td>
</tr>
</tbody>
</table>

Table 118 Overall evidence on beer consumption and ovarian cancer

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

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
<tr>
<td>Pooling project and CTS</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
</tbody>
</table>

| Continuous Update Project                                                           |
| Studies (n)                                                                          |
| Cases (n)                                                                            |
| Increment unit used                                                                 |
| Overall RR (95%CI)                                                                  |

*No meta-analysis was conducted in the 2nd report
<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11633</td>
<td>Tworoger</td>
<td>2008</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11626</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort Study</td>
<td>California Teacher Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA010867</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Swedish Mammography Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases per category estimation mid-exposure values and person/years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA09692</td>
<td>Schouten</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Netherland Cohort Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Only two categories</td>
</tr>
</tbody>
</table>
Figure 111 Highest versus lowest forest plot of beer consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tworoger</td>
<td>2008</td>
<td>0.86 (0.44, 1.68)</td>
<td>OVA11633</td>
<td>NHS</td>
<td>&gt;= 1 drink/d vs non drinkers</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.54 (0.17, 1.70)</td>
<td>OVA11626</td>
<td>CTS</td>
<td>&gt;=13.2 g/d vs non drinkers</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>1.35 (1.00, 1.81)</td>
<td>OVA10867</td>
<td>SMC</td>
<td>&gt;=1 glass/wk vs non drinkers</td>
</tr>
<tr>
<td>Schouten</td>
<td>2004</td>
<td>0.91 (0.52, 1.58)</td>
<td>OVA09692</td>
<td>NCS</td>
<td>Yes vs. no</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 g per</th>
<th>%</th>
<th>day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tworoger</td>
<td>2008</td>
<td></td>
<td></td>
<td>0.96 (0.73, 1.28)</td>
<td>47.96</td>
<td>OVA11633</td>
<td>NHS</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td></td>
<td></td>
<td>0.69 (0.37, 1.27)</td>
<td>33.14</td>
<td>OVA11626</td>
<td>CTS</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td></td>
<td></td>
<td>2.95 (1.03, 8.46)</td>
<td>18.90</td>
<td>OVA10867</td>
<td>SMC</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td>1.06 (0.60, 1.88)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 113 Funnel plot of beer consumption and ovarian cancer

Funnel plot with pseudo 95% confidence limits

Figure 114 Dose-response graph of beer and ovarian cancer

Beer (g/day)
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: 0.88-1.29; I²= 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 (I²= 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; I²=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; I²=95%) and 1.04 (95% CI, 0.88 to 1.22; I²=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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tworoger, 2008</td>
<td>United States</td>
<td>Nurses’ Health Study</td>
<td>507</td>
<td>24</td>
<td>0.85</td>
<td>0.56</td>
<td>1.26</td>
<td>&gt;=1 drink/d vs. non drinkers</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>United States</td>
<td>California Teacher Study</td>
<td>253</td>
<td>8.1</td>
<td>1.57</td>
<td>1.11</td>
<td>1.22</td>
<td>&gt;=11.1 g/d vs. non drinkers</td>
</tr>
</tbody>
</table>

Table 122 Overall evidence on wine consumption and ovarian cancer

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

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
<tr>
<td>Pooling project and CTS</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11633</td>
<td>Tworoger</td>
<td>2008</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11626</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort Study</td>
<td>California Teacher Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA010867</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Swedish Mammography Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases per category estimation mid-exposure values person/years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA09692</td>
<td>Schouten</td>
<td>2004</td>
<td>Case-Cohort Study</td>
<td>Netherland Cohort Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Rescale of RR for continuous increase</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 115 Highest versus lowest forest plot of wine consumption and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tworoger</td>
<td>2008</td>
<td>0.85 (0.56, 1.27)</td>
<td>OVA11633</td>
<td>NHS</td>
<td>&gt;= 1 drink/ d vs non drinkers</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.57 (1.11, 2.22)</td>
<td>OVA11626</td>
<td>CTS</td>
<td>&gt;=11.1 g/d vs non drinkers</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.98 (0.65, 1.47)</td>
<td>OVA10867</td>
<td>SMC</td>
<td>&gt;=1 glass/wk vs non drinkers</td>
</tr>
<tr>
<td>Schouten</td>
<td>2004</td>
<td>1.01 (0.57, 1.75)</td>
<td>OVA09692</td>
<td>NCS</td>
<td>24.5 g/d vs non drinkers</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 g per</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tworoger</td>
<td>2008</td>
<td>0.93 (0.73, 1.17)</td>
<td>28.52</td>
<td>OVA11633</td>
<td>NHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.51 (1.11, 2.06)</td>
<td>21.63</td>
<td>OVA11626</td>
<td>CTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.92 (0.16, 5.41)</td>
<td>1.14</td>
<td>OVA10867</td>
<td>SMC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schouten</td>
<td>2004</td>
<td>1.00 (0.97, 1.02)</td>
<td>48.71</td>
<td>OVA09692</td>
<td>NCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 59.1%, p = 0.062)</td>
<td></td>
<td>1.07 (0.88, 1.29)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, I² = 0%, Pheterogeneity = 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 (I² = 0%, Pheterogeneity = 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

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

Table 126 Overall evidence on dietary vitamin A and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>Two studies were identified during the SLR; both studies found no association between dietary vitamin A intake and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>
Table 127 Summary of results of the dose response meta-analysis of dietary vitamin A intake and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>704</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 2000 IU/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>0.99 (0.95 - 1.03)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>0 %, p=0.5</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women's Health Initiative</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Different units</td>
</tr>
<tr>
<td>OVA11645</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort study</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category, 95% confidence intervals</td>
<td>-</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category, mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
### Figure 119 Highest versus lowest forest plot of dietary vitamin A intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>0.91 (0.62, 1.32)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;=926 vs. &lt;486 µg RAE/day</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.77 (0.52, 1.14)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td>&gt;11534 vs. &lt;6589 IU/day</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.96 (0.60, 1.53)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>17940 vs. 4993 IU/day</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.11 (0.65, 1.88)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;18218 vs. &lt;8894 IU/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.95 (0.68, 1.32)</td>
<td>14.72</td>
<td>OVA11645</td>
<td>CNBSS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.98 (0.93, 1.03)</td>
<td>56.27</td>
<td>OVA01437</td>
<td>NHS</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.02 (0.95, 1.09)</td>
<td>29.01</td>
<td>OVA02880</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.99 (0.95, 1.03)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.94$) 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 ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.94$). 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 ($P_{\text{heterogeneity}} = 0.23$) (Koushik et al, 2006). The association was not modified by histological 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>USA</td>
<td>Women's Health Initiative</td>
<td>352</td>
<td>8.3</td>
<td>1.06</td>
<td>0.77</td>
<td>1.48</td>
<td>&gt;=885 vs. &lt;335µg/day</td>
</tr>
<tr>
<td>Silvera, 2006</td>
<td>Canada</td>
<td>Canadian National Breast Screening Study</td>
<td>264</td>
<td>16.4</td>
<td>0.94</td>
<td>0.64</td>
<td>1.38</td>
<td>&gt;15500 vs. 0 µg/day</td>
</tr>
</tbody>
</table>
Table 130 Overall evidence on dietary alpha-carotene and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>One study was identified during the SLR; no association was reported between dietary |</td>
</tr>
<tr>
<td>â€”carotene intake and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Two cohort studies were identified. No associations were reported between â€”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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
<tr>
<td>Pooling project and WHI study</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women's Health Initiative</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA11645</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort study</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category, 95% confidence intervals</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 123 Highest versus lowest forest plot of dietary alpha-carotene intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.06 (0.77, 1.48)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;=885 vs. &lt;335 µg/day</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.94 (0.64, 1.38)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td>&gt;15500 vs. 0 µg/day</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.94 (0.66, 1.35)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>1519 vs. 197 µg/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 600 µg</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.04 (0.83, 1.29)</td>
<td>0.40</td>
<td>OVA11660</td>
<td>WHI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.00 (0.98, 1.01)</td>
<td>98.68</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.99 (0.86, 1.15)</td>
<td>0.92</td>
<td>OVA01437</td>
<td>NHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.00 (0.98, 1.01)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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; I²= 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 (I²= 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>United States</td>
<td>Women’s Health Initiative</td>
<td>352</td>
<td>7</td>
<td>1.30</td>
<td>0.94</td>
<td>1.80</td>
<td>&gt;=7605µg/d vs &lt;2331µg/d</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>United States</td>
<td>California Teacher Study</td>
<td>280</td>
<td>8.1</td>
<td>1.41</td>
<td>0.85</td>
<td>2.33</td>
<td>&gt;4601µg/d vs &lt;=1409µg/d</td>
</tr>
</tbody>
</table>
Table 134 Overall evidence on total beta-carotene intake and ovarian cancer

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

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>933</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Per 1000 µg/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>1.02 (0.99-1.05)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>6.1%, p=0.34</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HV/L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women's Health Initiative</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category</td>
<td>Mid-exposure values</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort Study</td>
<td>California Teacher Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category</td>
<td></td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases per category</td>
<td>Confidence interval re-estimation</td>
</tr>
</tbody>
</table>

Table 136 Inclusion/exclusion table for meta-analysis of total beta-carotene intake and ovarian cancer
Figure 127 Highest versus lowest forest plot of total beta-carotene intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.30 (0.94, 1.80)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;=7605µg/d vs &lt;2331 µg/d</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.41 (0.85, 2.33)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>&gt;4601 µg/d vs &lt;=1409 µg/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.07 (0.74, 1.55)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>7639 µg/d vs 1622 µg/d</td>
</tr>
</tbody>
</table>

Overall  (I-squared = 6.1%, p = 0.345)

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.03 (0.99, 1.07)</td>
<td>50.29</td>
<td>OVA11660</td>
<td>WHI</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.04 (0.98, 1.10)</td>
<td>23.97</td>
<td>OVA11654</td>
<td>CTS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.99 (0.94, 1.04)</td>
<td>23.97</td>
<td>OVA01437</td>
<td>NHS</td>
</tr>
<tr>
<td>Overall (I-squared = 6.1%, p = 0.345)</td>
<td>1.02 (0.99, 1.05)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

200
Figure 129 Funnel plot of total beta-carotene intake and ovarian cancer

Funnel plot with pseudo 95% confidence limits

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, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.996$) 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 ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.996$). 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 ($P_{\text{heterogeneity}} = 0.43$) (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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>USA</td>
<td>Women's Health Initiative</td>
<td>352</td>
<td>8.3</td>
<td>1.02</td>
<td>0.74</td>
<td>1.41</td>
<td>$&gt;=4122$ vs. $&lt;1750\mu g/day$</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>USA</td>
<td>California Teachers Study, 1995</td>
<td>280</td>
<td>8.1</td>
<td>1.78</td>
<td>0.83</td>
<td>3.80</td>
<td>Highest vs. lowest</td>
</tr>
<tr>
<td>Silvera, 2006</td>
<td>Canada</td>
<td>Canadian National Breast Screening Study</td>
<td>264</td>
<td>16.4</td>
<td>0.97</td>
<td>0.66</td>
<td>1.43</td>
<td>$&gt;7000$ vs. $0\mu g/day$</td>
</tr>
</tbody>
</table>
Summary of evidence

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

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

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1056</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 2500µg/day</td>
</tr>
<tr>
<td>Overall RR (95% CI)</td>
<td>-</td>
<td>0.99 (0.92 - 1.07)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>0 %, p=0.996</td>
</tr>
</tbody>
</table>

Pooling project and WHI study

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Cases (n)</td>
<td></td>
<td>2364</td>
</tr>
<tr>
<td>Increment unit used</td>
<td></td>
<td>Per 2500 µg/day</td>
</tr>
<tr>
<td>Overall RR (95% CI)</td>
<td></td>
<td>0.98 (0.93-1.03)</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women's Health Initiative</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>California Teachers Study 1995</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Only high vs. low data</td>
</tr>
<tr>
<td>OVA11645</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort study</td>
<td>Nurses' Health Study (NHS) Cohort 1976-1996</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category, 95% confidence intervals</td>
<td>-</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category, intake in IU/day rescaled to µg/day, mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 131 Highest versus lowest forest plot of dietary beta-carotene intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.02 (0.74, 1.41)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;=4122 vs. &lt;1750 µg/day</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.78 (0.83, 3.80)</td>
<td>OVA11654</td>
<td>CTS</td>
<td></td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.97 (0.66, 1.43)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td>&gt;7000 vs. 0 µg/day</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.07 (0.74, 1.55)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>7639 vs. 1622 µg/day</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.91 (0.53, 1.55)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;7247 vs. &lt;3301 µg/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.01 (0.82, 1.26)</td>
<td>12.86</td>
<td>OVA11660</td>
<td>WHI</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.99 (0.86, 1.15)</td>
<td>28.82</td>
<td>OVA11645</td>
<td>CNBSS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.99 (0.88, 1.11)</td>
<td>45.29</td>
<td>OVA01437</td>
<td>NHS</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.98 (0.79, 1.21)</td>
<td>13.03</td>
<td>OVA02880</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.99 (0.92, 1.07)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 133 Funnel plot of dietary beta-carotene intake and ovarian cancer

![Funnel plot with pseudo 95% confidence limits](image)

