The Associations between Food, Nutrition and Physical Activity and the Risk of Skin Cancers

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List of abbreviations

List of Abbreviations used in the CUP Report

BCC	Basal cell carcinoma
BMI	Body Mass Index
CI	Confidence interval
CUP	Continuous Update Project
HR	Hazard ratio
HRT	Hormone replacement therapy
IRR	Incidence Rate Ratio
MM	Malignant melanoma
NA	Not available
NMSC	Non-melanoma skin cancer
NS	Not significant
OR	Odds ratio
RR	Relative risk
SCC	Squamous cell carcinoma
SLR	Systematic literature review
SMR	Standardized mortality ratio
WCRF	World Cancer Research Fund

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

AHS	Agricultural Health Study
AHS, 1974	Adventist Health Study
APCSC	Asia-Pacific Cohort Studies Collaboration
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention
CCHS	Copenhagen City Heart Study
CCPPS	Copenhagen Center for Prospective Population Studies
CGPS	Copenhagen General Population Study
CNBSS	Canadian National Breast Screening Study
CPRD	Clinical Practice Research Datalink
DCH	Danish Diet Cancer and Health Study
EPIC	European Prospective Investigation into Cancer and Nutrition
E3N	Etude Epidemiologique aupres de femmes de l'Education Nationale
EPIC-Norfolk	European Prospective Investigation into Cancer and Nutrition-Norfolk
EPIC-Oxford	European Prospective Investigation into Cancer and Nutrition-Oxford
FMCHES	Mobile Clinic Health Examination Survey in Finland
HAHS	Harvard Alumni Cohort
HPALS	Harvard and Pennsylvania Alumni Study

HPFS	Health Professionals Follow-Up
ISOBCC	Isotretinoin-basal cell carcinoma prevention trial
KNHIC	Korean National Health Insurance Corporation Study
KPMCP	Kaiser Permanent Medical Care Program
KPNC	Kaiser Permanente Northern California
Me-Can	The Metabolic Syndrome and Cancer Project
MrOS	Osteoporotic Fractures in Men
MWS	Million Women Study
NHS	Nurses' Health Study
NHS II	Nurses' Health Study II
NSHDC	Northern Sweden Health and Disease Cohort
NSCS	Nambour Skin Cancer Study
NSPT	Norwegian Screening Programme for Tuberculosis
OFPACS	Oxford Family Planning Association Contraceptive Study
PHS	Physicians' Health Study
SCWC	Swedish Construction Workers Cohort
SKICAP	Skin Cancer Prevention Study
SU.VI.MAX	The Supplémentation en Vitamines et Minéraux Antioxydants Study
UBCOS	Uppsala Birth Cohort Multigeneration Study
USRT	United States Radiologic Technologists
VHM-PP	The Vorarlverg Health Monitoring and Prevention Programme
VIP	Västerbotten Intervention Project
VITAL	Vitamins And Lifestyle Study
WHI	Women's Health Initiative
WHI-OS	Women's Health Initiative Observational Study
WHI-DM	Women's Health Initiative Dietary Modification Trial

Background

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

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

The methods of the SLR are described in detail in the protocol for the CUP review on skin cancer (see Appendix 1).

Figure 1 Summary of judgements of the WCRF-AICR Second Expert Report, 2005

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

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Arsenic in drinking water**[1]
Limited — suggestive	Retinol[2]	Selenium supplements[3]
Limited — no conclusion	Potatoes; non-starchy vegetables; fruits; fish; eggs; milk; total fat; cholesterol; coffee; tea; alcohol; protein; vitamin A; retinol (foods); folate; vitamin C; vitamin D; vitamin E; multivitamins; selenium; carotenoids; beta-carotene (melanoma); alpha-carotene; lycopene; physical activity; body fatness; energy intake	
Substantial effect on risk unlikely	Beta-carotene[4] (non-melanoma)	

1 The International Agency for Research on Cancer has graded arsenic and arsenic compounds as Class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water.
2 The evidence is derived from studies using supplements at a dose of 25 000 international units/day. Applies only to squamous cell carcinoma.
3 The evidence is derived from studies using supplements at a dose of 200 µg/day.
4 The evidence is derived from studies using supplements at doses of 30, and 50 mg/day, and from foods containing beta-carotene. See chapter 4.2.

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.

Modifications to the existing protocol

The protocol on skin cancer was prepared in 2005 (see Appendix 1). The modifications to the protocol are outlined in Appendix 2.

Timeline: The current review includes publications included in Medline up to April 19th 2016. The CUP team at ICL updated the search from June 8th 2005 to April 19th 2016 (see Flowchart).

Notes on methods:

The current review and meta-analyses include studies identified during the 2005 SLR and studies identified during the CUP SLR.

Skin cancer (any type or non-specified), malignant melanoma (cutaneous or non-specified), non-melanoma skin cancer, basal cell carcinoma, and squamous cell carcinoma were reviewed separately. The term melanoma has been used as an abbreviation of malignant melanoma in the text. Cutaneous melanoma has been used when the authors explicitly refers to cutaneous melanoma. The term "non-melanoma skin cancer", which refers to keratinocyte cancer, was used in this review for consistency with the reviewed studies.

Linear dose-response meta-analysis was conducted when at least two new publications on skin cancer were identified during the CUP with enough data for dose-response meta-analysis and if the total number of studies was five or more. Only the summary relative risks obtained using random effect models are shown. When the number of studies was insufficient to conduct a dose-response meta-analysis (or other analyses such as stratified analyses, or publication bias tests) this was indicated as "not enough studies".

The increment units used in the linear dose-response meta-analyses were those used in CUP SLR for other cancer sites, and may not be the same used in the meta-analyses in the 2005 SLR on skin cancer. However, when most of the identified studies reported servings or times, these were used as increment unit, as indicated in the Protocol.

Pooled analyses of cohort studies or randomized controlled trials were included with other individual studies in the meta-analysis when possible.

The results of studies on arsenic in drinking water, retinol, selenium, and beta-carotene are presented because the evidence of their association with skin cancer was judged probable, limited suggestive or unlikely in the 2007 Second Expert Report. The results of studies on some other exposures may also be described when meta-analyses were not possible.

The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins, 2002). Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects. The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.

In the funnel plots, the outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of publication or small study bias and heterogeneity. The orange line is the regression line corresponding to the Egger test for funnel-plot asymmetry.

Highest vs. lowest forest plots show the relative risk estimates for the highest vs. the reference category in each study.

The method of Hamling (Hamling, 2008) was used to recalculate relative risks (RRs) and confidence intervals (CIs) for a categorical comparison alternative to that reported by the study.
The dose-response forest plots show the relative risk per unit of increase for each study (most often derived by the CUP review team from categorical data). The relative risk is denoted by a box (larger boxes indicate that the study has higher precision and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and in the summary table for each exposure.

When the 95% CI of a RR spanned 1.00, the association was considered as statistically not significant. When the upper or lower CI was 1.00, the association was considered statistically non-significant.
Dose-response plots showing the RR estimates for each exposure level in the studies are also presented for each exposure in the review. The relative risks estimates were plotted in the mid-point of each category level (x-axis) and connected through lines.

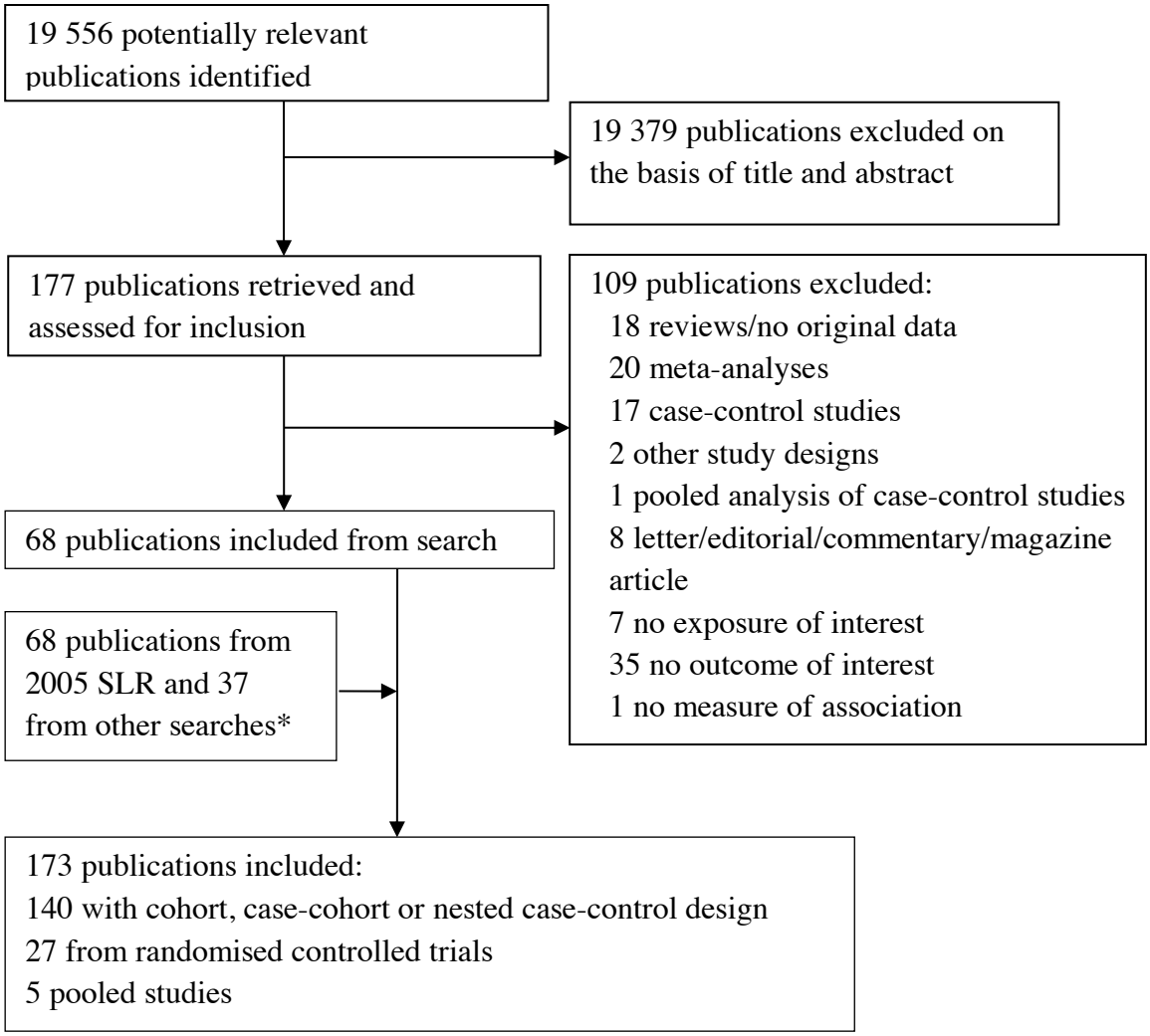
Exploratory non-linear dose-response meta-analyses were conducted only when there were five or more studies with three or more categories of exposure – a requirement of the restricted cubic splines method. Non-linear dose response curves were plotted using restricted cubic splines for each study, with knots fixed at percentiles 10%, 50%, and 90% through the distribution. These were combined using multivariate meta-analysis. Non-linear meta-analyses are not included when there were not enough studies with the required data.
The non-linear dose-response curve and the bubble graph were presented when a statistically significant non-linear association was observed. The interpretation of the non-linear dose-response analyses should be based on the shape of the curve and not only on the p-value because the number of observations tended to be low. Bubble graphs are also presented to support the interpretation.
In many instances, HR is indicated as RR.