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

![Dose-response graph](image)

dietary beta-carotene (µg/day)
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-cryptoxanthin 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>United States</td>
<td>Women’s Health Initiative</td>
<td>352</td>
<td>7</td>
<td>1.02</td>
<td>0.74</td>
<td>1.41</td>
<td>&gt;=196 µg/day vs &lt;78 µg/day</td>
</tr>
<tr>
<td>Silvera, 2006</td>
<td>Canada</td>
<td>Canadian National Breast Cancer Study</td>
<td>264</td>
<td>8.1</td>
<td>1.01</td>
<td>0.67</td>
<td>1.55</td>
<td>&gt;143 µg/day vs 0 µg/day</td>
</tr>
</tbody>
</table>
Table 142 Overall evidence on dietary beta-cryptoxanthin intake and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>One prospective cohort study (Nurses' Health Study, Fairfield et al., 2001) suggested no association between dietary beta-cryptoxanthin intake and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>917</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 100 µg /day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.02 (0.90-1.15)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.99</td>
</tr>
<tr>
<td>Pooling project and WHI study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies (n)</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Cases (n)</td>
<td></td>
<td>2364</td>
</tr>
<tr>
<td>Increment unit used</td>
<td></td>
<td>Per 100 µg /day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td></td>
<td>0.99 (0.96-1.02)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 144 Inclusion/exclusion table for meta-analysis of dietary beta-carotene intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HVL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women's Health Initiative</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Canadian National Breast Cancer Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases per category Confidence interval re-estimation Person/ years per category</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 135 Highest versus lowest forest plot of dietary beta-cryptoxanthin intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.02 (0.74, 1.41)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;= 196 μg/day vs &lt;78 μg/day</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.01 (0.67, 1.51)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td>&gt;143 μg/day vs 0 μg/day</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.05 (0.72, 1.52)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>&gt;166 μg/day vs 11 μg/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 100μg per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.02 (0.86, 1.21)</td>
<td>48.28</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.01 (0.78, 1.30)</td>
<td>21.20</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.02 (0.82, 1.27)</td>
<td>30.51</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.995)</td>
<td></td>
<td>1.02 (0.90, 1.15)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Figure 137 Funnel plot of dietary beta-cryptoxanthin intake and ovarian cancer

![Funnel plot with pseudo 95% confidence limits](image)

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

![Dose-response graph](image)
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; I²= 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 (I²= 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

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

Table 146 Overall evidence on dietary lycopene intake and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>One prospective cohort study (Nurses' Health Study, Fairfield et al., 2001) suggested no association between dietary lycopene intake and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Study, year</td>
</tr>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Heterogeneity (I^2,p-value)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Pooling project and WHI study</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>-</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 148 Inclusion/exclusion table for meta-analysis of dietary lycopene intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-responsive meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women's Health Initiative</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td>Mid-exposure values</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Canadian National Breast Cancer Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases per category</td>
<td>Confidence interval re-estimation Person/ years per category</td>
</tr>
</tbody>
</table>
**Figure 139** Highest versus lowest forest plot of dietary lycopene intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>Study Description</th>
<th>WCRF_Code</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.02 (0.73, 1.43)</td>
<td>WHI</td>
<td>OVA11660</td>
<td>9.15</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.92 (0.63, 1.34)</td>
<td>CNBSS</td>
<td>OVA11645</td>
<td>61.12</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.98 (0.63, 1.54)</td>
<td>NHS</td>
<td>OVA01437</td>
<td>9.15</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.06 (0.84, 1.34)</td>
<td>9.15</td>
<td>OVA11660</td>
<td>WHI</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.99 (0.90, 1.08)</td>
<td>61.12</td>
<td>OVA11645</td>
<td>CNBSS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.01 (0.89, 1.15)</td>
<td>29.73</td>
<td>OVA01437</td>
<td>NHS</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.848)</td>
<td></td>
<td>1.00 (0.93, 1.07)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 (I²=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

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

Table 150 Overall evidence on total folate and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>One publication identified and no association was reported</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Two publications were identified. None of them reported significant associations.</td>
</tr>
</tbody>
</table>
Table 151 Summary of results of the dose response meta-analysis of total folate and ovarian cancer

<table>
<thead>
<tr>
<th>Ovarian cancer incidence</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>908</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>50 µg/day</td>
</tr>
<tr>
<td>Overall RR (95% CI)</td>
<td>-</td>
<td>1.00 (95% CI: 0.97-1.03)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.526</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the SLR
### Table 152 Inclusion/exclusion table for meta-analysis of total folate and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person years per intake category</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11651</td>
<td>Tworoger</td>
<td>2006</td>
<td>Prospective Cohort</td>
<td>Nurses’ Health Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA10451</td>
<td>Kelemen</td>
<td>2004</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 143: Highest versus lowest forest plot of total folate and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>Study_Description</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.81 (0.49, 1.32)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>&gt;711 vs &lt;272 µg/d</td>
</tr>
<tr>
<td>Tworoger</td>
<td>2006</td>
<td>0.84 (0.60, 1.18)</td>
<td>OVA11651</td>
<td>NHS</td>
<td>Q5 vs Q1</td>
</tr>
<tr>
<td>Kelemen</td>
<td>2004</td>
<td>1.73 (0.90, 3.33)</td>
<td>OVA10451</td>
<td>IOWA</td>
<td>&gt;540 vs &lt;258 µg/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 50</th>
<th>%</th>
<th>mcg/d RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>Study_Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.99 (0.95, 1.03)</td>
<td>57.07</td>
<td>OVA11654</td>
<td>CTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tworoger</td>
<td>2006</td>
<td>0.99 (0.94, 1.06)</td>
<td>23.53</td>
<td>OVA11651</td>
<td>NHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelemen</td>
<td>2004</td>
<td>1.03 (0.96, 1.10)</td>
<td>19.39</td>
<td>OVA10451</td>
<td>IOWA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.526)</td>
<td></td>
<td>1.00 (0.97, 1.03)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 145 Funnel plot of total folate and ovarian cancer

Funnel plot with pseudo 95% confidence limits

Chang
Tworoger
Kelemen

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

Chang 2007
Tworoger 2006
Kelemen 2004

Total folate (μg/day)
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 (I² = 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LC1</th>
<th>UC1</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kabat, 2008</td>
<td>USA</td>
<td>Canadian National Breast Cancer Screening Study</td>
<td>264</td>
<td>16.4</td>
<td>1.05</td>
<td>0.71</td>
<td>1.54</td>
<td>&gt;374 vs. &lt;237 µg /d</td>
</tr>
<tr>
<td>Navarro, 2006</td>
<td>USA</td>
<td>Canadian National Breast Cancer Screening Study</td>
<td>264</td>
<td>16.4</td>
<td>0.78</td>
<td>0.44</td>
<td>1.70</td>
<td>&gt;357 vs. &lt;248 µg /day</td>
</tr>
<tr>
<td>Tworoger, 2006</td>
<td>USA</td>
<td>Nurses’ Health Study</td>
<td>481</td>
<td>22</td>
<td>0.90</td>
<td>0.59</td>
<td>1.36</td>
<td>Q5 (median 460 µg /d) vs. Q1 (198 µg /d)</td>
</tr>
</tbody>
</table>

Table 154 Overall evidence on dietary folate and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>Three publications of two cohort studies were identified. None of them reported significant associations.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>
Table 155 Summary of results of the dose response meta-analysis of dietary folate and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>SLR</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>413</td>
<td>1158</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>100 µg/day</td>
<td>50 µg/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>0.98 (0.92-1.04)</td>
<td>0.96 (0.88-1.05)</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>72.9</td>
<td>35.4%, p=0.20</td>
</tr>
</tbody>
</table>
Table 156 Inclusion/exclusion table for meta-analysis of dietary folate and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CUP dose-response</th>
<th>CUP H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11681</td>
<td>Kabat</td>
<td>2008</td>
<td>Prospective Cohort Study</td>
<td>Canadian National Breast Cancer Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>Navarro, 2006 had more complete information</td>
</tr>
<tr>
<td>OVA11624</td>
<td>Navarro</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Canadian National Breast Cancer Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA11651</td>
<td>Tworoger</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence EOC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA09696</td>
<td>Larsson</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Swedish Mammography Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>OVA10451</td>
<td>Kelemen</td>
<td>2004</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td></td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>Superseded by Kelemen, 2004</td>
</tr>
</tbody>
</table>
Figure 147 Highest versus lowest forest plot of dietary folate and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarro</td>
<td>2006</td>
<td>0.78 (0.44, 1.70)</td>
<td>OVA11624</td>
<td>CNBSS</td>
<td>&gt;357 vs. &lt;248 μg/day</td>
</tr>
<tr>
<td>Tworoger</td>
<td>2006</td>
<td>0.90 (0.59, 1.36)</td>
<td>OVA11651</td>
<td>NHS</td>
<td>&gt;323 vs. &lt;=178 μg/day</td>
</tr>
<tr>
<td>Kelemen</td>
<td>2004</td>
<td>1.45 (0.83, 2.53)</td>
<td>OVA10451</td>
<td>IOWA</td>
<td>&gt;=347 vs. &lt;=238 μg/day</td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.67 (0.43, 1.04)</td>
<td>OVA09696</td>
<td>SMC</td>
<td>&gt;=204 vs. &lt;=155 μg/day</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 50</th>
<th>%</th>
<th>mcg/d RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarro</td>
<td>2006</td>
<td>0.89 (0.74, 1.07)</td>
<td>17.95</td>
<td>OVA11624</td>
<td>CNBSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tworoger</td>
<td>2006</td>
<td>0.98 (0.91, 1.05)</td>
<td>48.25</td>
<td>OVA11651</td>
<td>NHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelemen</td>
<td>2004</td>
<td>1.07 (0.92, 1.26)</td>
<td>22.11</td>
<td>OVA10451</td>
<td>IOWA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsson</td>
<td>2004</td>
<td>0.81 (0.64, 1.03)</td>
<td>11.69</td>
<td>OVA09696</td>
<td>SMC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 35.4%, p = 0.200)</td>
<td></td>
<td>0.96 (0.88, 1.05)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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; I²= 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 (I²=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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>United States</td>
<td>Women Health Initiative</td>
<td>352</td>
<td>7</td>
<td>1.22</td>
<td>0.89</td>
<td>1.67</td>
<td>&gt;=555 mg/d vs. &lt;90 mg/d</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>United States</td>
<td>California Teachers Study</td>
<td>280</td>
<td>8.1</td>
<td>1.96</td>
<td>1.11</td>
<td>3.46</td>
<td>1222 mg/d vs. 51 mg/d</td>
</tr>
<tr>
<td>Silvera, 2006</td>
<td>Canada</td>
<td>Canadian National Breast Screening Study</td>
<td>264</td>
<td>7.2</td>
<td>1.11</td>
<td>0.75</td>
<td>1.66</td>
<td>&gt;247 mg/d vs. &lt;122 mg/d</td>
</tr>
</tbody>
</table>
Table 158 Overall evidence on total vitamin C and ovarian cancer

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

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort Study</td>
<td>Women Health Initiative</td>
<td>Incidence Invasive cancer</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort Study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA11645</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence EOC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Confidence intervals estimation Person/ years per category</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 151 Highest versus lowest forest plot of total vitamin C and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.22 (0.89,1.67)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;=555 mg/d vs &lt;90 mg/d</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.96 (1.11,3.46)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>1222 mg/d vs 51 mg/d</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.11 (0.75,1.66)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td>&gt;247 mg/d vs &lt;122 mg/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.01 (0.69,1.47)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>752 mg/d vs 79 mg/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 200 mg per day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.04 (0.96,1.12)</td>
<td>35.10</td>
<td>OVA11660</td>
<td>WHI</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.05 (0.98,1.13)</td>
<td>40.54</td>
<td>OVA11654</td>
<td>CTS</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.09 (0.74,1.62)</td>
<td>1.40</td>
<td>OVA11645</td>
<td>CNBSS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.98 (0.89,1.08)</td>
<td>22.96</td>
<td>OVA01437</td>
<td>NHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.03 (0.98,1.08)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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; $I^2=0\%$, $P_{\text{heterogeneity}}=0.87$) 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>United States</td>
<td>Women Health Initiative</td>
<td>352</td>
<td>7</td>
<td>1.07</td>
<td>0.77</td>
<td>1.48</td>
<td>$\geq 130\text{ mg/d vs.} &lt;58\text{ mg/d}$</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>United States</td>
<td>California Teachers Study</td>
<td>280</td>
<td>8.1</td>
<td>1.50</td>
<td>0.71</td>
<td>3.19</td>
<td>Highest vs. lowest quintile</td>
</tr>
<tr>
<td>Silvera, 2006</td>
<td>Canada</td>
<td>Canadian National Breast Screening Study</td>
<td>264</td>
<td>7.2</td>
<td>0.90</td>
<td>0.58</td>
<td>1.37</td>
<td>$&gt;206\text{ mg/d vs &lt;115 mg/d}$</td>
</tr>
</tbody>
</table>
Table 162 Overall evidence on dietary vitamin C and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>Two studies were identified during the SLR (Fairfield et al, 2001 and Kushi et al, 1999). None of them suggested association with ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Three additional cohort studies were identified. Overall, four studies could be included in the final meta-analysis.</td>
</tr>
</tbody>
</table>
Table 164 Inclusion/exclusion table for meta-analysis of dietary vitamin C and ovarian cancer

<table>
<thead>
<tr>
<th>WC RF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HxL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort Study</td>
<td>Women Health Initiative</td>
<td>Incidence Invasive cancer</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Mid-exposure values Person/ years per category</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort Study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>- Two categories</td>
</tr>
<tr>
<td>OVA11645</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Canadian National Breast Screening Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Mid-exposure values</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Confidence intervals estimation Person/ years per category</td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort Study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Person/ years per category Mid-exposure values</td>
</tr>
</tbody>
</table>
Figure 155 Highest versus lowest forest plot of dietary vitamin C and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.07 (0.77, 1.48)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;=130 mg/d vs &lt;58 mg/d</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.50 (0.71, 3.19)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>Highest vs. lowest quintile</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.90 (0.58, 1.37)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td>&gt;206 mg/d vs &lt;115 mg/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.22 (0.83, 1.81)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>219 mg/d vs 67 mg/d</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.05 (0.63, 1.76)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&gt;321.9 mg/d vs &lt;129.2 mg/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>day RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.01 (0.94, 1.08)</td>
<td>15.57</td>
<td>OVA11660</td>
<td>WHI</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.97 (0.90, 1.05)</td>
<td>13.25</td>
<td>OVA11645</td>
<td>CNBSS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.01 (0.95, 1.07)</td>
<td>24.28</td>
<td>OVA01437</td>
<td>NHS</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.00 (0.96, 1.04)</td>
<td>46.90</td>
<td>OVA02880</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.00 (0.97, 1.03)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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; I² = 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 (I²=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

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

Table 166 Overall evidence on serum vitamin D and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>No studies were identified during the SLR.</td>
</tr>
<tr>
<td>Continuous Update</td>
<td>Five cohort studies were identified; all of them could be included in the meta-analysis.</td>
</tr>
<tr>
<td>Project</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>593</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 10 nmol/litre</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.01 (0.87-1.17)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>0%, p=0.85</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 168 Inclusion/exclusion table for meta-analysis of serum vitamin D and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HVL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11665</td>
<td>Toriola</td>
<td>2008</td>
<td>Nested case-control study</td>
<td>Finnish Maternity Cohort</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Risk rate re-estimation Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11630</td>
<td>Arslan</td>
<td>2009</td>
<td>Nested case-control study</td>
<td>New York University Women’s Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11631</td>
<td>Arslan</td>
<td>2009</td>
<td>Nested case-control study</td>
<td>Northern Sweden Health and Disease Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11663</td>
<td>Tworoger</td>
<td>2007</td>
<td>Nested case-control study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11664</td>
<td>Tworoger</td>
<td>2007</td>
<td>Nested case-control study</td>
<td>Women Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 159 Highest versus lowest forest plot of serum vitamin D and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WC obsessed</th>
<th>Study Description</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toriola</td>
<td>2010</td>
<td>0.89 (0.36, 2.18)</td>
<td>16.54</td>
<td>OVA11665</td>
<td>FMC</td>
<td>&gt;=53.1 nmol/L vs &lt;26 nmol/L</td>
</tr>
<tr>
<td>Arslan</td>
<td>2009</td>
<td>1.50 (0.53, 4.23)</td>
<td>12.44</td>
<td>OVA11630</td>
<td>NYU-WHS</td>
<td>&gt;=57.8 nmol/L vs &lt;=36.7 nmol/L</td>
</tr>
<tr>
<td>Arslan</td>
<td>2009</td>
<td>0.83 (0.38, 1.81)</td>
<td>22.02</td>
<td>OVA11631</td>
<td>NSHDC</td>
<td>&gt;=44.8 nmol/L vs &lt;=34.0 nmol/L</td>
</tr>
<tr>
<td>Tworeger</td>
<td>2007</td>
<td>0.84 (0.47, 1.52)</td>
<td>38.94</td>
<td>OVA11663</td>
<td>NHS</td>
<td>&gt;=32.5 ng/mL vs &lt;20.6 ng/mL</td>
</tr>
<tr>
<td>Tworeger</td>
<td>2007</td>
<td>0.88 (0.28, 2.82)</td>
<td>10.06</td>
<td>OVA11664</td>
<td>WHS</td>
<td>&gt;=27.7 ng/mL vs &lt;=17.4 ng/mL</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.907)</td>
<td></td>
<td>0.91 (0.63, 1.32)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10</th>
<th>%</th>
<th>nmol/L RR (95% CI)</th>
<th>Weight</th>
<th>WC obsessed</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toriola</td>
<td>2010</td>
<td>1.01 (0.80, 1.26)</td>
<td>42.72</td>
<td>OVA11665</td>
<td>FMC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arslan</td>
<td>2009</td>
<td>1.11 (0.85, 1.44)</td>
<td>31.32</td>
<td>OVA11630</td>
<td>NYU-WHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arslan</td>
<td>2009</td>
<td>0.89 (0.62, 1.28)</td>
<td>16.47</td>
<td>OVA11631</td>
<td>NSHDC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tworeger</td>
<td>2007</td>
<td>0.87 (0.51, 1.46)</td>
<td>7.98</td>
<td>OVA11663</td>
<td>NHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tworeger</td>
<td>2007</td>
<td>1.17 (0.35, 3.86)</td>
<td>1.51</td>
<td>OVA11664</td>
<td>WHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.850)</td>
<td></td>
<td>1.01 (0.87, 1.17)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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; \(I^2=0\%\), \(P_{\text{heterogeneity}}=0.61\)) 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>USA</td>
<td>Women’s Health Initiative</td>
<td>451</td>
<td>8.3</td>
<td>1.22</td>
<td>0.89</td>
<td>1.66</td>
<td>(\geq403.2) mg/d ATE vs. (&lt;7.4) mg/d ATE*</td>
</tr>
<tr>
<td>Chang, 2007</td>
<td>USA</td>
<td>California Teachers Study</td>
<td>280</td>
<td>8.1</td>
<td>1.46</td>
<td>0.76</td>
<td>2.79</td>
<td>295 mg/d vs 6 mg/d</td>
</tr>
<tr>
<td>Silvera 2006</td>
<td>Canada</td>
<td>Canadian National Breast Cancer Screening</td>
<td>264</td>
<td>16.4</td>
<td>1.24</td>
<td>0.85</td>
<td>1.82</td>
<td>(&gt;28) mg/d vs (&lt;17) mg/d</td>
</tr>
</tbody>
</table>

*ATE: alpha-tocopherol equivalents
Table 170 Overall evidence on total vitamin E and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR*</td>
</tr>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 172 Inclusion/exclusion table for meta-analysis of total vitamin E and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF_Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women’s Health Initiative</td>
<td>Incidence Invasive cancer</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td>-</td>
</tr>
<tr>
<td>OVA11645</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Cancer Screening</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort study</td>
<td>Nurses’ Health Study</td>
<td>Incidence EOC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Confidence intervals</td>
<td>-</td>
</tr>
</tbody>
</table>
**Figure 163** Highest versus lowest forest plot of total vitamin E and ovarian cancer incidence.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.22 (0.89, 1.66)</td>
<td>OVA11660</td>
<td>WHI</td>
<td>&gt;= 403.2 mg/d ATE vs &lt; 7.4 mg/d ATE</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.46 (0.76, 2.79)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>295 mg/d vs 6 mg/d</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.24 (0.85, 1.82)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td>&gt;28 mg/d vs 0-17 mg/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.88 (0.61, 1.27)</td>
<td>OVA01437</td>
<td>NHS</td>
<td>327 IU/d vs 5 IU*/d</td>
</tr>
</tbody>
</table>

*IU: International Units

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 50 mg per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.01 (0.98, 1.04)</td>
<td>78.43</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>1.03 (0.95, 1.12)</td>
<td>8.85</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.13 (0.56, 2.25)</td>
<td>0.13</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>0.97 (0.90, 1.04)</td>
<td>12.60</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.618)</td>
<td></td>
<td>1.01 (0.98, 1.03)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
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 metaanalysis 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; $I^2= 4.1\%$, $P_{\text{heterogeneity}}=0.37$) 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Study name</th>
<th>Cases</th>
<th>Years of follow up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson, 2008</td>
<td>USA</td>
<td>Women’s Health Initiative</td>
<td>451</td>
<td>8.3</td>
<td>1.05</td>
<td>0.71</td>
<td>1.57</td>
<td>$\geq 9.4 \text{ mg/d ATE vs. } &lt;4.9 \text{ mg/d ATE}$</td>
</tr>
<tr>
<td>Silvera, 2006</td>
<td>Canada</td>
<td>Canadian National Breast Cancer Screening</td>
<td>264</td>
<td>16.4</td>
<td>0.87</td>
<td>0.57</td>
<td>1.31</td>
<td>$&gt; 25 \text{ mg/d vs. } &lt;17 \text{ mg/d}$</td>
</tr>
</tbody>
</table>

*ATE: alpha-tocopherol equivalents
Summary of evidence

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
<td>Two studies were identified during the SLR,</td>
</tr>
<tr>
<td></td>
<td>the Nurses’ Health Study (Fairfield et al.,</td>
</tr>
<tr>
<td></td>
<td>2001), showed a significant increased risk</td>
</tr>
<tr>
<td></td>
<td>(RR = 1.52; 95% CI: 1.04-2.21)</td>
</tr>
<tr>
<td>Continuous Update</td>
<td>Two cohort studies were identified and overall</td>
</tr>
<tr>
<td>Project</td>
<td>four studies were included in the CUP meta-</td>
</tr>
<tr>
<td></td>
<td>analysis.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Ovarian cancer incidence and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLR*</td>
</tr>
<tr>
<td>Studies (n)</td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td></td>
</tr>
<tr>
<td>Increment unit used</td>
<td></td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td></td>
</tr>
<tr>
<td>Continuous Update</td>
<td></td>
</tr>
<tr>
<td>Project</td>
<td></td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 176 Inclusion/exclusion table for meta-analysis of dietary vitamin E and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HVL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11660</td>
<td>Thomson</td>
<td>2008</td>
<td>Prospective Cohort study</td>
<td>Women’s Health Initiative</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA11645</td>
<td>Silvera</td>
<td>2006</td>
<td>Prospective Cohort study</td>
<td>Canadian National Breast Cancer Screening</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mid-exposure values</td>
<td>-</td>
</tr>
<tr>
<td>OVA01437</td>
<td>Fairfield</td>
<td>2001</td>
<td>Prospective Cohort study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values Confidence intervals</td>
<td>-</td>
</tr>
<tr>
<td>OVA</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category Mid-exposure values</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 167 Highest versus lowest forest plot of dietary vitamin E and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>1.05 (0.71, 1.57)</td>
<td>OVA11660</td>
<td>WHI</td>
<td></td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>0.87 (0.57, 1.31)</td>
<td>OVA11645</td>
<td>CNBSS</td>
<td></td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>1.52 (1.04, 2.21)</td>
<td>OVA01437</td>
<td>NHS</td>
<td></td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>0.91 (0.56, 1.48)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td></td>
</tr>
</tbody>
</table>

High vs low

*IU: International Units

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 mg per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>2008</td>
<td>0.97 (0.47, 2.02)</td>
<td>3.20 OVA11660 WHI</td>
</tr>
<tr>
<td>Silvera</td>
<td>2006</td>
<td>1.01 (0.83, 1.24)</td>
<td>39.12 OVA11645 CNBSS</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2001</td>
<td>2.01 (0.96, 4.23)</td>
<td>3.11 OVA01437 NHS</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.04 (0.88, 1.23)</td>
<td>54.57 OVA02880 IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.05 (0.92, 1.19)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

day RR (95% CI) Weight WCRF_Code StudyDescription

Overall (I-squared = 4.1%, p = 0.372)
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

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

Table 178 Overall evidence on total calcium intake and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>941</td>
</tr>
<tr>
<td>Increment unit used</td>
<td>-</td>
<td>Per 200 mg/day</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
<td>-</td>
<td>1.00 (0.97-1.04)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
<td>-</td>
<td>10.2%, p=0.32</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 180 Inclusion/exclusion table for meta-analysis of total calcium intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11694</td>
<td>Park</td>
<td>2009</td>
<td>Prospective Cohort Study</td>
<td>National Institute of Health-American Association of Retired Persons</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases per category Person/ years per category</td>
<td></td>
</tr>
<tr>
<td>OVA11654</td>
<td>Chang</td>
<td>2007</td>
<td>Prospective Cohort Study</td>
<td>California Teacher Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td></td>
</tr>
<tr>
<td>OVA11662</td>
<td>Koralek</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/ years per category</td>
<td></td>
</tr>
<tr>
<td>OVA11491</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>-</td>
<td>Only RR for the highest vs lowest category</td>
</tr>
</tbody>
</table>
Figure 171 Highest versus lowest forest plot of total calcium intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park</td>
<td>2009</td>
<td>1.14 (0.85, 1.52)</td>
<td>OVA11694</td>
<td>NIH-AARP</td>
<td>1881 mg/d vs 494 mg/d</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.90 (0.57, 1.43)</td>
<td>OVA11654</td>
<td>CTS</td>
<td>&gt;1127 mg/d vs &lt;=461 mg/d</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.65 (0.36, 1.16)</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td>1596 mg/d vs 406 mg/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>1.47 (0.88, 2.47)</td>
<td>OVA11491</td>
<td>NHS</td>
<td>Highest vs lowest quintile</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 200 mg per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park</td>
<td>2009</td>
<td>1.02 (0.98, 1.06)</td>
<td>66.92</td>
</tr>
<tr>
<td>Chang</td>
<td>2007</td>
<td>0.99 (0.92, 1.07)</td>
<td>19.73</td>
</tr>
<tr>
<td>Koralek</td>
<td>2006</td>
<td>0.94 (0.86, 1.04)</td>
<td>13.35</td>
</tr>
<tr>
<td>Overall (I-squared = 10.2%, p = 0.328)</td>
<td></td>
<td>1.00 (0.97, 1.04)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Figure 173 Funnel plot of total calcium intake and ovarian cancer

Funnel plot with pseudo 95% confidence limits

- Koralek 2006
- Chang 2007
- Park 2009

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

Dose-response graph showing the relationship between total calcium intake (Total Calcium (mg/day)) and the risk of ovarian cancer. The graph includes data from Park 2009, Chang 2007, and Koralek 2006.
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; \( \hat{I}^2 = 59.1\% \), \( P_{\text{heterogeneity}} = 0.08 \)) 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 (\( \hat{I}^2 = 59.1\% \), \( p=0.08 \)). 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, \( P_{\text{heterogeneity}} = 0.53 \)) for \( \geq 1,300 \) 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