The statistical methods are described in the protocol. The analyses were performed in Stata 12.0.

Continuous Update Project: Results of the search

Figure 2 Flow chart of the search for skin cancer – Continuous Update Project

Search period June Week 2 2005 – April 19th 2016



*Publications identified in the searches of CUP SLRs on other cancers and through screening of references of relevant articles.

Results by exposure

Table 1 Number of relevant publications identified during the 2005 SLR and the CUP and total number of publications by exposure.

The exposure code is the exposure identification in the database. Only exposures identified during the CUP are shown. Studies are for all types of skin cancers reviewed

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
1.	**Patterns of diet**			
1.3.1	Vegetarianism/Pescetarianism	0	1	1
1.3.2	Seventh Day Adventists Diet	1	0	1
1.4.1	Low fat diet	1	2	3
1.4.2	Healthy diet indices	0	2	2
1.4.3	Low-carbohydrate, high-protein diet score (LCHP)	0	1	1
1.4.4	Meat and fat dietary (MF) pattern/ Vegetable and fruit dietary (VF) pattern	0	1	1
1.4.5	Organic food consumption	0	1	1
2.	**Foods**			
2.2	Fruit and (non-starchy) vegetables	2	1	3
2.2.1.2	Cruciferous vegetables	0	3	3
2.2.1.4	Green leafy vegetables	0	3	3
2.2.1.5	Red and yellow vegetables	0	3	3
2.2.2	Fruits	3	1	4
2.2.2.1	Citrus fruits	0	2	2
2.2.2.2	Other fruits	0	3	3
2.2.2.2.12	Vitamin A or C rich fruits	0	3	3
2.2.3	All vegetables	3	2	5
2.3	Pulses (legumes)	1	2	3
2.5.1.2	Processed meat	1	4	5
2.5.1.3	Red meat	0	3	3
2.5.1.4	Poultry	0	3	3
2.5.2	Fish	2	2	4
2.5.2.5	Oily fish	0	2	2
2.5.4	Eggs	2	2	4
2.6.0.3	Fats (all)	1	2	3
2.7.0	Milk and dairy products	1	3	4
3.	**Beverages**			
3.4.1	Sugary drinks	0	1	1
3.6.1	Coffee	5	6	11
3.6.1	Decaffeinated coffee	0	5	5

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
3.6.2	Tea	3	1	4
3.6.2.1	Black tea	0	3	3
3.7.1	Total alcoholic drinks	9	8	17
3.7.1.1	Beers	3	6	9
3.7.1.2	Wines	2	5	7
3.7.1.3	Spirits	1	5	6
4.	**Food production, preservation processing and preparation**			
4.1.2.7.2	Arsenic in diet	2	1	3
5.	**Dietary constituents**			
5.1.5	Glycaemic index	0	1	1
5.1.5	Glycaemic load	0	1	1
5.2.3	Monounsaturated fatty acids in diet	2	1	3
5.2.4	Polyunsaturated fatty acids in diet	2	1	3
5.2.4.1	N-3 fatty acids in diet	1	1	2
5.2.4.1	N-3 fatty acids in blood	0	1	1
5.2.4.1	Alpha-linolenic acid in diet	0	1	1
5.2.4.1	Alpha-linolenic acid in blood	0	1	1
5.2.4.1	EPA in diet	0	1	1
5.2.4.1	EPA in blood	0	1	1
5.2.4.1	DHA in diet	0	1	1
5.2.4.1	DHA in blood	0	1	1
5.2.4.1	DPA in diet	0	1	1
5.2.4.1	Arachidonic fatty acid	0	1	1
5.2.4.1	Arachidonic fatty acid in blood	0	1	1
5.2.4.2	Linoleic fatty acid in diet	0	1	1
5.2.4.2	Linoleic fatty acid in blood	0	1	1
5.2.4.2	N-6 fatty acids in diet	0	1	1
5.2.4.2	N-6 fatty acids in blood	0	1	1
5.2.5	Trans fatty acids in diet	0	1	1
5.5.1	Vitamin A in diet	2	1	3
5.5.1	Vitamin A in diet and supplement	1	1	2
5.5.1	Vitamin A in supplement	2	1	3
5.5.1	Retinol in blood	8	0	8
5.5.1.1	Retinol in diet	3	2	5
5.5.1.1	Retinol in diet and supplement	4	1	5
5.5.1.1	Retinol in supplement	3	1	4
5.5.1.2.2	Beta-carotene in blood	10	1	11
5.5.1.2.2	Beta-carotene in diet	2	1	3

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
5.5.1.2.2	Beta-carotene in diet and supplement	4	1	5
5.5.1.2.2	Beta-carotene in supplement	7	2	9
5.5.1.2.2	Beta-carotene and alpha-tocopherol supplementation	0	1	1
5.5.1.2.3	Alpha-carotene in blood	2	1	3
5.5.1.2.3	Alpha-carotene in diet	2	1	3
5.5.1.2.4	Beta-cryptoxanthin in blood	2	1	3
5.5.1.2.4	Beta-cryptoxanthin in diet	2	1	3
5.5.2.1	Carotenoids in diet	1	1	2
5.5.2.3	Lycopene in diet	2	2	4
5.5.2.3	Lycopene in supplement	0	1	1
5.5.2.5	Lutein and zeaxanthin in blood	0	1	1
5.5.2.5	Lutein and zeaxanthin in diet	2	2	4
5.5.2.7	Lutein in supplement	0	1	1
5.5.3.1	Folate in diet	2	1	3
5.5.3.1	Folate in diet and supplement	2	1	3
5.5.9	Vitamin C in diet	3	1	4
5.5.9	Vitamin C in diet and supplement	4	1	5
5.5.9	Vitamin C in supplement	3	1	4
5.5.10	Vitamin D in blood	0	8	8
5.5.10	Vitamin D in diet	2	1	3
5.5.10	Vitamin D in diet and supplement	2	1	3
5.5.10	Vitamin D in supplement	0	1	1
5.5.10	Vitamin D (and calcium) in supplement	0	2	2
5.5.11	Vitamin E in diet	5	1	6
5.5.11	Vitamin E in diet and supplement	5	1	6
5.5.11	Vitamin E in supplement	5	1	6
5.5.11.1	Alpha-tocopherol in blood	6	1	7
5.5.18	Multivitamins supplement	8	5	13
5.5.19	Folate, pyridoxine (B6) and cobalamin (B12) in supplement	0	4	4
5.6.4	Selenium in blood	6	1	7
5.6.4	Selenium in diet	2	1	3
5.6.4	Selenium in supplement	3	4	8
5.7.6	Caffeine in diet	0	3	3
6.	**Physical activity**			
6.1	Total physical activity (overall summary measures)	1	2	3
6.1.1.1	Occupational physical activity	1	1	2

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
6.1.1.2	Recreational physical activity	3	1	4
6.1.1.4	Walking	0	1	1
6.3.3	Heavy work occupation	1	1	2
8.	**Anthropometry**			
8.1.1	BMI	15	23	38
8.1.1	BMI in early adulthood	0	2	2
8.1.3	Weight	5	5	10
8.1.6	Change in weight	0	2	2
8.2.1	Waist circumference	0	4	4
8.2.2	Hip circumference	0	2	2
8.2.3	Waist to hip ratio	0	4	4
8.3.1	Height (and proxy measures)	6	15	21
8.4.1	Birthweight	1	5	6

1 Patterns of diet

No meta-analysis was conducted.

Randomized controlled trials

1.4.1 Low fat diet

One study on melanoma and NMSC (two publications) were identified in the CUP. One study (one publication on NMSC) was identified in the 2005 SLR.

Malignant melanoma

In the WHI randomised controlled trial, postmenopausal women were assigned to either the low-fat diet intervention (with the goal to decrease fat intake to 20% or less of total energy intake and increase consumption of fruits, vegetables and grains) or usual diet. The study reported no effect of low-fat diet on melanoma risk (RR: 1.04; 95% CI= 0.82-1.32, 279 cases). There was a significant interaction of baseline fat intake and group assignment ($P_{interaction}$= 0.006). Women in the intervention group with higher total fat intake at baseline had a statistically significant increased melanoma risk (RR: 1.48; 95% CI=1.06-2.07), while women with lower fat intake had a statistically non-significant lower risk of melanoma $P_{interaction}$ (RR: 0.72; 95% CI= 0.50-1.02) (Gamba, 2013).

No effect of low-fat diet had been reported in a previous publication of the same study (RR: 1.04; 95% CI= 0.78-1.38, Prentice, 2007). Melanoma was not a primary outcome of the study.

Non-melanoma skin cancer

The WHI randomised controlled trial, found no effect of low-fat diet on the risk of NMSC (RR: 0.98; 95% CI= 0.92-1.04, 4 907 cases; Gamba, 2013).

In a small trial in United States, 135 patients with previous diagnosis of NMSC were randomly assigned to low fat diet intervention (20% of calories from fat) or usual diet. NMSC occurrence in the dietary intervention group was statistically significantly lower ($p<0.01$) than in the non-intervention group during the last eight months of two-years evaluation period (Black, 1998; Black, 1995).

Cohort studies

1.3.1 Vegetarianism/ Pescetarianism

No studies were identified in the 2005 SLR and one study on melanoma was identified in the CUP.

Malignant melanoma

A publication including data from the Oxford Vegetarian study and EPIC-Oxford, United Kingdom, reported that vegetarians had a statistically non-significant decreased risk of melanoma compared to meat eaters (RR: 0.89; 95% CI= 0.61-1.29, 164 cases). Similar results were found for pescetarians (RR: 0.90; 95% CI= 0.55-1.47, 136 cases) (Key, 2009).

1.3.2 Seventh Day Adventists Diet

One study on melanoma was identified in the 2005 SLR and no new studies were identified in the CUP.

Malignant melanoma

In a prospective cohort study in California, statistically non-significant increased risk of melanoma among Adventist men (SMR: 1.77; 95% CI=0.99-2.43, 13 cases) and statistically significant increased risk among Adventist women (SMR: 1.71; 95% CI=1.03-2.40, 14 cases) was observed, compared to residents of Connecticut. Most Adventists do not consume tobacco, alcohol or pork; approximately half of the population follow a lactoovovegetarian lifestyle (Mills, 1994).

1.4.2 Healthy lifestyle indices

No studies were identified in the 2005 SLR and two new studies (two publications on melanoma, one of which also reported on NBSC) were identified in the CUP. Both indices include physical activity as a component.

Malignant melanoma

In the NIH-AARP Diet and Health Study, higher adherence to a score based on the American Cancer Society (ACS) prevention guidelines was associated with increased melanoma risk among men (RR: 1.19; 95% CI= 1.07-1.33, p-trend= 0.002, 3 538 cases) and statistically non-significantly among women (RR: 1.21; 95% CI= 0.98-1.49, p-trend= 0.04, 1 210 cases) compared to lower adherence (Kabat, 2015). The score included body weight, physical activity, healthy dietary choices and limited alcohol intake. The analyses were not adjusted for UV exposure or skin sensitivity (skin, eye or hair colour) because these data were not available.