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

Table 182 Overall evidence on dietary calcium intake and ovarian cancer

<table>
<thead>
<tr>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLR</td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td>Continuous Update Project</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer incidence and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
</tr>
<tr>
<td>Cases (n)</td>
</tr>
<tr>
<td>Increment unit used</td>
</tr>
<tr>
<td>Overall RR (95%CI)</td>
</tr>
<tr>
<td>Heterogeneity (I²,p-value)</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
### Table 184 Inclusion/exclusion table for meta-analysis of dietary calcium intake and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF Code</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Name</th>
<th>Cancer Outcome</th>
<th>SLR</th>
<th>CUP dose-response meta-analysis</th>
<th>CUP HvL forest plot</th>
<th>Estimated values</th>
<th>Exclusion reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11694</td>
<td>Park</td>
<td>2009</td>
<td>Prospective Cohort Study</td>
<td>National Institute of Health-American Association of Retired Persons</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cases per category</td>
<td>Person/years per category</td>
</tr>
<tr>
<td>OVA11662</td>
<td>Koralek</td>
<td>2006</td>
<td>Prospective Cohort Study</td>
<td>Breast Cancer Detection Demonstration Project</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category</td>
<td></td>
</tr>
<tr>
<td>OVA11491</td>
<td>Fairfield</td>
<td>2004</td>
<td>Prospective Cohort Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Only RR for highest versus lowest category</td>
<td></td>
</tr>
<tr>
<td>OVA02880</td>
<td>Kushi</td>
<td>1999</td>
<td>Prospective Cohort Study</td>
<td>Iowa Women Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Person/years per category and mid-exposure values</td>
<td></td>
</tr>
</tbody>
</table>
Figure 175 Highest versus lowest forest plot of dietary calcium intake and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>low RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park</td>
<td>2009</td>
<td>1.02 (0.75, 1.37)</td>
<td>OVA11694</td>
<td>NIH-AARP</td>
<td>1101 mg/d vs 409 mg/d</td>
</tr>
<tr>
<td>Koralik</td>
<td>2006</td>
<td>0.67 (0.43, 1.04)</td>
<td>OVA11662</td>
<td>BCDDP</td>
<td>946 mg/d vs 359 mg/d</td>
</tr>
<tr>
<td>Fairfield</td>
<td>2004</td>
<td>0.85 (0.36, 2.00)</td>
<td>OVA11491</td>
<td>NHS</td>
<td>Highest vs lowest quintile</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.66 (0.96, 2.88)</td>
<td>OVA02880</td>
<td>IWHS</td>
<td>&lt;731 mg/d vs &gt;1372 mg/d</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 200 mg per</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>day RR (95% CI)</td>
<td>Weight</td>
</tr>
<tr>
<td>Park</td>
<td>2009</td>
<td>1.02 (0.94, 1.10)</td>
<td>41.20</td>
</tr>
<tr>
<td>Koralik</td>
<td>2006</td>
<td>0.87 (0.75, 1.01)</td>
<td>24.71</td>
</tr>
<tr>
<td>Kushi</td>
<td>1999</td>
<td>1.06 (0.96, 1.18)</td>
<td>34.10</td>
</tr>
<tr>
<td>Overall (I-squared = 59.1%, p = 0.087)</td>
<td></td>
<td>0.99 (0.90, 1.10)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Figure 177 Funnel plot of dietary calcium intake and ovarian cancer

Funnel plot with pseudo 95% confidence limits

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 Occupational

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 activity (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, $I^2=0\%$, $p_{\text{heterogeneity}}=0.76$).

Heterogeneity

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

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

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

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

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Three cohort studies (four publications) had reported on leisure-time physical activity and ovarian cancer. All of these reported no significant association.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>
Table 187 Summary of results of the dose-response meta-analysis of leisure-time physical activity and ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1422</td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.05 (0.97-1.14)</td>
<td></td>
</tr>
<tr>
<td>Increment</td>
<td>-</td>
<td>Per 20 MET-hrs/wk</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.76</td>
<td></td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11669</td>
<td>Weiderpass</td>
<td>2011</td>
<td>Prospective Study</td>
<td>Japan Public Health Center-based Prospective Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Only two categories of exposure</td>
</tr>
<tr>
<td>OVA11629</td>
<td>Chionh</td>
<td>2010</td>
<td>Prospective Study</td>
<td>Melbourne Collaborative Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>No quantification of physical activity</td>
</tr>
<tr>
<td>OVA11652</td>
<td>Leitzmann</td>
<td>2009</td>
<td>Prospective Study</td>
<td>NIH-AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>No quantification of physical activity</td>
</tr>
<tr>
<td>OVA11641</td>
<td>Lahmann</td>
<td>2008</td>
<td>Prospective Study</td>
<td>EPIC</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, person-years</td>
<td></td>
</tr>
<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective Study</td>
<td>Japan Collaborative Cohort Study</td>
<td>Mortality</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Only two categories of exposure</td>
</tr>
<tr>
<td>OVA11618</td>
<td>Biesma</td>
<td>2006</td>
<td>Prospective Study</td>
<td>Netherlands Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Too few studies to conduct analyses by min/day</td>
</tr>
<tr>
<td>OVA11625</td>
<td>Patel</td>
<td>2006</td>
<td>Prospective Study</td>
<td>Women’s Lifestyle and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>OVA11634</td>
<td>Weiderpass</td>
<td>2006</td>
<td>Prospective Study</td>
<td>Cancer Prevention Study II</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>No quantification of physical activity</td>
</tr>
<tr>
<td>OVA10078</td>
<td>Schnohr</td>
<td>2005</td>
<td>Prospective Study</td>
<td>Copenhagen Centre for Prospective Population Studies</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>No quantification of physical activity</td>
</tr>
<tr>
<td>OVA09688</td>
<td>Anderson</td>
<td>2004</td>
<td>Prospective Study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>No quantification of physical activity</td>
</tr>
<tr>
<td>OVA00455</td>
<td>Bertone</td>
<td>2001</td>
<td>Prospective Study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, person-years</td>
<td></td>
</tr>
<tr>
<td>OVA03556</td>
<td>Mink</td>
<td>1996</td>
<td>Prospective Study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Overlap with OVA09688 (Anderson et al, 2004)</td>
</tr>
</tbody>
</table>
Figure 179 Highest versus lowest forest plot of leisure-time physical activity and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass</td>
<td>2011</td>
<td>1.10 (0.60, 1.70)</td>
<td>OVA11669</td>
<td>JPHC</td>
<td>Yes vs. no</td>
</tr>
<tr>
<td>Chionh</td>
<td>2010</td>
<td>2.21 (1.16, 4.24)</td>
<td>OVA11629</td>
<td>MCCS</td>
<td>High vs. none</td>
</tr>
<tr>
<td>Leitzmann</td>
<td>2009</td>
<td>1.10 (0.82, 1.48)</td>
<td>OVA11652</td>
<td>NIH- AARP</td>
<td>Moderate/vigorous activity vs. neither</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2008</td>
<td>1.18 (0.94, 1.47)</td>
<td>OVA11641</td>
<td>EPIC</td>
<td>&gt;42 vs. &lt;12 MET-hrs/wk</td>
</tr>
<tr>
<td>Sakauchi</td>
<td>2007</td>
<td>0.51 (0.24, 1.07)</td>
<td>OVA11661</td>
<td>JACC</td>
<td>&gt;=1-2 hrs/wk vs. seldom</td>
</tr>
<tr>
<td>Biesma</td>
<td>2006</td>
<td>0.72 (0.48, 1.06)</td>
<td>OVA11618</td>
<td>NLCS</td>
<td>&gt;50 vs. &lt;30 min/d</td>
</tr>
<tr>
<td>Patel</td>
<td>2006</td>
<td>0.73 (0.40, 1.34)</td>
<td>OVA11625</td>
<td>CPS II Nutrition Cohort</td>
<td>&gt;=31.5 vs. 0 MET-hrs/wk</td>
</tr>
<tr>
<td>Weiderpass</td>
<td>2006</td>
<td>1.03 (0.64, 1.66)</td>
<td>OVA11634</td>
<td>WLHS</td>
<td>Vigorous vs. moderate</td>
</tr>
<tr>
<td>Schnohr</td>
<td>2009</td>
<td>0.33 (0.16, 0.67)</td>
<td>OVA10078</td>
<td>CCPPS</td>
<td>Vigorous vs. low</td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td>1.42 (1.03, 1.97)</td>
<td>OVA00688</td>
<td>NHS</td>
<td>High vs. low</td>
</tr>
<tr>
<td>Bertone</td>
<td>2001</td>
<td>1.27 (0.75, 2.14)</td>
<td>OVA00455</td>
<td>NHS</td>
<td>&gt;=30 vs. 0-&lt;2.5 MET-hrs/wk</td>
</tr>
</tbody>
</table>

Overall (I-squared = 0.0%, p = 0.761) 1.05 (0.97, 1.14) 100.00

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>MET-hrs/wk RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahmann</td>
<td>2008</td>
<td>1.05 (0.96, 1.15)</td>
<td>74.69</td>
<td>OVA11641</td>
<td>EPIC</td>
</tr>
<tr>
<td>Patel</td>
<td>2006</td>
<td>1.01 (0.82, 1.25)</td>
<td>14.07</td>
<td>OVA11625</td>
<td>CPS II Nutrition Cohort</td>
</tr>
<tr>
<td>Bertone</td>
<td>2001</td>
<td>1.14 (0.90, 1.45)</td>
<td>11.24</td>
<td>OVA00455</td>
<td>NHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.05 (0.97, 1.14)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 181 Dose-response graph of leisure-time physical activity and ovarian cancer

Leisure-time physical activity (MET-hrs/wk)
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$^2$ ($p_{nonlinearity}<0.0001$) (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, $p_{\text{heterogeneity}}=0.001$) for obesity and 1.16 (95% CI: 1.01-1.32, $p_{\text{heterogeneity}}=0.001$) 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 $p_{\text{heterogeneity}}=0.04$) for obesity and 1.07 (95% CI: 0.92-1.25, $p_{\text{heterogeneity}}=0.14$) 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, $I^2=55\%$, $p_{\text{heterogeneity}}=0.30$) 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 $\geq 30$ 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>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass, 2012</td>
<td>Japan</td>
<td>Japan Public Health Center-based Prospective Study</td>
<td>86</td>
<td>16 years</td>
<td>0.8</td>
<td>0.2</td>
<td>3.3</td>
<td>&gt;29.9 vs. 20-22.9 Per unit</td>
</tr>
<tr>
<td>Brändstedt, 2011</td>
<td>Sweden</td>
<td>Malmo Diet and Cancer Cohort</td>
<td>93</td>
<td>13.1 years</td>
<td>0.90</td>
<td>0.47</td>
<td>1.75</td>
<td>≥30 vs. &lt;25</td>
</tr>
<tr>
<td>Yang, 2011</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>849</td>
<td>~9.8 years</td>
<td>1.15</td>
<td>0.98</td>
<td>1.35</td>
<td>≥30 vs. &lt;30</td>
</tr>
<tr>
<td>Andreotti, 2010</td>
<td>USA</td>
<td>Agricultural Health Study</td>
<td>48</td>
<td>&gt;10 years</td>
<td>0.48</td>
<td>0.14</td>
<td>1.63</td>
<td>≥30 vs. &lt;25</td>
</tr>
<tr>
<td>Kotsopoulos, 2010</td>
<td>USA</td>
<td>Nurses’ Health Study 1</td>
<td>732</td>
<td>30 years</td>
<td>1.11</td>
<td>0.85</td>
<td>1.45</td>
<td>≥30 vs. &lt;21</td>
</tr>
<tr>
<td>Kotsopoulos, 2010</td>
<td>USA</td>
<td>Nurses’ Health Study 2</td>
<td>130</td>
<td>16 years</td>
<td>1.36</td>
<td>0.80</td>
<td>2.33</td>
<td>≥30 vs. &lt;21</td>
</tr>
<tr>
<td>Chionh, 2010</td>
<td>Australia</td>
<td>Melbourne Collaborative Cohort Study</td>
<td>113</td>
<td>10.2 years</td>
<td>1.58</td>
<td>0.96</td>
<td>2.62</td>
<td>30 vs. 25-29 Per 5 units</td>
</tr>
<tr>
<td>Canchola, 2010</td>
<td>USA</td>
<td>California Teachers Study</td>
<td>277</td>
<td>12.1 years</td>
<td>1.2</td>
<td>0.72</td>
<td>2.0</td>
<td>≥30 vs. &lt;25, never used HT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.54</td>
<td>0.21</td>
<td>1.39</td>
<td>≥30 vs. &lt;25, HT ≤5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
<td>0.26</td>
<td>1.45</td>
<td>≥30 vs. &lt;25, HT &gt;5 years</td>
</tr>
<tr>
<td>Lahmann, 2009</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>611</td>
<td>8.9 years</td>
<td>1.27</td>
<td>0.98</td>
<td>1.63</td>
<td>&gt;27.9 vs. &lt;22.2</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>1.33</td>
<td>1.05</td>
<td>1.68</td>
<td>≥30 vs. &lt;25</td>
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<td></td>
<td>1.05</td>
<td>1.01</td>
<td>1.08</td>
<td>≥30 vs. &lt;25</td>
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<tr>
<td>Leitzmann, 2009</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>303</td>
<td>7 years</td>
<td>1.26</td>
<td>0.94</td>
<td>1.68</td>
<td>≥30 vs. &lt;25</td>
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<tr>
<td>Song, 2008</td>
<td>Korea</td>
<td>Korean Cancer Prevention Study</td>
<td>176</td>
<td>8.75 years</td>
<td>0.93</td>
<td>0.32</td>
<td>2.67</td>
<td>≥30 vs. 21-22.9 Per 1 unit</td>
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<tr>
<td>Lundqvist, 2007</td>
<td>Sweden, Finland</td>
<td>Sweden, Finland Cohort twin study</td>
<td>313</td>
<td>26.3 years</td>
<td>0.7</td>
<td>0.3</td>
<td>1.5</td>
<td>≥30 vs. 18.5-25.0 Per 1 unit</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.96</td>
<td>1.04</td>
<td>≥30 vs. 18.5-25.0 Per 1 unit</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>0.2</td>
<td>2.6</td>
<td>≥30 vs. 18.5-25.0 Per 1 unit</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.06</td>
<td>1.02</td>
<td>1.11</td>
<td>≥30 vs. 18.5-25.0 Per 1 unit</td>
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<tr>
<td>Sakauchi,</td>
<td>Japan</td>
<td>Japan</td>
<td>77</td>
<td>13.3 years</td>
<td>1.69</td>
<td>0.99</td>
<td>2.87</td>
<td>≥25.0 vs.</td>
</tr>
<tr>
<td>Year</td>
<td>Study Name</td>
<td>Country</td>
<td>Study Design/Size</td>
<td>Observation Period</td>
<td>Hazard Ratio (95% CI)</td>
<td>Temporal Comparison</td>
<td>Baseline Age Range</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------</td>
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<td>--------------------</td>
<td>-----------------------</td>
<td>---------------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Collaborative Cohort Study</td>
<td>United Kingdom</td>
<td>Million Women's Study</td>
<td>2406</td>
<td>5.4 years</td>
<td>1.12 (1.14 - 1.02)</td>
<td>1.03 (1.02 - 1.27)</td>
<td>≥30 vs. 22.5-24.9 Per 10 units</td>
</tr>
<tr>
<td>2006</td>
<td>Kiani, UK</td>
<td>USA</td>
<td>Adventist Health Study</td>
<td>71</td>
<td>Up to 16 years</td>
<td>1.33 (0.72 - 2.47)</td>
<td>≥25.9 vs. ≤23.2</td>
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</tr>
<tr>
<td>2006</td>
<td>Lacey, USA</td>
<td>USA</td>
<td>NIH-AARP Diet and Health Study</td>
<td>214</td>
<td>~4 years</td>
<td>1.07 (0.68 - 1.39)</td>
<td>≥30 vs. &lt;25</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Lacey, USA</td>
<td>USA</td>
<td>Breast Cancer Detection Demonstration Project Follow-Up Study</td>
<td>346</td>
<td>14.5 years</td>
<td>1.55 (0.84 - 2.84)</td>
<td>≥35 vs. 18.5-24.9</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Kuriyama, Japan</td>
<td>Japan</td>
<td>Miyagi Cohort Study</td>
<td>20</td>
<td>9 years</td>
<td>0.85 (0.19 - 3.81)</td>
<td>27.5-29.9 vs. 18.5-24.9</td>
<td></td>
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<tr>
<td>2005</td>
<td>Rapp, Austria</td>
<td>Austria</td>
<td>VHM &amp; PP</td>
<td>121</td>
<td>9.9 years</td>
<td>1.25 (0.75 - 2.08)</td>
<td>≥30 vs. 18.5-24.9</td>
<td></td>
</tr>
</tbody>
</table>
Table 190 Overall evidence on BMI and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>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.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLR</td>
</tr>
<tr>
<td>Studies (n)</td>
<td>7(^1)</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>8801</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>Quantity</td>
<td>Per 2 units</td>
</tr>
<tr>
<td>Heterogeneity ((I^2), p-value)</td>
<td>62.1%, p=not available</td>
</tr>
</tbody>
</table>

\(^1\)Number of risk estimates = 5
\(^2\)Number of risk estimates = 22
Table 192 Inclusion/exclusion table for meta-analysis of BMI and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11669</td>
<td>Weiderpass</td>
<td>2012</td>
<td>Prospective cohort study</td>
<td>Japan Public Health Center-based Prospective Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, person-years</td>
<td></td>
</tr>
<tr>
<td>OVA11644</td>
<td>Brändstedt</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>Malmo Diet and Cancer Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11672</td>
<td>Yang</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>NIH-AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
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<tr>
<td>OVA11691</td>
<td>Andreotti</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Agricultural Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, person-years</td>
<td></td>
</tr>
<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 1</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
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<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 2</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
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<tr>
<td>OVA11629</td>
<td>Chionh</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Melbourne Collaborative Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>OVA11627</td>
<td>Canchola</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, RRs were recalculated using the lowest</td>
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</tr>
<tr>
<td>ID</td>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Institution</td>
<td>Category of BMI</td>
<td>Analysis of Death</td>
<td>Analysis of Incidence</td>
<td>Midpoints</td>
<td>Notes</td>
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<tr>
<td>OVA11636</td>
<td>Lahmann</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, distribution of person-years</td>
<td></td>
</tr>
<tr>
<td>OVA11623</td>
<td>Leitzmann</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>NIH-AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
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<tr>
<td>OVA11688</td>
<td>Song</td>
<td>2008</td>
<td>Prospective cohort study</td>
<td>Korean Cancer Prevention Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
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<tr>
<td>OVA11657</td>
<td>Lundqvist</td>
<td>2007</td>
<td>Prospective cohort study</td>
<td>Sweden, Finland Co-twin study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, person-years</td>
<td></td>
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<tr>
<td>OVA11661</td>
<td>Sakauchi</td>
<td>2007</td>
<td>Prospective cohort study</td>
<td>Japan Collaborative Cohort Study</td>
<td>Mortality</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Overlap with Niwa et al, 2005 OVA09951, which was used because it analysed incidence instead of mortality</td>
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<tr>
<td>OVA11653</td>
<td>Reeves</td>
<td>2007</td>
<td>Prospective cohort study</td>
<td>Million Women’s Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, person-years</td>
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<tr>
<td>OVA11647</td>
<td>Kiani</td>
<td>2006</td>
<td>Prospective cohort study</td>
<td>Adventist Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, person-years</td>
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<tr>
<td>OVA11655</td>
<td>Lacey</td>
<td>2006</td>
<td>Prospective cohort study</td>
<td>NIH-AARP Diet and Health Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Overlap with Leitzmann et al, 2009, OVA11623, which had a larger number of cases</td>
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<tr>
<td>OVA12070</td>
<td>Lukanova</td>
<td>2006</td>
<td>Prospective cohort study</td>
<td>Northern Sweden Health And Disease Cohort Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Overlap with Lukanova, 2002 OVA 03222, which was used in the dose-response analysis</td>
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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.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Study Description</th>
<th>End Points</th>
<th>Midpoints</th>
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<tr>
<td>OVA11649</td>
<td>Lacey</td>
<td>2006</td>
<td>Prospective cohort study</td>
<td>Breast cancer Detection Demonstration Project</td>
<td>Incidence</td>
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<td>OVA11690</td>
<td>Kuriyama</td>
<td>2005</td>
<td>Prospective cohort study</td>
<td>Miyagi Cohort Study</td>
<td>Incidence</td>
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<td>OVA11689</td>
<td>Rapp</td>
<td>2005</td>
<td>Prospective cohort study</td>
<td>VHM &amp; PP</td>
<td>Incidence</td>
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<td>OVA09951</td>
<td>Niwa</td>
<td>2005</td>
<td>Prospective cohort study</td>
<td>Japan Collaborative Cohort Study</td>
<td>Incidence</td>
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<td>OVA09688</td>
<td>Anderson</td>
<td>2004</td>
<td>Prospective cohort study</td>
<td>Iowa Women's Health Study</td>
<td>Incidence</td>
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<td>OVA04756</td>
<td>Schouten</td>
<td>2003</td>
<td>Prospective cohort study</td>
<td>Netherlands Cohort Study</td>
<td>Incidence</td>
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<td>OVA01399</td>
<td>Engeland</td>
<td>2003</td>
<td>Prospective cohort study</td>
<td>Norwegian Tuberculosis Screening Study</td>
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<td>OVA00733</td>
<td>Calle</td>
<td>2003</td>
<td>Prospective cohort study</td>
<td>Cancer Prevention Study II</td>
<td>Mortality</td>
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<td>Jonsson</td>
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<td>Swedish Twin Cohort</td>
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<td>OVA04449</td>
<td>Rodriguez</td>
<td>2002</td>
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<td>Cancer</td>
<td>Mortality</td>
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<td>Study ID</td>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Location</td>
<td>Incidence</td>
<td>Yes</td>
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<td>OVA01439</td>
<td>Fairfield</td>
<td>2002</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study</td>
<td>Incidence</td>
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<td>OVA03222</td>
<td>Lukanova</td>
<td>2002</td>
<td>Nested case-control study</td>
<td>New York University Women’s Health Study, Northern Sweden Health and Disease Study &amp; ORDET</td>
<td>Incidence</td>
<td>Yes</td>
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<td>OVA03556</td>
<td>Mink</td>
<td>1996</td>
<td>Prospective cohort study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
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<td>OVA05379</td>
<td>Tornberg</td>
<td>1994</td>
<td>Prospective cohort study</td>
<td>Central Sweden</td>
<td>Incidence</td>
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<td>OVA02953</td>
<td>Lapidus</td>
<td>1988</td>
<td>Prospective cohort study</td>
<td>Gothenburg</td>
<td>Incidence</td>
<td>Yes</td>
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</table>


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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>Study/Description</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass 2012</td>
<td></td>
<td>0.80 (0.20, 3.30)</td>
<td>OVA11669</td>
<td>JPHC</td>
<td>&gt;=30 vs 18.5-19.9</td>
</tr>
<tr>
<td>Andreotti 2010</td>
<td></td>
<td>0.48 (0.14, 1.63)</td>
<td>OVA11691</td>
<td>Agricultural Health Study</td>
<td>&gt;=30 vs &lt;25</td>
</tr>
<tr>
<td>Canchola 2010</td>
<td></td>
<td>0.69 (0.60, 1.32)</td>
<td>OVA11627</td>
<td>CTS</td>
<td>&gt;=30 vs &lt;25</td>
</tr>
<tr>
<td>Chiong 2010</td>
<td></td>
<td>1.58 (0.96, 2.62)</td>
<td>OVA11629</td>
<td>MICS</td>
<td>&gt;=30 vs 25-29</td>
</tr>
<tr>
<td>Kotsopoulos 2010</td>
<td></td>
<td>1.11 (0.85, 1.45)</td>
<td>OVA11658</td>
<td>NHS I</td>
<td>&gt;=30 vs &lt;21</td>
</tr>
<tr>
<td>Kotsopoulos 2010</td>
<td></td>
<td>1.36 (0.80, 2.33)</td>
<td>OVA11658</td>
<td>NHS II</td>
<td>&gt;=30 vs &lt;21</td>
</tr>
<tr>
<td>Lahmann 2009</td>
<td></td>
<td>1.33 (1.05, 1.68)</td>
<td>OVA11636</td>
<td>EPIC</td>
<td>&gt;=30 vs &lt;25</td>
</tr>
<tr>
<td>Leitzmann 2009</td>
<td></td>
<td>1.26 (0.94, 1.68)</td>
<td>OVA11623</td>
<td>NIH-AARP</td>
<td>&gt;=30 vs &lt;25</td>
</tr>
<tr>
<td>Song 2006</td>
<td></td>
<td>0.93 (0.32, 2.67)</td>
<td>OVA11688</td>
<td>KOPS</td>
<td>&gt;=30 vs 21-22.9</td>
</tr>
<tr>
<td>Lundbycst 2007</td>
<td></td>
<td>0.73 (0.37, 1.44)</td>
<td>OVA11656</td>
<td>Sweden, Finland Co-twin study</td>
<td>&gt;=30 vs 18.5-25</td>
</tr>
<tr>
<td>Reeves 2007</td>
<td></td>
<td>1.12 (1.02, 1.23)</td>
<td>OVA11653</td>
<td>MNHS</td>
<td>&gt;=30 vs 22.5-24.9</td>
</tr>
<tr>
<td>Kiani 2006</td>
<td></td>
<td>1.13 (0.72, 2.47)</td>
<td>OVA11647</td>
<td>AHS</td>
<td>&gt;=25.9 vs &lt;=23.2</td>
</tr>
<tr>
<td>Lacey 2006</td>
<td></td>
<td>1.55 (0.84, 2.84)</td>
<td>OVA11649</td>
<td>BCDDP</td>
<td>&gt;=35 vs 18.5-24.9</td>
</tr>
<tr>
<td>Lukanova 2006</td>
<td></td>
<td>2.09 (1.13, 4.13)</td>
<td>OVA12070</td>
<td>MSHDC</td>
<td>&gt;=27.2 vs &lt;18.5-22.1</td>
</tr>
<tr>
<td>Kuriyama 2005</td>
<td></td>
<td>0.85 (0.19, 3.81)</td>
<td>OVA11690</td>
<td>Miyagi Cohort Study</td>
<td>27.5-29.9 vs 18.5-24.9</td>
</tr>
<tr>
<td>Niwa 2005</td>
<td></td>
<td>1.78 (0.24, 13.34)</td>
<td>OVA09951</td>
<td>JACC Study</td>
<td>&gt;=30 vs 18.5-24.9</td>
</tr>
<tr>
<td>Rapp 2005</td>
<td></td>
<td>1.25 (0.75, 2.08)</td>
<td>OVA11689</td>
<td>VHM &amp; PP</td>
<td>&gt;=30 vs 18.5-24.9</td>
</tr>
<tr>
<td>Anderson 2004</td>
<td></td>
<td>1.18 (0.83, 1.69)</td>
<td>OVA09868</td>
<td>IVHS</td>
<td>&gt;=30 vs &lt;25</td>
</tr>
<tr>
<td>England 2003</td>
<td></td>
<td>0.98 (0.92, 1.05)</td>
<td>OVA01399</td>
<td>NTBS</td>
<td>&gt;=30 vs 18.5-24.9</td>
</tr>
<tr>
<td>Schouwen 2003</td>
<td></td>
<td>1.69 (1.06, 2.86)</td>
<td>OVA04756</td>
<td>NLCS</td>
<td>&gt;=30 vs &lt;24.9</td>
</tr>
<tr>
<td>Lukanova 2002</td>
<td></td>
<td>0.51 (0.24, 1.05)</td>
<td>OVA03322</td>
<td>MYVHHS</td>
<td>Tertile 3 vs 1</td>
</tr>
<tr>
<td>Lukanova 2002</td>
<td></td>
<td>0.15 (0.01, 1.93)</td>
<td>OVA03322</td>
<td>ORDET</td>
<td>Tertile 3 vs 1</td>
</tr>
<tr>
<td>Rodriguez 2002</td>
<td></td>
<td>1.54 (1.12, 2.14)</td>
<td>OVA04449</td>
<td>OPS II</td>
<td>&gt;=35 vs 18.5-20.5</td>
</tr>
<tr>
<td>Tomberg 1994</td>
<td></td>
<td>0.87 (0.64, 1.19)</td>
<td>OVA05379</td>
<td>Central Sweden</td>
<td>&gt;=28 vs &lt;22</td>
</tr>
</tbody>
</table>