A health index based on the recommendations of the French National Program for Health and Nutrition (PNNS), the French Food Safety Agency (ANSES) and World Health Organization (WHO), was applied in the French E3N prospective cohort of women. The lifestyle behaviours considered were weight control (BMI), recreational physical activity, fruit and vegetable consumption, smoking and alcohol consumption. Higher score of adherence was statistically non-significantly positively associated with melanoma in women (RR: 1.44; 95% CI= 0.88-2.37, 391 cases) (Dartois, 2014).

Nonbasal skin cancer

Higher adherence to the French Health Index was positively associated with nonbasal skin cancer ((ICD-10 C43-C44, excluding ICD-O-3M809-M811), in the French E3N cohort (RR for highest vs. lowest score: 1.75 (95% CI: 1.17–2.62) p-trend <0.001 (n=686) (Dartois, 2014).

1.4.3 Low-carbohydrate, high-protein diet score (LCHP)

No studies were identified in the 2005 SLR and one new study (one publication on melanoma) was identified in the CUP.

Malignant melanoma

A Swedish large population-based cohort study reported that a low-carbohydrate, high-protein (LCHP) diet score was statistically non-significantly inversely associated with melanoma risk comparing highest vs. lowest score (RR: 0.76; 95% CI= 0.42-1.37, p-trend= 0.509, 105 cases). Intake of macronutrients was calculated from an 84 or 65-item FFQs as well as photo-based portion-sized estimations (Nilsson, 2013).

1.4.4 Meat and fat dietary (MF) pattern/ Vegetable and fruit dietary (VF) pattern

No studies were identified in the 2005 SLR and one new study (one publication on BCC and SCC) was identified in the CUP.

Basal cell carcinoma

The Nambour Skin Cancer Study examined the association of dietary patterns derived by principal component analysis and BCC risk. The meat-fat (MF) pattern was characterized by higher weight of red and processed meat, discretionary fat, processed grains, snacks, sweets drinks and high-fat dairy products. The fruits and vegetables pattern (VF) had higher weight of vegetables, fruit, unprocessed grains, fish and low-fat dairy products. No statistically significant associations with BCC were found when comparing higher to lower scores of meat-fat (MF) pattern (RR: 1.31; 95% CI= 0.85-2.04, p-trend= NS) and VF pattern (RR: 1.14; 95% CI= 0.79-1.65, p-trend= NS) (Ibiebele, 2007).

Squamous cell carcinoma

A statistically non-significant positive trend of the MF pattern with SCC risk was observed (RR: 1.83; 95% CI= 1.00-3.37, p-trend= 0.05). However, the association was reversed when participants with history of skin cancer were excluded from the analysis (RR: 0.87; 95% CI= 0.32-2.34, p-trend= NS). Non-statistically significant inverse association was found for the VF pattern (RR: 0.83; 95% CI= 0.47-1.44, p-trend= NS) (Ibiebele, 2007).

1.4.5 Organic food consumption

No studies were identified in the 2005 SLR and one new study (one publication on melanoma) was identified in the CUP.

Malignant melanoma

In the MWS in United Kingdom, the consumption of organic products “usually or always” compared with “never” was not associated with melanoma (RR: 0.90; 95% CI= 0.78-1.05, 2 434 cases) (Bradbury, 2014).

Table 2 Dietary patterns and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison/ Intervention	RR (95%CI) Ptrend	Adjustment factors
Randomized controlled trials								
Gamba, 2013 USA (Same results in SKI22193 Prentice, 2007)	WHI-DM trial Randomised Control Trial, Age: 50-79 years, W, Postmenopausal	114 cases/ 19 541 randomized intervention group 165 cases/ 29 294 randomized comparison group 8.1 years	Through annual clinic visits during the trial and self-report in semi-annual mailed questionnaires, verified by medical records	Intervention target was lower (assessed by 4-day food record & FFQ): % energy from fat Difference intervention vs. the comparison group (8.1%, P < 0.001)	Incidence MM	Intervention – decrease fat intake to 20% of total energy, increase fruit and vegetables intake to ≥5 servings/day, increase grains intake to ≥6 servings/day; total energy was not restricted and weight loss was not advocated Comparison – received a printed copy of *Nutrition and Your Health: Dietary Guidelines for Americans*	Intervention vs. comparison 1.04 (0.82-1.32)	No details on randomization.
		1 923/ 19541 intervention group 2 984/ 29 294 comparison group			Incidence NMSC		0.98 (0.92-1.04)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison/ Intervention	RR (95%CI) Ptrend	Adjustment factors
Black, 1998 SKI01983 USA (Same results in SKI02773 Black, 1995)	Low Fat Diet Trial, Randomised Control Trial, M, Patients presenting with NMSC	57 intervention group/ 58 control group	Incoming patients	Intervention goal attained (assessed in four-day food records in a week) % energy from fat was 20.7 and 37.8 in intervention and control groups respectively	Cumulative number/patient/period NMSC	Intervention group vs. Control group Intervention: adopt a diet with 20% of total energy intake as fat	Cumulative NMSC/patient/time period: 0.21 and 0.19 during the first 8-month period and 0.26 and 0.02 during the last 8-month period for control and intervention groups, respectively, p<0.01	
Cohort studies								
Kabat, 2015 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	3 538 men/ 566 401 10.5 years	Cancer registry	Semi-quantitative FFQ	Incidence MM Men	ACS score Q5 vs. Q1	1.19 (1.07-1.33) Ptrend: 0.002	Age, educational level, energy intake, ethnicity, marital status, smoking status, ultraviolet exposure
		1 210/			Women		1.21 (0.98-1.49) Ptrend: 0.04	
Bradbury, 2014 UK	MWS, Prospective	2 434/ 623,080	National Health Service central	Questionnaire	Incidence MM	Usually/always vs. never	0.90 (0.78-1.06)	Age, region, deprivation

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison/ Intervention	RR (95%CI) Ptrend	Adjustment factors
	Cohort W	9.3 years	registers			consumption of organic food		category, smoking, BMI, physical activity, alcohol intake, height, parity, age at first child birth, fibre intake, type of meat
Dartois, 2014 SKI22201 France	E3N EPIC-France, Prospective Cohort, Age: 43-68 years, W	391/ 64 732 8 years	Self- report verified by reviewing medical and pathological records by physicians	Self-administered questionnaire	Incidence MM	Health Index categories: 4.5; 5 vs. 0; 2	1.44 (0.88-2.37)	Age at first child birth, age at menarche, educational level, family history of cancer in first degree relatives, menopausal oestrogen use, menopausal status, number of children, professional activity, residence, use of oral contraception
Nilsson, 2013	VIP,	105/	Cancer registry	FFQ & 24-hr	Incidence	Low	0.76 (0.42-1.37)	Age, alcohol,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison/ Intervention	RR (95%CI) Ptrend	Adjustment factors
Sweden	Prospective Cohort, Age: 30- years, W	31 185 9.7 years		dietary recall	MM	carbohydrate and high protein diet score : 14-20 vs. 2-8 points	Ptrend: 0.509	educational level, energy intake, obesity, saturated fat, sedentary behaviour, smoking
Key, 2009 SKI22186 UK	EPIC-Oxford, Prospective Cohort, Age: 20-89 years, M/W	164/ 61 566 12.2 years	UK national health service central register	Semi-quantitative FFQ	Incidence MM	Vegetarians vs. meat eaters	0.89 (0.61-1.29)	Age, sex, alcohol consumption, BMI, physical activity level, smoking, study/method of recruitment
		136/				Pescetarians vs. meat eaters	0.90 (0.55-1.47)	
Ibiebele, 2007 Australia	NSCS, Prospective Cohort, Age: 20-69 years, M/W	267/ 1 360 11 years	Full body examination and then histological confirmed	FFQ	Tumour-based occurrence BCC	Meat and Fat dietary pattern: T3 vs. T1	1.31 (0.85-2.04)	Age, sex, skin colour, skin elastosis, smoking status, supplement use, burn-tan propensity of the skin, total energy, treatment
		127/			Tumour-based occurrence SCC	High consumption of red meats, processed meats discretionary fat, processed grains,	1.83 (1.00-3.37)	
					Tumour-based occurrence SCC History of skin cancer		3.77 (1.65-8.63) Ptrend: 0.002	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison/ Intervention	RR (95%CI) Ptrend	Adjustment factors
					Tumour-based occurrence SCC No history of skin cancer	snack, sweet drinks, and high-fat dairy products	0.87 (0.32-2.34)	allocation
					Tumour-based occurrence BCC	Vegetable and fruit dietary pattern T3 vs. T1	1.14 (0.79-1.65)	
					Tumour-based occurrence SCC	High consumption of veggies, fruit, unprocessed grains, fish and low-fat dairy products	0.83 (0.47-1.44)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison/ Intervention	RR (95%CI) Ptrend	Adjustment factors
Black, 1998 SKI01983 USA (Same results in SKI02773 Black, 1995)	Low Fat Diet Trial, Randomised Control Trial, M, Patients presenting with NMSC	57 intervention group/ 58 control group	Incoming patients	Four-day food records (Monday, Wednesday, Saturday and Sunday)	Cumulative number of NMSC	Intervention group vs. Control group Intervention: adopt a diet with 20% of total intake as fat	Intervention group: 0.30 Control group: 0.56 Cancer occurrence between groups during the last 8 months of evaluation period: P-value< 0.01	
Mills, 1994 SKI10108 USA	AHS, 1974, Prospective Cohort, Age: 25- years, M/W, Seventh-day Adventists	24/ 34 198	Church members address lists	Questionnaire	Incidence MM Men	Seventh-day Adventists vs. General population	1.77 (0.99-2.43)	Age, calendar year
		23/			Women		1.71 (1.03-2.40)	

2 Foods

2.2.3 All vegetables

Cohort studies

Summary

Four studies (three publications on melanoma and BCC) were identified in the 2005 SLR and one new study (two publications on skin cancer, SCC and BCC) were identified in the CUP.

No meta-analysis was conducted.

Skin cancer

In the NIH-AARP study (George, 2009), vegetable intake (excluding potatoes) was not associated with skin cancer risk in men (1 634 cases) (RR: 0.90, 95% CI= 0.76-1.05) when comparing 1.1-3.25 vs. 0-0.44 cup equivalents per 1000 kcal/day) and women (577 cases) (RR: 1.04, 95% CI= (0.79-1.37, comparing 1.44-4.38 vs. 0-0.56 cup equivalents per 1000 kcal/day).

Malignant melanoma

In the NHS and NHS II cohort studies combined, there was no association of total vegetable intake and melanoma risk (RR: 1.01, 95% CI= (0.68-1.50), comparing ≥5 vs. <2 servings/day) (Feskanich, 2003).

Basal cell carcinoma

In the pooled analysis of NHS and HPFS cohorts, total vegetable intake (26 items) was not associated with incidence of BCC (20 840 cases) (RR: 0.97, 95% CI= (0.92-1.03), comparing ≥5 vs. <2 times/day) (Wu, 2015a).

In the EPIC-Norfolk study, the unadjusted relative risk estimate for an increment of 62 g/day of intake of all vegetables was 1.10, 95% CI= 0.88-1.38 (Davies, 2002).