RR (95% CI): Relative Risk (95% Confidence Interval)
WCRF_Code: Whole Cancer Research Fund Study Code
Study/Description: Study description
contrast: Comparison of contrasts
### Figure 183 Dose-response meta-analysis of BMI and ovarian cancer, per 5 units

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 5 units</th>
<th>RR (95% CI)</th>
<th>%</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass</td>
<td>2012</td>
<td></td>
<td>1.00 (0.73, 1.47)</td>
<td>1.23</td>
<td></td>
<td>OVA11669</td>
<td>JPHC</td>
</tr>
<tr>
<td>Andreotti</td>
<td>2010</td>
<td></td>
<td>0.90 (0.66, 1.28)</td>
<td>1.34</td>
<td></td>
<td>OVA11691</td>
<td>Agricultural Health Study</td>
</tr>
<tr>
<td>Canchola</td>
<td>2010</td>
<td></td>
<td>0.98 (0.83, 1.15)</td>
<td>4.27</td>
<td></td>
<td>OVA11627</td>
<td>CTS</td>
</tr>
<tr>
<td>Chionh</td>
<td>2010</td>
<td></td>
<td>1.22 (1.00, 1.48)</td>
<td>3.21</td>
<td></td>
<td>OVA11629</td>
<td>MCCS</td>
</tr>
<tr>
<td>Kotzopoulos</td>
<td>2010</td>
<td></td>
<td>1.02 (0.93, 1.11)</td>
<td>8.08</td>
<td></td>
<td>OVA11658</td>
<td>NHS I</td>
</tr>
<tr>
<td>Kotzopoulos</td>
<td>2010</td>
<td></td>
<td>1.17 (0.98, 1.39)</td>
<td>3.84</td>
<td></td>
<td>OVA11658</td>
<td>NHS II</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td></td>
<td>1.13 (1.03, 1.21)</td>
<td>8.36</td>
<td></td>
<td>OVA11636</td>
<td>EPIC</td>
</tr>
<tr>
<td>Leitzmann</td>
<td>2009</td>
<td></td>
<td>1.07 (0.96, 1.20)</td>
<td>6.45</td>
<td></td>
<td>OVA11623</td>
<td>NIH- AARP</td>
</tr>
<tr>
<td>Song</td>
<td>2008</td>
<td></td>
<td>1.22 (0.95, 1.54)</td>
<td>2.32</td>
<td></td>
<td>OVA11688</td>
<td>KCPS</td>
</tr>
<tr>
<td>Lundqvist</td>
<td>2007</td>
<td></td>
<td>1.20 (0.98, 1.46)</td>
<td>3.18</td>
<td></td>
<td>OVA11656</td>
<td>Sweden, Finland Co-twin study</td>
</tr>
<tr>
<td>Reeves</td>
<td>2007</td>
<td></td>
<td>1.07 (1.01, 1.13)</td>
<td>10.71</td>
<td></td>
<td>OVA11653</td>
<td>MWS</td>
</tr>
<tr>
<td>Kiani</td>
<td>2006</td>
<td></td>
<td>1.24 (0.78, 1.97)</td>
<td>0.71</td>
<td></td>
<td>OVA11647</td>
<td>AHS</td>
</tr>
<tr>
<td>Lacey</td>
<td>2006</td>
<td></td>
<td>1.05 (0.90, 1.16)</td>
<td>5.84</td>
<td></td>
<td>OVA11649</td>
<td>BCDDP</td>
</tr>
<tr>
<td>Kuriyama</td>
<td>2005</td>
<td></td>
<td>0.87 (0.39, 1.94)</td>
<td>0.25</td>
<td></td>
<td>OVA11690</td>
<td>Miyagi Cohort Study</td>
</tr>
<tr>
<td>Niwa</td>
<td>2005</td>
<td></td>
<td>1.52 (1.05, 2.21)</td>
<td>1.07</td>
<td></td>
<td>OVA09951</td>
<td>JACC Study</td>
</tr>
<tr>
<td>Rapp</td>
<td>2005</td>
<td></td>
<td>1.08 (0.89, 1.32)</td>
<td>3.17</td>
<td></td>
<td>OVA11689</td>
<td>VHM &amp; PP</td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td></td>
<td>1.08 (0.93, 1.26)</td>
<td>4.55</td>
<td></td>
<td>OVA09688</td>
<td>IWHS</td>
</tr>
<tr>
<td>Engelund</td>
<td>2003</td>
<td></td>
<td>0.99 (0.96, 1.01)</td>
<td>12.48</td>
<td></td>
<td>OVA01399</td>
<td>NTBS</td>
</tr>
<tr>
<td>Schouten</td>
<td>2003</td>
<td></td>
<td>1.15 (0.92, 1.43)</td>
<td>2.68</td>
<td></td>
<td>OVA04756</td>
<td>NLCS</td>
</tr>
<tr>
<td>Lukanova</td>
<td>2002</td>
<td></td>
<td>0.68 (0.49, 0.95)</td>
<td>1.32</td>
<td></td>
<td>OVA03222</td>
<td>NYUWHS, NSHDS &amp; ORDET</td>
</tr>
<tr>
<td>Rodriguez</td>
<td>2002</td>
<td></td>
<td>1.09 (1.03, 1.16)</td>
<td>10.17</td>
<td></td>
<td>OVA04449</td>
<td>CPS II</td>
</tr>
<tr>
<td>Tomberg</td>
<td>1994</td>
<td></td>
<td>0.93 (0.81, 1.08)</td>
<td>4.78</td>
<td></td>
<td>OVA06379</td>
<td>Central Sweden</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.06 (1.02, 1.11)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 184 Figure Dose-response meta-analysis of BMI and ovarian cancer, per 5 units, by menopausal status**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 5 units</th>
<th>%</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>Study Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Postmenopausal women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canchola</td>
<td>2010</td>
<td>0.98 (0.83, 1.15)</td>
<td>5.93</td>
<td>OVA11627</td>
<td>CTS</td>
<td></td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>1.01 (0.92, 1.11)</td>
<td>11.83</td>
<td>OVA11658</td>
<td>NHS II</td>
<td></td>
</tr>
<tr>
<td>Lehmann</td>
<td>2009</td>
<td>1.18 (1.03, 1.38)</td>
<td>7.10</td>
<td>OVA11636</td>
<td>EPIC</td>
<td></td>
</tr>
<tr>
<td>Song</td>
<td>2008</td>
<td>1.29 (0.95, 1.76)</td>
<td>1.91</td>
<td>OVA11688</td>
<td>KCPS</td>
<td></td>
</tr>
<tr>
<td>Lundqvist</td>
<td>2007</td>
<td>1.00 (0.82, 1.22)</td>
<td>4.17</td>
<td>OVA11656</td>
<td>Sweden, Finland Co-twin study</td>
<td></td>
</tr>
<tr>
<td>Reeves</td>
<td>2007</td>
<td>1.06 (0.97, 1.14)</td>
<td>13.89</td>
<td>OVA11653</td>
<td>MWS</td>
<td></td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td>1.08 (0.93, 1.26)</td>
<td>6.38</td>
<td>OVA09688</td>
<td>IWHS</td>
<td></td>
</tr>
<tr>
<td>Engeland</td>
<td>2003</td>
<td>0.99 (0.96, 1.03)</td>
<td>21.65</td>
<td>OVA01399</td>
<td>NTBS</td>
<td></td>
</tr>
<tr>
<td>Schouten</td>
<td>2003</td>
<td>1.15 (0.92, 1.43)</td>
<td>3.55</td>
<td>OVA04756</td>
<td>NLCS</td>
<td></td>
</tr>
<tr>
<td>Rodriguez</td>
<td>2002</td>
<td>1.10 (1.03, 1.17)</td>
<td>16.83</td>
<td>OVA04449</td>
<td>CPS II</td>
<td></td>
</tr>
<tr>
<td>Tornberg</td>
<td>1994</td>
<td>0.93 (0.81, 1.08)</td>
<td>6.76</td>
<td>OVA05379</td>
<td>Central Sweden</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (I-squared = 45.9%, p = 0.047)</strong></td>
<td></td>
<td>1.04 (1.00, 1.09)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Premenopausal women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>1.06 (0.93, 1.22)</td>
<td>20.96</td>
<td>OVA11658</td>
<td>NHS I</td>
<td></td>
</tr>
<tr>
<td>Lehmann</td>
<td>2009</td>
<td>1.09 (0.84, 1.40)</td>
<td>11.18</td>
<td>OVA11636</td>
<td>EPIC</td>
<td></td>
</tr>
<tr>
<td>Lundqvist</td>
<td>2007</td>
<td>1.34 (1.10, 1.69)</td>
<td>13.88</td>
<td>OVA11656</td>
<td>Sweden, Finland Co-twin study</td>
<td></td>
</tr>
<tr>
<td>Reeves</td>
<td>2007</td>
<td>1.13 (0.90, 1.41)</td>
<td>12.82</td>
<td>OVA11653</td>
<td>MWS</td>
<td></td>
</tr>
<tr>
<td>Engeland</td>
<td>2003</td>
<td>0.98 (0.95, 1.02)</td>
<td>31.64</td>
<td>OVA01399</td>
<td>NTBS</td>
<td></td>
</tr>
<tr>
<td>Tornberg</td>
<td>1994</td>
<td>1.23 (0.93, 1.63)</td>
<td>9.52</td>
<td>OVA05379</td>
<td>Central Sweden</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (I-squared = 59.6%, p = 0.030)</strong></td>
<td></td>
<td>1.10 (0.99, 1.22)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

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

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

- Reference categories
- RR for BMI exposure
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, \(I^2=0\%\), \(p_{\text{heterogeneity}}=0.55\)).

Heterogeneity
There was no evidence of heterogeneity, \(I^2=0\%\), \(p_{\text{heterogeneity}}=0.55\).

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 \(\geq 80\) 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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brändstedt, 2011</td>
<td>Sweden</td>
<td>Malmo Diet and Cancer Cohort</td>
<td>93</td>
<td>13.1 years</td>
<td>0.96</td>
<td>0.57</td>
<td>1.59</td>
<td>(\geq 71) vs. (&lt; 62) kg</td>
</tr>
<tr>
<td>Lahmann, 2009</td>
<td>10 European</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>611</td>
<td>8.9 years</td>
<td>1.27</td>
<td>1.00</td>
<td>1.61</td>
<td>(&gt; 72.6) vs. (&lt; 58.1) kg Per 5 kg</td>
</tr>
<tr>
<td>Lacey, 2006</td>
<td>USA</td>
<td>Breast Cancer Detection Demonstration Project Follow-Up Study</td>
<td>346</td>
<td>14.5 years</td>
<td>1.09</td>
<td>0.77</td>
<td>1.55</td>
<td>(\geq 161) vs. (&lt; 120) lbs Per 5 lbs</td>
</tr>
</tbody>
</table>
Table 195 Overall evidence on weight and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Two cohort studies reported on weight and ovarian cancer. Both studies showed non-significant positive associations between weight and ovarian cancer risk.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1129</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.05 (1.02-1.07)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 5 kg</td>
</tr>
<tr>
<td>Heterogeneity (I^2, p-value)</td>
<td>-</td>
<td>0%, p=0.55</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
Table 197 Inclusion/exclusion table for meta-analysis of weight and ovarian cancer

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

287
Figure 189 Highest versus lowest forest plot of weight and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>1.27 (1.00, 1.61)</td>
<td>OVA11636</td>
<td>EPIC</td>
<td>&gt;72.6 vs. &lt;58.1 kg</td>
</tr>
<tr>
<td>Lacey</td>
<td>2006</td>
<td>1.09 (0.77, 1.55)</td>
<td>OVA11649</td>
<td>BCDP</td>
<td>&gt;=161 vs. &lt;=120 lbs</td>
</tr>
<tr>
<td>Schouten</td>
<td>2003</td>
<td>1.32 (0.78, 2.25)</td>
<td>OVA04756</td>
<td>NLCS</td>
<td>&gt;=80 vs. &lt;65 kg</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Gender</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>Female</td>
<td>1.05 (1.01, 1.08)</td>
<td>65.23</td>
<td>OVA11636</td>
<td>EPIC</td>
</tr>
<tr>
<td>Lacey</td>
<td>2006</td>
<td>Female</td>
<td>1.02 (0.97, 1.08)</td>
<td>24.34</td>
<td>OVA11649</td>
<td>BCDP</td>
</tr>
<tr>
<td>Schouten</td>
<td>2003</td>
<td>Female</td>
<td>1.08 (0.99, 1.17)</td>
<td>10.44</td>
<td>OVA04756</td>
<td>NLCS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.05 (1.02, 1.07)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1-squared = 0.0%, p = 0.550)
Figure 191 Dose-response graph of weight and ovarian cancer, per 5 kg

- Lahmann 2009
- Lacey 2006
- Schouten 2003

Weight (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, $\hat{I}^2=0\%$, $p_{\text{heterogeneity}}=0.69$).