Squamous cell carcinoma

In the pooled analysis of NHS and HPFS cohorts, total vegetable intake (26 items) was statistically non-significantly inversely associated with incidence of SCC (3 544 cases) (RR: 0.88, 95% CI= 0.77-1.01, comparing ≥5 vs. <2 times/day) (Wu, 2015a).

Table 3 Vegetable intake and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Wu, 2015a USA	HPFS Prospective Cohort, Age:40-75 years, M, health professionals	9 033/ 41 622 26 years	Self-report verified through medical and pathologic reports	Validated FFQ	Incidence, BCC	≥5 vs. <2 times/day	1.00 (0.92-1.08)	Age, hair colour, number of arm moles, sunburn susceptibility as a child/ adolescent, family history of melanoma, number of blistering sunburns, cumulative UV flux since baseline, average time spent in direct sunlight since high school, sunscreen use, BMI, physical activity, smoking status, alcohol intake, menopausal status and MHT use in women
		1 540/			SCC		0.90 (0.73-1.10)	
	NHS Prospective Cohort, Age:30-55 years, W, registered nurses	11 807/ 63 810 24 years			BCC		0.95 (0.88-1.02)	
		2 004/			SCC		0.87 (0.72-1.04)	
	Pooled (HPFS and NHS)	20 840/ 105 432			BCC		0.97 (0.92-1.03)	
		3 544/			SCC		0.88 (0.77-1.01)	
George, 2009 SKI22179 USA	NIH-AARP, Prospective Cohort, Age: 50-71	1 634/ 288 109 6.9 years (men and women)	Linkage with cancer registry databases	Self-administered validated 124-item FFQ	Incidence, skin cancer, men	1.1-3.25 vs. 0-0.44 cup equivalents per1000	0.90 (0.76-1.05) Ptrend:0.332	Age, alcohol, BMI, educational level, energy intake, family history of cancer, fruits, marital status, physical activity, race,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, M/W, Retired					kcal/day		smoking
		577/ 195 229			Women	1.44-4.38 vs. 0-0.56 cup equivalents per 1000 kcal/day	1.04 (0.79-1.37) Ptrend:0.60	Additionally adjusted for MHT
Feskanich, 2003 SKI00696 USA	NHS and NHS II, Prospective Cohort, Age: 25-77 years, W, nurses	414/ 162 078 >1.6 million person-years	Medical records	FFQ	Incidence, MM	≥5 vs. <2 servings/day	1.01 (0.68-1.50) Ptrend:0.81	Age, area of residence, BMI, energy intake, family history of specific cancer, follow-up cycle, hair colour, height, menopausal status, multivitamin supplement intake, number of moles, number of sunburns, oral contraceptive use, parity, MHT use, skin reaction, use of supplements
Davies, 2002 SKI00989 UK	EPIC-Norfolk, Nested Case Control, Age: 65 (W), 67.8 (M), M/W	109/ 356	East Anglian Cancer Registry	Validated self-reported 7-day food diary	Incidence, BCC	Per 62 g/day	1.10 (0.88-1.38)	Unadjusted
van Dam, 2000 SKI01672 USA	HPFS, Prospective Cohort, Age: 40-75	3 190/ 43 217	Family members, co-workers, postal authorities,	Validated 131-item FFQ	Incidence, BCC	>5 vs. <2 servings/day	1.06 (0.95-1.20)	Age, 2 year follow-up periods, energy intake, frequency of physical examinations, hair colour, major ancestry, mean

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, M, health professionals		National Death Index					solar radiation, smoking habits

5.1 Meat

This section includes studies in which the item "Meat" was reported. The item includes any type of white and red meat.

Cohort studies

Two studies (two publications on melanoma and BCC) were identified in the 2005 SLR and no new studies were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

A large Norwegian prospective study did not find association of meat consumption and melanoma in men and women (data not shown in the publication) (Veierod, 1997).

Basal cell carcinoma

Intake of meat and meat dishes was not related with BCC in the EPIC-Norfolk cohort (RR: 0.92; 95% CI= 0.73-1.18per 56.1g/ day increase of meat and meat dishes, 109 cases) (Davies, 2002).

2.5.1.2 Processed meat

Cohort studies

One study (one publication on BCC) was identified in the 2005 SLR and one new study (four publications on melanoma, BCC and SCC) was identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

In the NIH-AARP study (Cross, 2007), processed meat intake was statistically significantly inversely associated with melanoma risk (RR: 0.82; 95% CI=0.71-0.96 for the highest compared to the lowest intake of processed meat, p-trend= 0.13, 1 932 cases). Processed meat was defined as bacon, red meat sausage, poultry sausage, luncheon meats, cold cuts, ham, regular hot dogs and low-fat hot dogs made from poultry. The analyses were adjusted for age, sex, education, marital status, family history of cancer, race, BMI, smoking, frequency of vigorous physical activity , total energy intake, alcohol intake , and fruit and vegetable consumption.

Basal cell carcinoma

In the Nambour Skin Cancer Study highest vs. lowest processed meat intake was statistically non-significantly positively associated with BCC (RR: 1.30; 95% CI= 0.90-1.90, p-trend= 0.21, 217 cases, tumour based-analysis) (van der Pols, 2011). Processed meat was defined as sausages, bacon, processed meat, frankfurter/saveloy, sausage roll.

No association was found in the EPIC-Norfolk cohort, RR: 1.06; 95% CI=0.84-1.34 per 27.4g/day increase of processed meat, 109 cases (Davies, 2002).

Squamous cell carcinoma

The Nambour Skin Cancer Study reported no association of processed meat consumption and SCC in participants with history of skin cancer (RR: 1.13; 95% CI=0.56-2.29 for the highest vs. lowest comparison, p-trend=NS, tumour-based analysis) (Ibiebele, 2007).

Another publication also using the Nambour Skin Cancer Study and a performing tumour-based analysis found similar results for participants with history of skin cancer (RR: 1.41; 95% CI=0.65-3.02, p-trend= 0.44 for highest vs. lowest intake). In participants without a history of skin cancer the RR was 0.86; 95% CI=0.33-2.24, p-trend= 0.80 (Hughes, 2006).

2.5.1.3 Red and processed meat

Note: The studies included in this section included processed meat items in the definition of "Red meat".

Cohort studies

No studies were identified in the 2005 SLR and two studies (three publications on melanoma, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

In the NIH-AARP study there was no association between red meat consumption and melanoma (RR: 0.95; 95% CI=0.81-1.11 for the highest vs. lowest comparison, p-trend= 0.54, 1 541 cases) (Cross, 2007). Red meat was defined as all types of beef, pork and lamb which included bacon, cold cuts, ham, hamburger, hot dogs, liver, sausage and steak.

Basal cell carcinoma

In the Nambour Skin Cancer Study (van der Pols, 2011), there was a statistically non-significant inverse association red meat consumption and BCC (RR: 0.80; 95% CI=0.50-1.30 for the highest vs. lowest comparison, p-trend=0.40, 217 cases). The food group "meat" included beef, pork, lamb as main dish; ham, beef, pork in sandwich; beef, pork, lamb in mixed dishes; mince in tomato sauce; other mince meat dishes; meat pie; hamburger patty; liver. The analyses were tumour-based.

Squamous cell carcinoma

In the Nambour Skin Cancer Study, no association between SCC and red meat consumption was observed among participants with history of skin cancer (RR: 1.02; 95% CI= 0.49-2.15 for the highest vs. lowest comparison, p-trend=NS) (Ibiebele, 2007). In another publication of the same cohort (Hughes, 2006), the association of SCC and consumption of red meat in all participants was RR: 0.62; 95% CI= 0.34-1.13 for the highest vs. lowest comparison, p-trend=0.13, 127 cases. In analysis stratified by skin cancer history, the RR was 0.86; 95% CI=0.33-2.24, p-trend=0.80 in participants with no history of skin cancer and RR: 1.41; 95% CI= 0.65-3.02, p-trend= 0.44 in participants with skin cancer. The analyses were tumour-based in both publications.

2.5.1.4 Poultry

Cohort studies

No studies were identified in the 2005 SLR and two studies (three publications on melanoma, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

Melanoma was not associated with consumption of poultry in the NIH-AARP study (RR for highest vs. lowest intakes: 1.03; 95% CI= 0.91-1.17, p-trend= 0.86, 2 960 cases and for 10g/1000kcal increment, p-trend= 0.35 (Daniel, 2011). Models were adjusted for red meat and fish intake.

Basal cell carcinoma

Poultry intake was not associated with BCC (RR: 1.00; 95% CI= 0.70-1.50 for highest vs. lowest intake, p-trend= 0.94, 217 cases) in the Nambour Skin Cancer Cohort. The analyses were tumour-based (van der Pols, 2011).

Squamous cell carcinoma

Poultry intake was not associated with SCC risk (RR: 0.93; 95% CI= 0.53-1.62, p-trend= 0.84, 127 cases) in the Nambour Skin Cancer Cohort. The results did not change substantially when participants with antecedents of skin cancer were excluded from the analysis (RR: 0.55; 95% CI= 0.22-1.40, p-trend= 0.20). The analyses were tumour-based (Hughes, 2006).

2.5.1.5 Offal

Cohort studies

One study (one publication on BCC) was identified in the 2005 SLR and no new studies were identified in the CUP.

No meta-analysis was conducted.

Basal cell carcinoma

No association was observed in the EPIC-Norfolk study (RR: 1.06; 95% CI= 0.89-1.28 per 3.48g/ day increase of offal consumption, 109 cases) (Davies, 2002).

2.5.2 Fish

Cohort studies

Two studies (two publications on melanoma and SCC) were identified in the 2005 SLR and two new studies (two publications on melanoma and BCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

Fish intake was positively associated with melanoma risk in the NIH-AARP study (RR: 1.19; 95% CI= 1.05-1.34 for the highest vs. the lowest comparison, p-trend= 0.01, 2 960 cases)

(Daniel, 2011). The risk increase seemed to be driven by intake of canned tuna (RR for highest vs. lowest quintile: 1.30 (95% CI 1.16–1.46); Ptrend < 0.0001). Models were adjusted for poultry and red meat intake, and other factors, but not for UV exposure or skin sensitivity.

A large Norwegian prospective study did not find association of fish consumption (as fish sandwich spread main meals with fish liver or fish as main dish) and melanoma in men and women (data not shown in the publication) (Veierod, 1997).

Basal cell carcinoma

Fish intake was not related to BCC in the EPIC-Norfolk study (RR: 1.12; 95% CI= 0.89-1.39, 109 cases for 36.2g/ day increase of fish and selfish consumption) (Davies, 2002).

Squamous cell carcinoma

In the Nambour Skin Cancer Cohort, a non-statistically significant positive association of seafood consumption with SCC with was observed (RR: 1.29; 95% CI= 0.72-2.3 for the comparison of highest vs. lowest seafood consumption, p-trend= 0.43, 127 cases) (Hughes, 2006). An analysis including only participants without history of skin cancer showed similar results, RR: 1.26; 95% CI= 0.48-3.29, p-trend= 0.66. Authors reported tumour-based analyses. Seafood was defined as tuna, sardines, other fish, other seafood.

2.5.2.5 Oily fish

Cohort studies

No studies were identified in the 2005 SLR and one study (two publications on BCC and SCC) was identified in the CUP.

No meta-analysis was conducted.

Basal cell carcinoma

Oily fish consumption, defined as tuna, salmon and sardines, was statistically non-significantly positively associated with BCC in the Nambour Skin Cancer Study (RR: 1.30; 95% CI= 0.90-1.90 for the highest vs. lowest analysis, p-trend= 0.22, 217 cases). The analysis was tumour-based (van der Pols, 2011).

Squamous cell carcinoma

In the same study, the Nambour Skin Cancer Cohort, there was a not statistically significant inverse association between oily fish and SCC, RR: 0.78; 95% CI= 0.43-1.40, p-trend=NS (Ibiebele, 2007).

2.5.4 Egg

Cohort studies

Two studies (on melanoma and BCC) were identified in the 2005 SLR and one new study (on BCC and SCC) was identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

A large Norwegian cohort study reported no association of egg consumption and melanoma risk in men and women (108 cases) (results not shown in the publication) (Veierod, 1997).

Basal cell carcinoma

A marginal positive association of egg intake and BCC was found in the Nambour Skin Cancer Cohort, in tumour-based analysis (RR: 1.50; 95% CI= 1.00-2.20 for highest vs. lowest intake, p-trend= 0.06, 217 cases) (van der Pols, 2011).

In EPIC-Norfolk, BCC was not related with egg and egg products consumption (RR: 1.05; 95% CI= 0.83-1.33 for 19.6g/ day increase, 109 cases) (Davies, 2002).

Squamous cell carcinoma

In the Nambour Skin Cancer Cohort, SCC risk was not related to egg and egg products consumption, RR for 19.6g/ day increase: 0.95; 95% CI= 0.54-1.68, p-trend= 0.87 (Hughes, 2006). Analysis excluding participants with skin cancer history revealed statistically non-significant positive association, RR: 1.23; 95% CI= 0.48-3.13, p-trend= 0.66.

Table 4 Meat, poultry, fish and egg consumption and skin cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Daniel, 2011 SKI22180 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 960/ 492 186 9.1 years	Cancer registry	Validated FFQ	Incidence MM	**Poultry** 51.2 vs. 5.3 g/1000 kcal	1.03 (0.91-1.17) Ptrend:0.86	Age, alcohol intake, BMI, educational level, family history of cancer, fish or poultry (as applicable) intake, fruit intake, HRT use, marital status, race, red meat intake, smoking status, total energy intake, vegetable intake, vigorous physical activity
						Fish 21.4 vs. 3.6 g/1000 kcal	1.19 (1.05-1.34) Ptrend:0.01	
Van der Pols, 2011 Australia	NSCS, M/W	217/ 1 056 10 700 person-years	Medical records and histologically	Semi-quantitative FFQ	Tumour-based occurrence BCC	**Red meat** T3 vs. T1	0.80 (0.50-1.30) Ptrend:0.40	Age, sex, energy intake, skin colour, number of painful sunburns, elastosis of the neck, skin cancer history, treatment allocation
						Processed meat T3 vs. T1	1.30 (0.90-1.90) Ptrend:0.21	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						Poultry T3 vs. T1	1.00 (0.70-1.50) Ptrend:0.94	during trial, use of dietary supplements
						Oily fish T3 vs. T1	1.30 (0.90-1.90) Ptrend:0.22	
						Eggs T3 vs. T1	1.50 (1.00-2.20) Ptrend:0.06	
Cross, 2007 SKI22185 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	1 932/ 494 036 6.8 years	Cancer registry and national death index	FFQ	Incidence MM	**Red meat** 62.7 vs. 9.8 g/1000 kcal	0.95 (0.81-1.11) Ptrend:0.54	Age, sex, alcohol intake, BMI, educational level, family history of cancer, frequency of vigorous physical activity, fruits and vegetables intake, marital status, race, smoking status, total energy intake
						Processed meat 22.6 vs. 1.6 g/1000 kcal	0.82 (0.71-0.96) Ptrend:0.13	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Ibiebele, 2007 Australia	NSCS, Age: 25-75 M/W Participants with history of skin cancer	127/ 1 360 11 years	Medical records and histologically	Semi-quantitative FFQ	Tumour-based occurrence SCC	**Red meat** T3 vs. T1	1.02 (0.49-2.15) Ptrend:NS	Age, sex, total energy, skin colour, burn-tan propensity of the skin, elastosis of the neck, smoking status, dietary supplement use and trial treatment allocation
						Processed meat T3 vs. T1	1.13 (0.56-2.29) Ptrend:NS	
						Oily fish T3 vs. T1	0.78 (0.43-1.40) Ptrend:NS	
Hughes, 2006 Australia	NSCS Age: 25-75 M/W	127/ 1 056	Medical records and histologically	Semi-quantitative FFQ	Tumour-based occurrence SCC	**Red meat** T3 vs. T1 No skin cancer history History of skin cancer	0.62 (0.34-1.13) Ptrend:0.13 0.38 (0.14-1.06) Ptrend:0.07 0.96 (0.44-2.09) Ptrend:0.99	Age, sex, energy intake, skin colour, elastosis of the neck, occurrence of the skin cancer prior to the trial, pack-years of smoking, treatment allocation, use of dietary supplements
						Processed meat T3 vs. T1 No history of skin cancer History of skin cancer	1.11 (0.62-2.00) Ptrend:0.73 0.86 (0.33-2.24) Ptrend:0.80 1.41 (0.65-3.02) Ptrend:0.44	
						Poultry T3 vs. T1	0.93 (0.53-1.62) Ptrend:0.84	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						No history of skin cancer History of skin cancer	0.55 (0.22-1.40) Ptrend:0.20 1.27 (0.63-2.56) Ptrend:0.44	
						Fish and other seafood T3 vs. T1 No history of skin cancer History of skin cancer	1.29 (0.72-2.30) Ptrend:0.43 1.26 (0.48-3.29) Ptrend:0.66 1.43 (0.67-3.05) Ptrend:0.40	
						Eggs T3 vs. T1 No history of skin cancer History of skin cancer	0.95 (0.54-1.68) Ptrend:0.87 1.23 (0.48-3.13) Ptrend:0.66 0.78 (0.37-1.61) Ptrend:0.50	
Davies, 2002 SKI00989 UK	EPIC-Norfolk, Nested Case Control, M/W	109/ 1 976			Incidence BCC	**Meat and meat dishes** per 56.1 g/day	0.93 (0.73-1.18)	-
						Processed meat per 27.4 g/day	1.06 (0.84-1.34)	
						Offal per 3.48 g/day	1.06 (0.89-1.27)	
						Fish and shellfish per 36.2 g/day	1.12 (0.89-1.39)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						Egg and egg products per 19.6 g/day	1.05 (0.83-1.33)	
Veierod, 1997 SKI17728 Norway	Norway 1977-1983, Prospective Cohort, Age: 16-56 years, M/W	108/ 50 757 12.4 years	Health screening program	FFQ	Incidence MM	**Total meat** Comparison not reported	No association was found	-
						Fish Comparison not reported		
						Eggs Comparison not reported		

3 Beverages

3.6.1 Coffee

Cohorts

Four studies (five publications on melanoma, NMSC, BCC, and SCC) were identified in the 2005 SLR and seven new studies (six publications on melanoma, BCC and SCC) were identified in the CUP.

Dose-response meta-analyses were conducted on coffee intake and melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Table 5 Coffee intake and skin cancer risk. Number of studies in the CUP SLR.

	Number
Studies identified	11 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	9 (7 publications) melanoma NMSC risk – not enough studies 5 (4 publications) BCC 4 (3 publications) SCC
Studies included in linear dose-response meta-analysis	7 (7 publications) melanoma NMSC risk – not enough studies 3 (3 publications) BCC 3 (3 publications) SCC
Studies included in non-linear dose-response meta-analysis	6 (4 publications) melanoma NMSC, BCC, SCC – not enough studies

Skin cancer

Summary

Main results:

Seven studies out of 9 (8 publications) identified could be included in the dose-response meta-analysis on melanoma, 3 studies out of 5 (4 publications) on BCC, and 3 studies out of 4 (3 publications) on SCC.

Malignant melanoma

Coffee intake was not statistically significantly associated with melanoma risk (RR for 1 cup/day: 0.96, 95% CI= 0.92-1.00). Moderate heterogeneity was observed.

Of the two studies excluded from the dose-response meta-analysis, one study with 19 cases of melanoma reported a relative risk of 2.63 for the highest vs. lowest comparison (p-

trend=0.16) (Jacobsen, 1986) and a small study (11 male cases) in the Harvard Alumni cohort reported no association (relative risks not shown in the publication) (Whittemore, 1985).

The test of publication bias was statistically non-significant. Visual inspection of the funnel plot showed asymmetry driven by the smaller study (Veierod, 1997) from Norway that reported a strong inverse association. Exclusion of this study did not substantially modify the overall estimate.

In the study including the NHS, NHSII and PHS (Wu, 2015c), an association with coffee was more apparent in women (≥393 mg/day vs. . <60 mg/day: HR = 0.70, 95% CI = 0.58-0.85; *P*trend = 0.001) than in men (RR = 0.94, 95% CI = 0.75- 1.2;*P*trend = 0.81); more apparent for melanoma occurring on body sites with higher continuous sun exposure (head, neck, and extremities) than for melanoma occurring on body sites with lower continuous sun exposure (trunk including shoulder, back, hip, abdomen, and chest). This pattern of association was similar to that for caffeinated coffee consumption, whereas no association was found for decaffeinated coffee consumption and melanoma risk.

Overall, no substantial difference of association emerged in the stratified analyses. A statistically significant inverse association was found in studies in women and with <15 years of follow-up, for which the number of studies was higher.

Sensitivity analyses:

In influence analysis, the association ranged from 0.95 (95% CI=0.92-0.98) when the HPFS (Wu, 2015c HPFS, 17% weight) was omitted to 0.97 (95% CI=0.93-1.01) when the NHS II (Wu, 2015c 13.6% weight) was omitted.

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear association (p=0.54).

Basal cell carcinoma

Coffee intake was statistically significantly inversely associated with BCC (RR: 0.96, 95% CI= 0.94-0.97) with no evidence of heterogeneity.

Two studies were excluded from the dose-response meta-analysis. One study reported statistically non-significant positive association (RR: 1.64, 95% CI= 0.77-3.46) (Milan, 2003), comparing >3 cups/day intake vs. rarely or never. The other study reported relative risk of 0.45 in men, comparing ≥7 vs. ≤2 cups/day intake (no more data shown in the publication) (Jacobsen, 1986).

Squamous cell carcinoma

Coffee intake was not associated with SCC risk (RR: 0.98, 95% CI= 0.94-1.02) with no evidence of heterogeneity.

One study with only two levels of exposure reporting a relative risk of 0.35 in men for the ≥7 vs. ≤2 cups/day intake was excluded from the dose-response meta-analysis (Jacobsen, 1986).

Study quality:

All studies assessed coffee intake in cups/day apart from one which used times/day (Nilsson, 2010). The type of coffee was total coffee intake (Loftfield, 2015; Wu, 2015b, WHI-OS; Nilsson, 2010; Veierød, 1997) and caffeinated coffee (Wu, 2015c, NHS, NHS II, HPFS; Miura, 2014; Song, 2012).