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

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

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

*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

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>One study reported a positive correlation between waist circumference and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1049</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.03 (0.97-1.10)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 10 cm</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.69</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
### Table 201: Inclusion/exclusion table for meta-analysis of waist circumference and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11644</td>
<td>Brändstedt</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>Malmo Diet and Cancer Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Overlap with Lahmann et al OVA11636</td>
</tr>
<tr>
<td>OVA11629</td>
<td>Chionh</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Melbourne Collaborative Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Midpoints</td>
</tr>
<tr>
<td>OVA11627</td>
<td>Canchola</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Only two categories of exposure</td>
</tr>
<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 1</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 2</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11636</td>
<td>Lahmann</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Midpoints, distribution of person-years</td>
</tr>
<tr>
<td>OVA02953</td>
<td>Lapidus</td>
<td>1988</td>
<td>Prospective cohort study</td>
<td>Gothenburg</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
<td>No risk estimate reported</td>
</tr>
</tbody>
</table>
Figure 192 Highest versus lowest forest plot of waist circumference and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>1.12 (0.86, 1.45)</td>
<td>OVA11636</td>
<td>EPIC</td>
<td>&gt;87 vs. &lt;71.7 cm</td>
</tr>
<tr>
<td>Canchola</td>
<td>2010</td>
<td>1.41 (0.97, 2.05)</td>
<td>OVA11627</td>
<td>CTS</td>
<td>&gt;=35 vs. &lt;35 inches</td>
</tr>
<tr>
<td>Chionh</td>
<td>2010</td>
<td>0.96 (0.54, 1.69)</td>
<td>OVA11629</td>
<td>MCCS</td>
<td>&gt;=87 vs. &lt;71.2 cm</td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>0.99 (0.59, 1.64)</td>
<td>OVA11658</td>
<td>NHS I</td>
<td>&gt;=35 vs. &lt;28 inches</td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>1.12 (0.35, 3.57)</td>
<td>OVA11658</td>
<td>NHS II</td>
<td>&gt;=35 vs. &lt;28 inches</td>
</tr>
</tbody>
</table>

Figure 193 Dose-response meta-analysis of waist circumference and ovarian cancer, per 10 cm

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chionh</td>
<td>2010</td>
<td>1.03 (0.87, 1.23)</td>
<td>13.47</td>
<td>OVA11629</td>
<td>MCCS</td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>1.18 (0.86, 1.62)</td>
<td>3.99</td>
<td>OVA11658</td>
<td>NHS II</td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>0.97 (0.83, 1.13)</td>
<td>16.97</td>
<td>OVA11658</td>
<td>NHS I</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>1.04 (0.96, 1.13)</td>
<td>65.57</td>
<td>OVA11636</td>
<td>EPIC</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.694)</td>
<td></td>
<td></td>
<td></td>
<td>1.03 (0.97, 1.10)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
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, I²=81.1%, p heterogeneity=0.005).

Heterogeneity
There was high heterogeneity, I²=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

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brändstedt, 2011</td>
<td>Sweden</td>
<td>Malmo Diet and Cancer Cohort</td>
<td>93</td>
<td>13.1 years</td>
<td>0.77</td>
<td>0.45</td>
<td>1.29</td>
<td>≥101 vs. &lt;93 cm</td>
</tr>
<tr>
<td>Kotsopoulos, 2010</td>
<td>USA</td>
<td>Nurses’ Health Study I</td>
<td>273</td>
<td>20 years</td>
<td>0.67</td>
<td>0.39</td>
<td>1.17</td>
<td>43-65 vs. &lt;37 inches</td>
</tr>
<tr>
<td>Kotsopoulos, 2010</td>
<td>USA</td>
<td>Nurses’ Health Study II</td>
<td>52</td>
<td>12 years</td>
<td>1.12</td>
<td>0.35</td>
<td>3.57</td>
<td>43-65 vs. &lt;37 inches</td>
</tr>
<tr>
<td>Lahmann, 2009</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>611</td>
<td>8.9 years</td>
<td>1.33</td>
<td>1.06</td>
<td>1.70</td>
<td>&gt;106.0 vs &lt;94.7 cm Per 5 cm</td>
</tr>
</tbody>
</table>

Table 203 Overall evidence on hip circumference and ovarian cancer

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>One study reported a non-significant positive correlation between hip circumference and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Three cohort studies reported on hip circumference and ovarian cancer. The largest of these studies found a positive association.</td>
</tr>
</tbody>
</table>
**Table 204 Summary of results of the dose-response meta-analysis of hip circumference and ovarian cancer**

<table>
<thead>
<tr>
<th></th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>936</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.01 (0.75-1.36)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 10 cm</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>81.1%, p=0.005</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report*
Table 205 Inclusion/exclusion table for meta-analysis of hip circumference and ovarian cancer

<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11644</td>
<td>Brändstedt</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>Malmo Diet and Cancer Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Overlap with Lahmann et al OVA11636</td>
</tr>
<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 1</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 2</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA11636</td>
<td>Lahmann</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, distribution of person-years</td>
<td></td>
</tr>
<tr>
<td>OVA02953</td>
<td>Lapidus</td>
<td>1988</td>
<td>Prospective cohort study</td>
<td>Gothenburg</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
<td>No risk estimate reported</td>
</tr>
</tbody>
</table>
Figure 195 Highest versus lowest forest plot of hip circumference and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotsopulos</td>
<td>2010</td>
<td>1.12 (0.35, 3.57)</td>
<td>OVA11658</td>
<td>NHS II</td>
<td>43-65 vs. &lt;37 inches</td>
</tr>
<tr>
<td>Kotsopulos</td>
<td>2010</td>
<td>0.67 (0.39, 1.17)</td>
<td>OVA11658</td>
<td>NHS I</td>
<td>43-65 vs. &lt;37 inches</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>1.33 (1.04, 1.70)</td>
<td>OVA11636</td>
<td>EPIC</td>
<td>&gt;106.0 vs. &lt;94.7 cm</td>
</tr>
</tbody>
</table>

Figure 196 Dose-response meta-analysis of hip circumference and ovarian cancer, per 10 cm

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 10 cm</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotsopulos</td>
<td>2010</td>
<td></td>
<td></td>
<td>1.29 (0.82, 2.04)</td>
<td>21.83</td>
<td>OVA11658</td>
<td>NHS II</td>
</tr>
<tr>
<td>Kotsopulos</td>
<td>2010</td>
<td></td>
<td></td>
<td>0.76 (0.61, 0.96)</td>
<td>35.36</td>
<td>OVA11658</td>
<td>NHS I</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td></td>
<td></td>
<td>1.12 (1.03, 1.22)</td>
<td>42.81</td>
<td>OVA11636</td>
<td>EPIC</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td>1.01 (0.75, 1.36)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 197 Dose-response graph of hip circumference and ovarian cancer

Kotsopoulos 2010

Kotsopoulos 2010

Lahmann 2009

Hip circumference (cm)
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, I²=0%, p_heterogeneity=0.45).

Heterogeneity
There was no heterogeneity, I²=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>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LC1</th>
<th>UC1</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brändstedt, 2011</td>
<td>Sweden</td>
<td>Malmo Diet and Cancer Cohort</td>
<td>93</td>
<td>13.1 years</td>
<td>0.60</td>
<td>0.36</td>
<td>1.00</td>
<td>≥0.81 vs. &lt;0.77 units</td>
</tr>
<tr>
<td>Canchola, 2010</td>
<td>USA</td>
<td>California Teachers Study</td>
<td>277</td>
<td>12.1 years</td>
<td>0.95</td>
<td>0.79</td>
<td>1.06</td>
<td>≥0.80 vs. &lt;0.80 units, never used HT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
<td>0.48</td>
<td>1.60 vs. 1.68</td>
</tr>
<tr>
<td>Kotsopoulos, 2010</td>
<td>USA</td>
<td>Nurses’ Health Study I</td>
<td>273</td>
<td>20 years</td>
<td>0.78</td>
<td>0.52</td>
<td>1.16</td>
<td>≥0.84 vs. &lt;0.73 units</td>
</tr>
<tr>
<td>Kotsopoulos, 2010</td>
<td>USA</td>
<td>Nurses’ Health Study II</td>
<td>52</td>
<td>12 years</td>
<td>1.08</td>
<td>0.46</td>
<td>2.56</td>
<td>≥0.84 vs. &lt;0.73 units</td>
</tr>
<tr>
<td>Lahmann, 2009</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>611</td>
<td>8.9 years</td>
<td>0.91</td>
<td>0.72</td>
<td>1.17</td>
<td>&gt;0.83 vs. &lt;0.74 units Per 0.05 units</td>
</tr>
</tbody>
</table>
*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

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>One study reported a positive correlation between waist-to-hip ratio and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Seven cohort studies reported on waist-to-hip ratio and ovarian cancer.</td>
</tr>
<tr>
<td></td>
<td>None of these studies found a significant association.</td>
</tr>
</tbody>
</table>

Table 208 Summary of results of the dose-response meta-analysis of waist-to-hip ratio and ovarian cancer

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR*</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>-</td>
<td>1166</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>0.99 (0.92-1.06)</td>
</tr>
<tr>
<td>Quantity</td>
<td>-</td>
<td>Per 10 cm</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>-</td>
<td>0%, p=0.45</td>
</tr>
</tbody>
</table>

*No meta-analysis was conducted in the 2nd report
<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11644</td>
<td>Brändstedt</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>Malmo Diet and Cancer Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Overlap with Lahmann et al OVA11636</td>
</tr>
<tr>
<td>OVA11627</td>
<td>Canchola</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>California Teachers Study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Only two categories of exposure</td>
</tr>
<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 1</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
</tr>
<tr>
<td>OVA11658</td>
<td>Kotsopoulos</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study 2</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
</tr>
<tr>
<td>OVA11636</td>
<td>Lahmann</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, distribution of person-years</td>
</tr>
<tr>
<td>OVA09688</td>
<td>Andersson</td>
<td>2004</td>
<td>Prospective cohort study</td>
<td>Iowa Women’s Health Initiative</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>OVA03222</td>
<td>Lukanova</td>
<td>2002</td>
<td>Nested case-control study</td>
<td>New York University Women’s Health Study &amp; the ORDET Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Exposure level not available</td>
<td></td>
</tr>
<tr>
<td>OVA03556</td>
<td>Mink</td>
<td>1996</td>
<td>Prospective cohort study</td>
<td>Iowa Women’s Health Initiative</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Overlap with Andersson et al, 2004, OVA09688</td>
</tr>
<tr>
<td>OVA02953</td>
<td>Lapidus</td>
<td>1988</td>
<td>Prospective cohort study</td>
<td>Gothenburg</td>
<td>Incidence</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No risk estimate reported</td>
</tr>
</tbody>
</table>
Figure 198 Highest versus lowest forest plot of waist-to-hip ratio and ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canchola</td>
<td>2010</td>
<td>0.93 (0.64, 1.36)</td>
<td>OVA11627</td>
<td>CTS</td>
<td>&gt;=0.80 vs. &lt;0.80 units</td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>0.78 (0.52, 1.16)</td>
<td>OVA11658</td>
<td>NHS I</td>
<td>&gt;=0.84 vs. &lt;0.73 units</td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>1.08 (0.46, 2.55)</td>
<td>OVA11658</td>
<td>NHS II</td>
<td>&gt;=0.84 vs. &lt;0.73 units</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>0.91 (0.72, 1.17)</td>
<td>OVA11636</td>
<td>EPIC</td>
<td>&gt;0.83 vs. &lt;0.74 units</td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td>1.59 (1.05, 2.40)</td>
<td>OVA09688</td>
<td>IWHS</td>
<td>&gt;0.89 vs. &lt;=0.78 units</td>
</tr>
<tr>
<td>Lukanova</td>
<td>2002</td>
<td>1.58 (0.45, 5.48)</td>
<td>OVA03222</td>
<td>NYUWHS &amp; ORDET</td>
<td>Tertile 3 vs. 1</td>
</tr>
</tbody>
</table>

Figure 199 Dose-response meta-analysis of waist-to-hip ratio and ovarian cancer, per 0.1 units