The level of adjustment for skin type and sunlight exposure varied. One study adjusted for erythemal UV exposure (Loftfield, 2015), one study adjusted for skin type characteristics (Miura, 2014), five studies adjusted for sun exposure as well as skin type characteristics (Wu, 2015b, WHI-OS; Wu, 2015c NHS, NHS II, HPFS; Song, 2012). Two studies did not adjust for the aforementioned variables (Nilsson, 2010; Veierød, 1997). All studies adjusted for multiple confounders with the least adjusted study considering the confounding effect of age, sex and area of residence (Veierød, 1997).

Regarding study population, one Australian study originated from a skin cancer prevention trial of daily sunscreen use and beta-carotene supplementation (Miura, 2014). The Norwegian study included participants in a continuous screening program for cardiovascular diseases (Veierød, 1997).

No study reported important loses to follow-up. Skin cancer diagnoses were documented.

Table 6 Coffee and skin cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP.

	2005 SLR	**CUP**
Increment unit used	1 cup/day	
Malignant melanoma		
Studies (n)	2	7
Cases	91	6 401
RR (95%CI)	1.04 (0.63-1.72)	0.96 (0.92-1.00)
Heterogeneity (I^2, p-value)	86%, <0.01	50%, 0.06
P value Egger test	-	0.56
	Basal cell carcinoma	**Squamous cell carcinoma**
Studies (n)	3	3
Cases	23 109	2 149
RR (95%CI)	0.96 (0.94-0.97)	0.98 (0.94-1.02)
Heterogeneity (I^2, p-value)	0%, 0.75	0%, 0.47
P value Egger test	-	-
Malignant Melanoma: stratified and sensitivity analysis		
Sex	**Men**	**Women**

Studies (n)	2	4
Cases	818	1 830
RR (95%CI)	1.03 (0.97-1.10)	0.91 (0.86-0.96)
Heterogeneity (I^2, p-value)	0%, 0.45	36%, 0.20
Geographic area	**Europe**	**North America**
Studies (n)	2	5
RR (95%CI)	0.86 (0.54-1.36)	0.96 (0.92-1.00)
Heterogeneity (I^2, p-value)	59%, 0.12	57%, 0.05
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**
Studies (n)	5	2
RR (95%CI)	0.96 (0.92-1.00)	0.86 (0.54-1.36)
Heterogeneity (I^2, p-value)	57%, 0.05	59%, 0.12
Duration of follow-up	**<15 years**	**≥15 years**
Studies (n)	3	4
RR (95%CI)	0.96 (0.93-0.99)	0.96 (0.89-1.04)
Heterogeneity (I^2, p-value)	6%, 0.35	69%, 0.02
Number of cases	**<500 cases**	**≥500 cases**
Studies (n)	3	4
RR (95%CI)	0.97 (0.89-1.05)	0.96 (0.91-1.01)
Heterogeneity (I^2, p-value)	24%, 0.27	68%, 0.03
Publication year	**<2015**	**≥2015**
Studies (n)	2	5
RR (95%CI)	0.86 (0.54-1.36)	0.96 (0.92-1.00)
Heterogeneity (I^2, p-value)	59%, 0.15	57%, 0.05

Table 7 Coffee intake and skin cancer risk. Results of meta-analyses including prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Liu, 2016*	7 cohort studies	5 737	USA, Sweden, Norway	Malignant melanoma	Caffeinated coffee per 1 cup/day	0.96 (0.91-1.00)	
					Highest vs. lowest	0.84 (0.71-0.99)	57.3%
Wang, 2016*	6 cohort and 1 case control study	6 094	USA, Sweden, Italy	Cutaneous melanoma	Total coffee intake per 1 cup/day	0.97 (0.93-1.00)	
	7 cohort studies	5 660	USA, Sweden, Norway		Highest vs. lowest	0.83 (0.72-0.97)	50.7%, 0.048
Caini, 2016	3 cohorts* ,1 hospital-based case-control and 1 cross-sectional study	33 352	Australia, USA,	NMSC	Caffeinated coffee, highest vs. lowest	0.82 (0.75-0.89)	48%
	3 cohorts* and 1 hospital-based case-control study	23 750		BCC		0.83 (0.76-0.91)	35%
	3 cohort studies	2 120		SCC		0.93 (0.68-1.27)	50%

*All studies were included in the CUP dose-response meta-analysis

Table 8 Coffee intake and skin cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Loftfield, 2015 SKI23424 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 904/ 447 357 10.5 years	Cancer registry	Validated FFQ, **total coffee**	Incidence, MM	≥4 vs. 0 cups/day	0.80 (0.68-0.93) Ptrend:0.01	Age, sex, alcohol intake, BMI, cigar or pipe smoking, cigarette smoking, educational level, family history of cancer, July erythemal exposure, physical activity, smoking intensity	Mid-points of exposure categories
Wu, 2015b SKI23426 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	286/ 66 484 7.73 years	Questionnaire, medical records or pathology reports reviewed by physicians	Interview, **total coffee**	Incidence, MM	≥4 vs. ≤0.9 cups/day	0.84 (0.61-1.17) Ptrend:0.22	Age, alcohol intake, aspirin use, educational level, height, income, region of residence, skin reaction to sun, smoking, summer sunlight exposure in 30s, use of sunscreen, waist-to-hip ratio, history of non-melanoma skin cancer	Mid-points of exposure categories
Wu, 2015c SKI23425 USA	NHS, Prospective Cohort, Age: 30-55 years, M/W	841/ 74 666 23.6 years	Biennial follow-up questionnaires and medical records	Validated FFQ, **caffeinated coffee**	Incidence, MM	>2 cups/day vs. never	0.81 (0.65-1.00) Ptrend:0.04	Age, family history of melanoma, personal history of non-skin cancer, natural hair colour, number of moles on legs or arms, sunburn reaction as a	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	NHS II Prospective Cohort, Age: 25-42 years, M/W	642/ 89 220 17.3 years	Biennial follow-up questionnaires and medical records	Validated FFQ, **caffeinated coffee**	Incidence, MM	>2 cups/day vs. never	0.70 (0.55-0.89) Ptrend:0.008	child/adolescent, number of blistering, time spent in direct sunlight since high school, cumulative ultraviolet flux since baseline, BMI, smoking status, physical activity, total energy intake, and alcohol intake, caffeinated tea/carbonated beverages/ caffeine-containing chocolate, decaffeinated coffee/tea/carbonated beverages. Analyses on women further adjusted for rotating night shifts, menopausal status, postmenopausal hormone use	
	HPFS, Prospective Cohort, Age: 40-75 years, M/W	771/ 39 424 16.8 years	Biennial follow-up questionnaires and medical records	Validated FFQ, **caffeinated coffee**	Incidence, MM	>2 cups/day vs. never	1.10 (0.86-1.30) Ptrend:0.55		
Miura, 2014 SKI23423 Australia	NSCS, Prospective Cohort, Age: 49.3 years, M/W	323/ 1 325 11 years	Biennial follow-up questionnaires, histological reports	Validated FFQ, **caffeinated coffee**	Incidence, BCC	≥2 vs. 0 cup/day	0.92 (0.67-1.28) Ptrend:0.34	Age, sex, tanning ability, treatment allocation, elastosis of neck, freckling back, history of skin cancer	Mid-points of exposure categories, number of cases per category
		196/			Incidence, SCC		1.17 (0.71-1.91) Ptrend:0.31	Additionally adjusted for pack years of smoking	
Song, 2012 SKI23421	NHS, Prospective	14 230/ 72 921	Biennial follow-up	Validated FFQ,	Incidence, BCC	>3 cups/day vs. <1	0.79 (0.74-0.85) Ptrend:<0.0001	Age, BMI, childhood sun reaction, family history of	Mid-points of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Cohort, Age: 30-55 years, W	24 years	questionnaires pathologically unconfirmed	**caffeinated coffee**		cup/month		melanoma, hair colour, history of severe sunburn, physical activity, presence of moles, smoking status, UV index at birth, age 15, age 30, history of non-skin cancer, sun exposures at different age intervals	categories,
	HPFS, Prospective Cohort, Age: 40-75 years, M	8 556/ 39 976 22 years					0.90 (0.80-1.01) Ptrend:0.003		
	NHS, Prospective Cohort, Age: 30-55 years, W	1 043/ 72 921 24 years	Biennial follow-up questionnaires and medical records		Incidence, SCC		1.03 (0.80-1.32) Ptrend:0.81		
	HPFS, Prospective Cohort, Age: 40-75 years, M	910/ 39 976 22 years					0.66 (0.44-1.01) Ptrend:0.11		
	NHS, Prospective Cohort, Age: 30-55 years,	403/ 72 921 24 years			Incidence, MM		1.10 (0.78-1.56) Ptrend:0.48		Superseded by Wu, 2015c

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W								
	HPFS, Prospective Cohort, Age: 40-75 years, M	338/ 39 976 22 years					1.04 (0.60-1.82) Ptrend:0.57		
Nilsson, 2010 SKI22192 Sweden	VIP, Prospective Cohort, Age: 30-60 years, M/W	108/ 64 603 15 years	Cancer registry	FFQ, **total coffee**	Incidence, MM	≥4 vs. <1 times/day	0.97 (0.50-1.89)	Age, sex, BMI, educational level, recreational physical activity, smoking	Mid-points of exposure categories, times/day used as cups/day
				boiled coffee			1.16 (0.52-2.55)		
				filtered coffee			1.13 (0.64-1.59)		
Veierod, 1997 SKI17728 Norway	Norway 1977-1983, Prospective Cohort, Age: 16-56 years, M/W	47/ 25 708 6.9 years	Health screening programme	FFQ, **total coffee**	Incidence, MM, men	≥7 vs. ≤2 cups/day	1.50 (0.50-4.60)	Age, sex, area of residence	Mid-points of exposure categories, total persons per category, RR in men and women combined using fixed effects model
		61/ 24 946 6.9 years			Women		0.40 (0.20-0.90)		

Table 9 Coffee intake and skin cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Milan, 2003 SKI00640 Finland	Finnish Adult Twin Cohort Study, Case Cohort, M/W	184/ 13 888 15.2 years	Population registry	Questionnaire, **total coffee**	Incidence, BCC, Men	>3 cups/day vs. rarely or never	1.75 (0.73-4.17)	Age, ethnicity, sunlight (shared environment in twin pairs)	Excluded, two levels of exposure, used in the highest vs. lowest figure
					Women		1.64 (0.77-3.46)		
Stensvold, 1994 SKI02913 Norway	Norway 1977-1982, Prospective Cohort, Age: 35-54 years, M/W	36/ 42 973 10.1 years	Health screening programme	FFQ, **total coffee**	Incidence, MM, men	per 1 cup/day	0.02 (-0.25-0.30)	Age, cigarettes per day, country of residence	Superseded by Veierod, 1997
		48/			Women		-0.37 (-0.64--0.11)		
Jacobsen, 1986 SKI04329 Norway	Norway 1967-1969, Prospective Cohort, Age: 59 years, M/W	19/ 16 555 11.5 years	Probability sample, brothers, spouses, siblings	FFQ, **total coffee**	Incidence, MM	≥7 vs. ≤2 cups/day	2.63	Age, sex, area of residence	Excluded, only two levels of exposure, used in the highest vs. lowest analysis
		207/			NMSC		0.56		
		118/			BCC, men		0.45	Age, sex, area of residence, smoking habits	
		23/			SCC, men		0.35		
		12/			MM, men		3.47		
Whittemore,	HPALS,	104/	Alumni offices,	Not stated,	Incidence,	-	-	-	No risk estimate

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
1985 SKI22091 USA	Case Cohort, M/W, College alumni	51 977	questionnaires	**total coffee**	MM				

Figure 3 RR estimates of skin cancer by levels of coffee intake

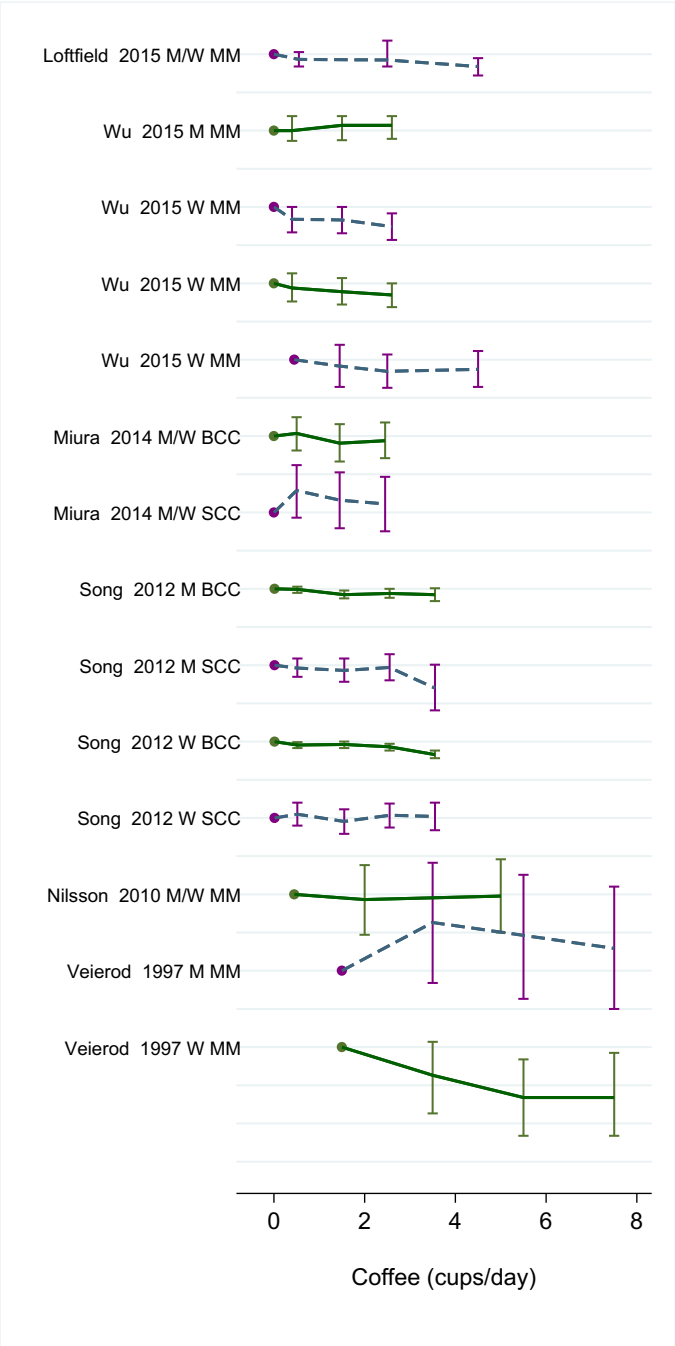


Figure 4 RR (95% CI) of melanoma for the highest compared with the lowest level of coffee intake, by cancer type

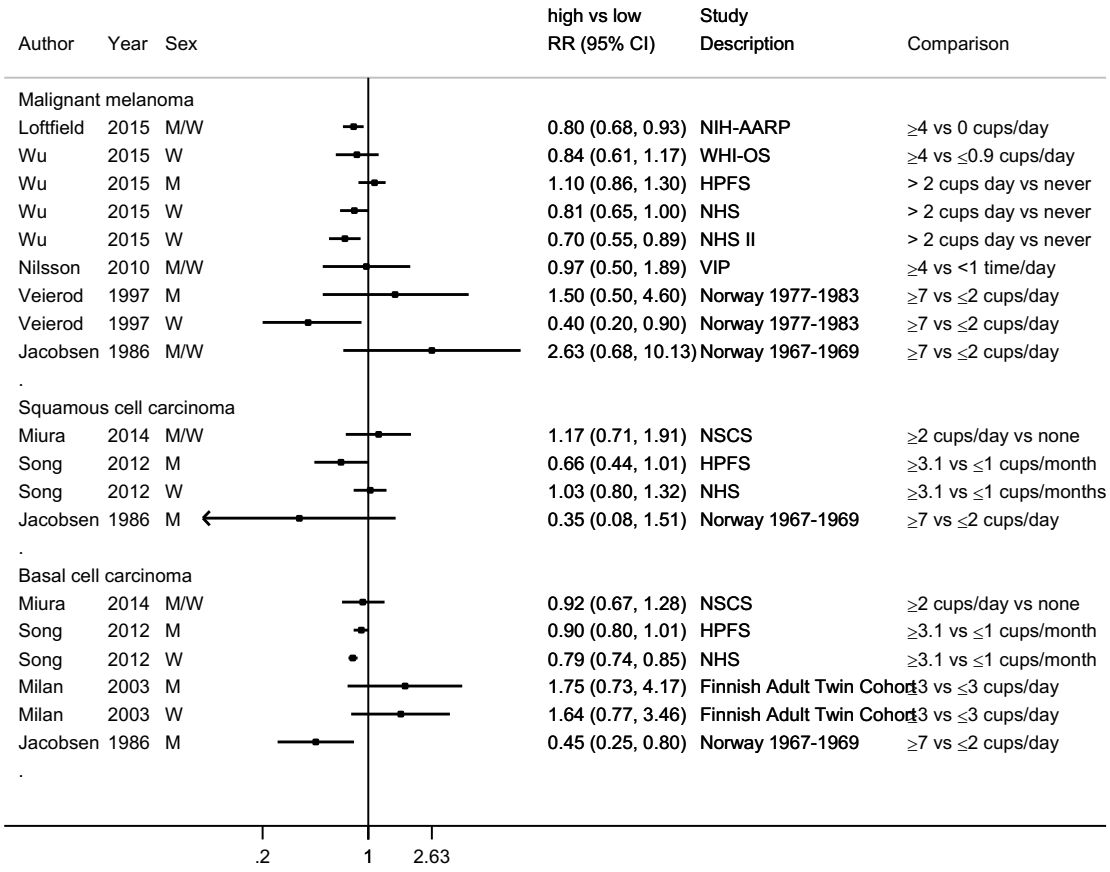


Figure 5 Relative risk of melanoma for 1 cup/day increase of coffee intake, by cancer type

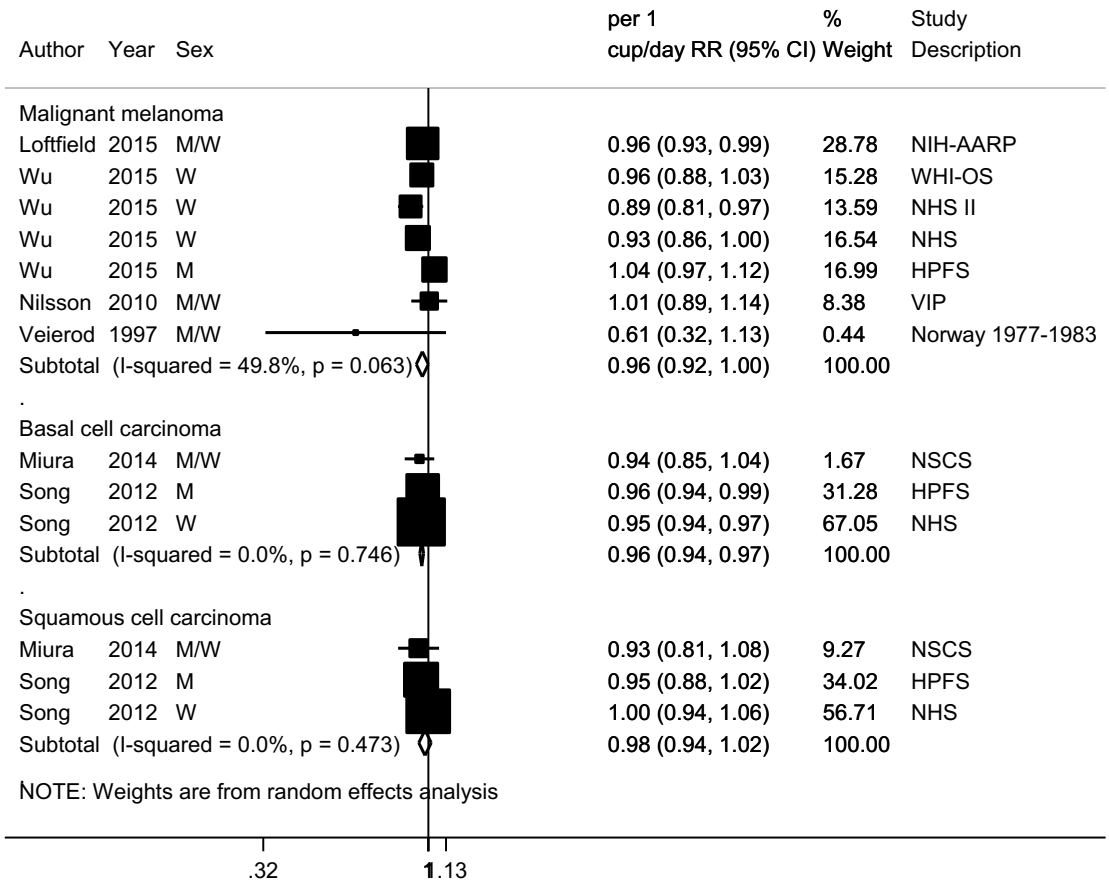


Figure 6 Funnel plot of studies included in the dose response meta-analysis of coffee and melanoma

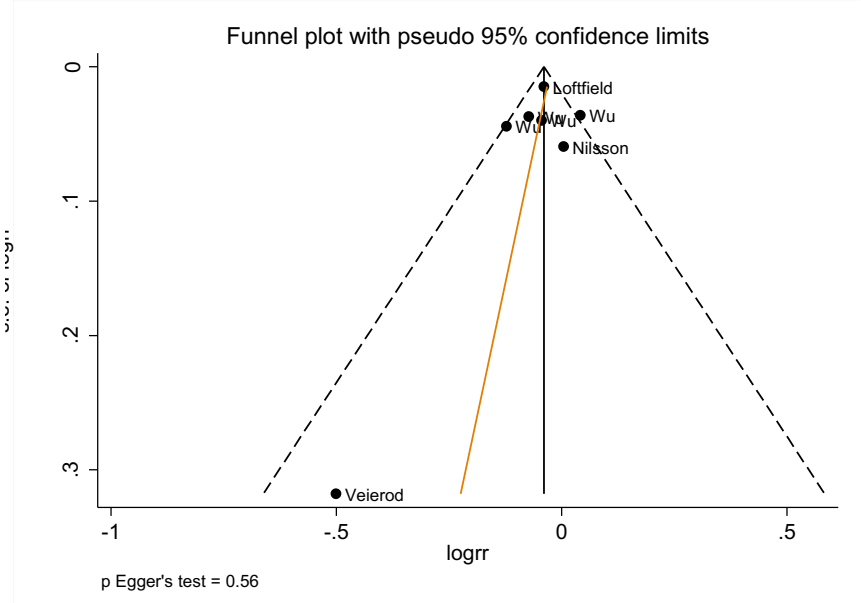


Figure 7 Relative risk of melanoma for 1 cup/day increase of coffee intake, by sex