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Per 0.1 units RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>0.99 (0.81, 1.20)</td>
<td>13.55</td>
<td>OVA11658</td>
<td>NHS I</td>
</tr>
<tr>
<td>Kotsopoulos</td>
<td>2010</td>
<td>1.00 (0.64, 1.56)</td>
<td>2.72</td>
<td>OVA11658</td>
<td>NHS II</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>0.96 (0.88, 1.05)</td>
<td>68.85</td>
<td>OVA11636</td>
<td>EPIC</td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td>1.14 (0.94, 1.38)</td>
<td>14.88</td>
<td>OVA09688</td>
<td>IWHS</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.99 (0.92, 1.06)</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Author/year</th>
<th>Country</th>
<th>Study name</th>
<th>Number of cases</th>
<th>Years of follow-up</th>
<th>RR</th>
<th>LCI</th>
<th>UCI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass, 2012</td>
<td>Japan</td>
<td>Japan Public Health Center-based Prospective Study</td>
<td>86</td>
<td>16 years</td>
<td>1.03</td>
<td>0.68</td>
<td>1.55</td>
<td>Per 10 cm</td>
</tr>
<tr>
<td>Green, 2011</td>
<td>United Kingdom</td>
<td>Million Women’s Study</td>
<td>4830</td>
<td>9.4 years</td>
<td>1.17</td>
<td>1.09</td>
<td>1.25</td>
<td>Per 10 cm</td>
</tr>
<tr>
<td>Brändstedt, 2011</td>
<td>Sweden</td>
<td>Malmo Diet and Cancer Cohort</td>
<td>93</td>
<td>13.1 years</td>
<td>1.15</td>
<td>0.69</td>
<td>1.91</td>
<td>≥166 vs. &lt;160 cm</td>
</tr>
<tr>
<td>Chionh, 2010</td>
<td>Australia</td>
<td>Melbourne Collaborative Cohort Study</td>
<td>113</td>
<td>10.2 years</td>
<td>1.13</td>
<td>0.82</td>
<td>1.55</td>
<td>Per 10 cm ≥164.3 vs. &lt;155.2 cm</td>
</tr>
<tr>
<td>Lahmann, 2009</td>
<td>Europe</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>611</td>
<td>8.9 years</td>
<td>1.12</td>
<td>0.87</td>
<td>1.45</td>
<td>&gt;166.2 vs. &lt;157.0 cm</td>
</tr>
<tr>
<td>Sung, 2009</td>
<td>Korea</td>
<td>Korean Cancer Prevention Study</td>
<td>398</td>
<td>8.72 years</td>
<td>1.68</td>
<td>1.08</td>
<td>2.48</td>
<td>&gt;158 vs. &lt;151.1 cm Per 5 cm</td>
</tr>
<tr>
<td>Song, 2008</td>
<td>Korea</td>
<td>Korean Cancer Prevention Study</td>
<td>143 deaths</td>
<td>9.86 years</td>
<td>2.73</td>
<td>1.31</td>
<td>5.70</td>
<td>≥161 vs. &lt;149 cm Per 5 cm</td>
</tr>
<tr>
<td>Baer, 2008</td>
<td>USA</td>
<td>Nurses’ Health Study 1</td>
<td>735</td>
<td>28 years</td>
<td>1.27</td>
<td>0.88</td>
<td>1.82</td>
<td>≥1.75 vs. &lt;1.6 m</td>
</tr>
<tr>
<td>Baer, 2008</td>
<td>USA</td>
<td>Nurses’ Health Study 2</td>
<td>137</td>
<td>16 years</td>
<td>2.35</td>
<td>1.19</td>
<td>4.63</td>
<td>≥1.75 vs. &lt;1.6 m</td>
</tr>
<tr>
<td>Lundqvist, 2007</td>
<td>Sweden</td>
<td>Swedish and Finnish Twin Cohort Studies</td>
<td>268</td>
<td>26.3 years</td>
<td>1.7</td>
<td>0.8</td>
<td>3.5</td>
<td>Quartile 4 vs. 1</td>
</tr>
<tr>
<td>Lacey, 2006</td>
<td>USA</td>
<td>Breast Cancer Detection Demonstration Project Follow-Up Study</td>
<td>346</td>
<td>14.5 years</td>
<td>0.90</td>
<td>0.64</td>
<td>1.26</td>
<td>≥66 vs. &lt;62 inches Per 1 inch</td>
</tr>
</tbody>
</table>
Table 211 Table of overall evidence

<table>
<thead>
<tr>
<th>SLR</th>
<th>Summary of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 SLR</td>
<td>Six cohort studies reported on height and ovarian cancer.</td>
</tr>
<tr>
<td>Continuous Update Project</td>
<td>Ten additional cohort studies reported on height and ovarian cancer, of which three found statistically significant positive associations and the remaining studies were null.</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>SLR</th>
<th>Continuous Update Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies (n)</td>
<td>3</td>
<td>14*</td>
</tr>
<tr>
<td>Cases (n)</td>
<td>8277</td>
<td>17312</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.15 (1.08-1.21)</td>
<td>1.08 (1.05-1.10)</td>
</tr>
<tr>
<td>Quantity</td>
<td>Per 10 cm</td>
<td>Per 5 cm</td>
</tr>
<tr>
<td>Heterogeneity (I², p-value)</td>
<td>32.5%, p=not available</td>
<td>34.8%, p=0.10</td>
</tr>
</tbody>
</table>

* One study reported a risk estimate for two studies combined (Lundqvist et al, 2007). Thirteen risk estimates are included in the analysis.
<table>
<thead>
<tr>
<th>WCRF code</th>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>Study name</th>
<th>Cancer outcome</th>
<th>SLR</th>
<th>CU dose-response</th>
<th>CU H vs. L forest plot</th>
<th>Estimated values</th>
<th>Exclusion reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVA11669</td>
<td>Weiderpass</td>
<td>2012</td>
<td>Prospective cohort study</td>
<td>Japan Public Health-Center Based Prospective Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Only continuous result</td>
</tr>
<tr>
<td>OVA11677</td>
<td>Green</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>Million Women’s Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Only continuous result</td>
</tr>
<tr>
<td>OVA11644</td>
<td>Brändstedt</td>
<td>2011</td>
<td>Prospective cohort study</td>
<td>Malmo Diet and Cancer Cohort study</td>
<td>Incidence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Overlap with Lahmann et al 2009</td>
</tr>
<tr>
<td>OVA11629</td>
<td>Chionh</td>
<td>2010</td>
<td>Prospective cohort study</td>
<td>Melbourne Collaborative Cohort Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>OVA11636</td>
<td>Lahmann</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, distribution of person-years</td>
<td></td>
</tr>
<tr>
<td>OVA11687</td>
<td>Sung</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>Korean Cancer Prevention Study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>OVA11688</td>
<td>Song</td>
<td>2008</td>
<td>Prospective cohort study</td>
<td>Korean Cancer Prevention Study</td>
<td>Mortality</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Overlap with Sung et al, 2009</td>
</tr>
<tr>
<td>OVA11632</td>
<td>Baer</td>
<td>2008</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study I</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>OVA11632</td>
<td>Baer</td>
<td>2008</td>
<td>Prospective cohort study</td>
<td>Nurses’ Health Study II</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>OVA11656</td>
<td>Lundqvist</td>
<td>2007</td>
<td>Prospective cohort study</td>
<td>Sweden, Finland Co-twin study</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints, distribution of person-years</td>
<td></td>
</tr>
<tr>
<td>OVA11649</td>
<td>Lacey</td>
<td>2006</td>
<td>Prospective cohort study</td>
<td>Breast cancer Detection Demonstration Project</td>
<td>Incidence</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>OVA09688</td>
<td>Anderson</td>
<td>2004</td>
<td>Prospective cohort study</td>
<td>Iowa Women’s Health Study</td>
<td>Incidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
</tr>
<tr>
<td>Study ID</td>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Population</td>
<td>Incidence</td>
<td>Mortality</td>
<td>Risk Estimate</td>
<td>Midpoints</td>
<td>Overlap with Lundqvist et al OVA11656</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-------</td>
<td>------------------------------</td>
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<td>-----------</td>
<td>-----------</td>
<td>---------------</td>
<td>-----------</td>
<td>--------------------------------------</td>
<td></td>
</tr>
<tr>
<td>OVA02429</td>
<td>Jonsson</td>
<td>2003</td>
<td>Prospective cohort study</td>
<td>Swedish Twin Cohort</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVA04756</td>
<td>Schouten</td>
<td>2003</td>
<td>Prospective cohort study</td>
<td>Netherlands Cohort Study</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
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<tr>
<td>OVA01399</td>
<td>Engeland</td>
<td>2003</td>
<td>Prospective cohort study</td>
<td>Norwegian Tuberculosis Screening Programme</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
<td></td>
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<tr>
<td>OVA03222</td>
<td>Lukanova</td>
<td>2002</td>
<td>Nested case-control study</td>
<td>New York University Women’s Health Study, Northern Sweden Health and Disease Study, ORDET Study</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
<td>Results reported in text only, cut-points and results for the overall sample not available, only subgroup below age 55 years</td>
<td></td>
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<tr>
<td>OVA04449</td>
<td>Rodriguez</td>
<td>2002</td>
<td>Prospective cohort study</td>
<td>Cancer Prevention Study II</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Midpoints</td>
<td></td>
<td></td>
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<tr>
<td>OVA02953</td>
<td>Lapidus</td>
<td>1987</td>
<td>Prospective cohort study</td>
<td>Gothenburg</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
<td>No risk estimate reported</td>
<td></td>
</tr>
</tbody>
</table>
Figure 201 Height and ovarian cancer, cancer, highest vs. lowest

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
<th>contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chionh</td>
<td>2010</td>
<td>0.97 (0.64, 1.47)</td>
<td>OVA11629</td>
<td>MCCS</td>
<td>&gt;=164.3 vs. &lt;155.2 cm</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>1.12 (0.87, 1.45)</td>
<td>OVA11636</td>
<td>EPIC</td>
<td>&gt;166.2 vs. &lt;157.0</td>
</tr>
<tr>
<td>Sung</td>
<td>2009</td>
<td>1.68 (1.14, 2.48)</td>
<td>OVA11687</td>
<td>KCPS</td>
<td>&gt;158.0 vs. &lt;151.0 cm</td>
</tr>
<tr>
<td>Baer</td>
<td>2008</td>
<td>1.27 (0.88, 1.82)</td>
<td>OVA11632</td>
<td>NHS I</td>
<td>&gt;=175 vs. &lt;160 cm</td>
</tr>
<tr>
<td>Baer</td>
<td>2008</td>
<td>2.35 (1.19, 4.63)</td>
<td>OVA11682</td>
<td>NHS II</td>
<td>&gt;=175 vs. &lt;160 cm</td>
</tr>
<tr>
<td>Lundqvist</td>
<td>2007</td>
<td>1.50 (1.10, 2.00)</td>
<td>OVA11656</td>
<td>Sweden, Finland Co-twin study</td>
<td>&gt;=167.34 vs. &lt;157.58 cm</td>
</tr>
<tr>
<td>Lacey</td>
<td>2006</td>
<td>0.90 (0.64, 1.26)</td>
<td>OVA11649</td>
<td>BCDDP</td>
<td>&gt;=167.64 vs. &lt;157.23 cm</td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td>1.12 (0.78, 1.61)</td>
<td>OVA09688</td>
<td>IWHS</td>
<td>&gt;165 vs. &lt;155 cm</td>
</tr>
<tr>
<td>England</td>
<td>2003</td>
<td>1.29 (1.11, 1.51)</td>
<td>OVA01399</td>
<td>NTBS</td>
<td>&gt;=175 vs. 160-164 cm</td>
</tr>
<tr>
<td>Schouten</td>
<td>2003</td>
<td>2.17 (1.14, 4.13)</td>
<td>OVA04756</td>
<td>NLCS</td>
<td>176.7 vs. 155.7 cm</td>
</tr>
<tr>
<td>Rodriguez</td>
<td>2002</td>
<td>1.41 (0.95, 2.09)</td>
<td>OVA04449</td>
<td>CPS II</td>
<td>&gt;=177 vs. 152-157 cm</td>
</tr>
</tbody>
</table>

Figure 202 Dose-response meta-analysis of height and ovarian cancer, per 5 cm

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>WCRF_Code</th>
<th>StudyDescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiderpass</td>
<td>2012</td>
<td>1.01 (0.82, 1.24)</td>
<td>1.28</td>
<td>OVA11669</td>
<td>JPHC</td>
</tr>
<tr>
<td>Green</td>
<td>2011</td>
<td>1.08 (1.04, 1.15)</td>
<td>13.20</td>
<td>OVA11677</td>
<td>MWS</td>
</tr>
<tr>
<td>Chionh</td>
<td>2010</td>
<td>1.08 (0.91, 1.24)</td>
<td>2.08</td>
<td>OVA11629</td>
<td>MCCS</td>
</tr>
<tr>
<td>Lahmann</td>
<td>2009</td>
<td>1.05 (0.98, 1.12)</td>
<td>8.78</td>
<td>OVA11636</td>
<td>EPIC</td>
</tr>
<tr>
<td>Sung</td>
<td>2009</td>
<td>1.24 (1.08, 1.41)</td>
<td>2.87</td>
<td>OVA11687</td>
<td>KCPS</td>
</tr>
<tr>
<td>Baer</td>
<td>2008</td>
<td>1.08 (1.01, 1.15)</td>
<td>9.86</td>
<td>OVA11632</td>
<td>NHS I</td>
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<tr>
<td>Baer</td>
<td>2008</td>
<td>1.21 (1.06, 1.38)</td>
<td>2.89</td>
<td>OVA11632</td>
<td>NHS II</td>
</tr>
<tr>
<td>Lundqvist</td>
<td>2007</td>
<td>1.18 (1.06, 1.27)</td>
<td>5.90</td>
<td>OVA11656</td>
<td>Sweden, Finland Co-twin study</td>
</tr>
<tr>
<td>Lacey</td>
<td>2006</td>
<td>1.00 (0.90, 1.08)</td>
<td>5.71</td>
<td>OVA11649</td>
<td>BCDDP</td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td>1.03 (0.94, 1.13)</td>
<td>5.49</td>
<td>OVA09688</td>
<td>IWHS</td>
</tr>
<tr>
<td>England</td>
<td>2003</td>
<td>1.07 (1.05, 1.09)</td>
<td>24.09</td>
<td>OVA01399</td>
<td>NTBS</td>
</tr>
<tr>
<td>Schouten</td>
<td>2003</td>
<td>1.19 (1.04, 1.37)</td>
<td>2.72</td>
<td>OVA04756</td>
<td>NLCS</td>
</tr>
<tr>
<td>Rodriguez</td>
<td>2002</td>
<td>1.05 (1.00, 1.09)</td>
<td>15.13</td>
<td>OVA04449</td>
<td>CPS II</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1.08 (1.05, 1.10)</td>
<td>100.00</td>
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</tbody>
</table>
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

\[ p = 0.09 \]

![Graph of height and ovarian cancer](image)

Table 214 Non-linear relative risks of height and ovarian cancer

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>150</td>
<td>1.00</td>
</tr>
<tr>
<td>155</td>
<td>1.04 (1.00-1.08)</td>
</tr>
<tr>
<td>160</td>
<td>1.09 (1.03-1.16)</td>
</tr>
<tr>
<td>165</td>
<td>1.17 (1.09-1.25)</td>
</tr>
<tr>
<td>170</td>
<td>1.27 (1.18-1.35)</td>
</tr>
<tr>
<td>175</td>
<td>1.39 (1.31-1.48)</td>
</tr>
<tr>
<td>180</td>
<td>1.56 (1.45-1.68)</td>
</tr>
</tbody>
</table>

Figure 206 Scatter plot of relative risks of ovarian cancer for height categories

![Scatter plot](image)

- X: Reference categories
- ○: RR for Height exposure
Reference List