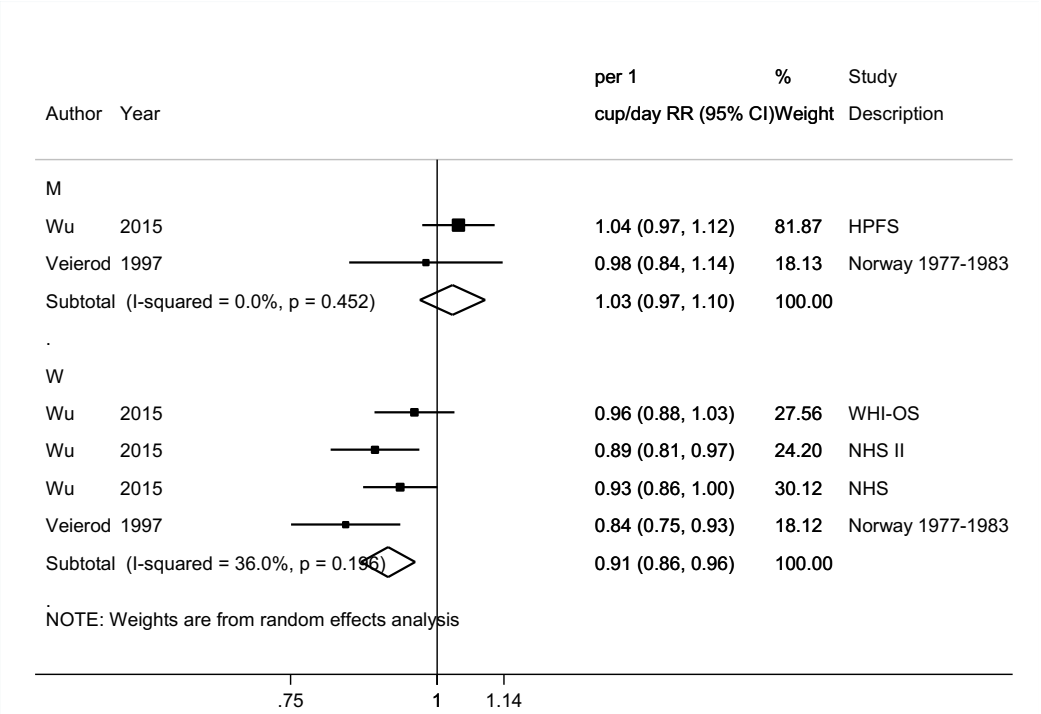
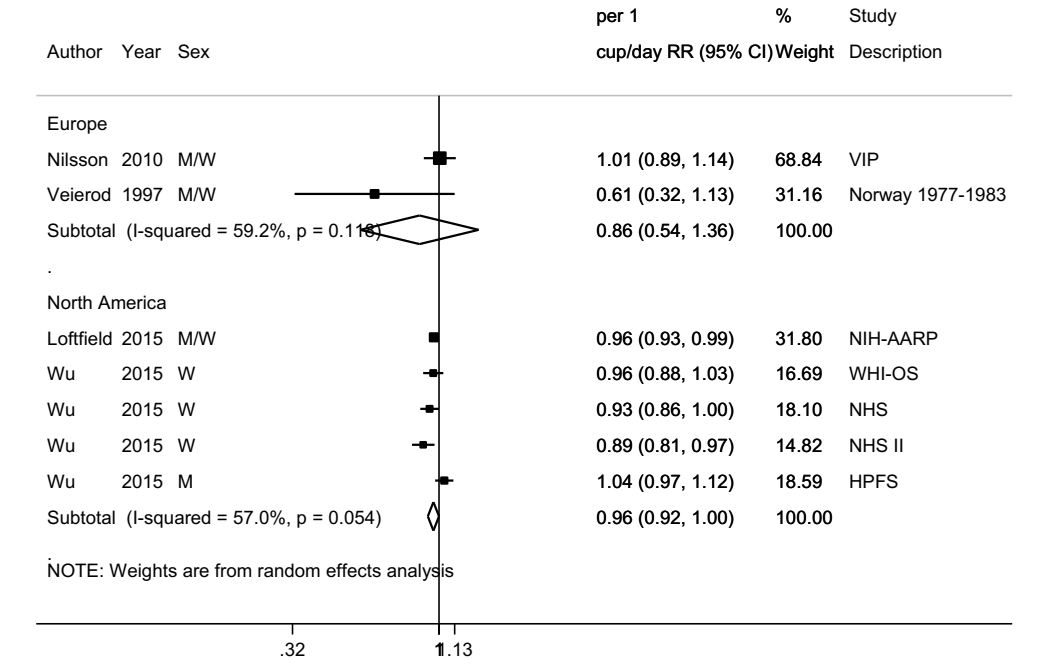


Figure 8 Relative risk of melanoma for 1 cup/day increase of coffee intake, by geographic location



3.6.1 Decaffeinated coffee

Overall summary

No studies were identified in the 2005 SLR and six studies (five publications on melanoma, BCC and SCC) were identified in the CUP.

Dose-response meta-analyses were conducted for Melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Table 10 Decaffeinated coffee intake and skin cancer risk. Number of studies in the CUP SLR.

	Number
Studies identified	6 (5 publications)
Studies included in forest plot of highest compared with lowest exposure	5 (3 publications) melanoma risk NMSC risk – no studies 3 (2 publications) BCC 3 (2 publications) SCC risk
Studies included in linear dose-response meta-analysis	5 (3 publications) melanoma risk NMSC risk – no studies 3 (2 publications) BCC 3 (2 publications) SCC risk
Studies included in non-linear dose-response meta-analysis	5 (3 publications) melanoma risk NMSC, BCC, SCC – not enough studies

Skin cancer

Summary

Main results:

All identified studies were included in the dose response meta-analysis on melanoma, SCC and BCC.

Malignant melanoma

Decaffeinated coffee intake was not associated with melanoma risk (RR for 1 cup increase: 0.99, 95% CI= 0.95-1.02). No heterogeneity was observed.

Sensitivity analyses:

In influence analysis, the association ranged from 0.98 (95% CI=0.95-1.02) when Wu, 2015c (NHS II, 10.7% weight) was omitted to 0.99 (95% CI=0.93-1.04) when Loftfield, 2015 (39.7% weight) was omitted.

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear relationship between decaffeinated coffee intake and risk of melanoma (p=0.58).

Basal cell carcinoma

Decaffeinated coffee intake was not associated with BCC risk (RR: 1.02, 95% CI= 1.00-1.04) with no heterogeneity.

Squamous cell carcinoma

Decaffeinated coffee intake was not associated with SCC risk (RR: 1.05, 95% CI= 0.98-1.12). Low heterogeneity was observed.

Study quality:

See section 3.6.1 on total coffee intake.

Table 11 Decaffeinated coffee and skin cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP.

	2005 SLR*	**CUP**
Increment unit used	1 cup/day	
Malignant melanoma		
Studies (n)	-	5
Cases	-	30 628
RR (95%CI)	-	0.99 (0.95-1.02)
Heterogeneity (I^2, p-value)	-	0%, 0.98
P value Egger test	-	0.92
	Basal cell carcinoma	**Squamous cell carcinoma**
Studies (n)	3	3
Cases	23 109	2 149
RR (95%CI)	1.02 (1.00-1.04)	1.05 (0.98-1.12)
Heterogeneity (I^2, p-value)	0%, 0.83	19%, 0.29
P value Egger test	-	-
Malignant Melanoma: stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	1	3
Cases	771	1 695
RR (95%CI)	0.99 (0.90-1.09)	0.98 (0.92-1.05)
Heterogeneity (I^2, p-value)	-	0%, 0.80

P value Egger test	-	-
Geographic area	**Europe**	**North America**
Studies (n)	-	5
RR (95%CI)	-	0.99 (0.95-1.02)
Heterogeneity (I^2, p-value)	-	0%, 0.98
P value Egger test	-	0.92
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**
Studies (n)	5	-
RR (95%CI)	0.99 (0.95-1.02)	-
Heterogeneity (I^2, p-value)	0%, 0.98	-

*No studies were identified in the 2005 SLR.

Table 12 Decaffeinated coffee and skin cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Liu, 2016*	5 cohort studies	-	USA	Malignant melanoma	Highest vs. lowest	0.94 (0.74-1.18)	0%
Wang, 2016*	5 cohort and 1 case control study	4 183	USA, Italy	Cutaneous melanoma	Highest vs. lowest	0.92 (0.81-1.05)	0%, 0.97
Caini, 2016*	3 cohort and 1 case-control study	-	Australia, USA	NMSC	Higest vs. lowest	1.01 (0.85-1.21)	0%

*All studies are included in the CUP dose-response meta-analysis.

Table 13 Decaffeinated coffee intake and skin cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Loftfield, 2015 SKI23424 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 904/ 447 357 10.5 years	Cancer registry	Validated FFQ	Incidence, MM	≥4 vs. 0 cups/day	0.95 (0.76-1.18) Ptrend:0.55	Age, sex, alcohol intake, BMI, cigar or pipe smoking, cigarette smoking, educational level, family history of cancer, July erythemal UV exposure, physical activity, smoking intensity	Mid-points of exposure categories
Wu, 2015b SKI23426 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	314/ 66 484 7.73 years	Questionnaire, medical records or pathology reports reviewed by physicians	Interview	Incidence, MM	≥4 vs. ≤0.9 cups/day	0.73 (0.36-1.49) Ptrend:0.44	Age, alcohol intake, aspirin use, educational level, height, income, region of residence, skin reaction to sun, smoking, summer sunlight exposure in 30s, use of sunscreen, waist-to-hip ratio, history of non-melanoma skin cancer, history of non-melanoma skin cancer	Mid-points of exposure categories
Wu, 2015c SKI23425 USA	NHS, Prospective Cohort, Age: 25-75 years, M/W	739/ 74 666 23.6 years	Biennial follow-up questionnaires and medical records	Validated FFQ	Incidence, MM,	>2 cups/day vs. never	0.98 (0.72-1.30) Ptrend:0.76	Age, family history of melanoma, personal history of non-skin cancer, natural hair colour, number of moles on legs or arms,	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	NHS II, Prospective Cohort, Age: 25-75 years, M/W	642/ 89 220 17.3 years			Incidence, MM,	>2 cups/day vs. never	0.93 (0.60-1.40) Ptrend:0.91	sunburn reaction as a child/adolescent, number of blistering, time spent in direct sunlight since high school, cumulative ultraviolet flux since baseline, BMI, smoking status, physical activity, total energy intake, and alcohol intake, caffeinated tea/carbonated beverages/ caffeine-containing chocolate, decaffeinated coffee/tea/carbonated beverages. Analyses on women further adjusted for rotating night shifts, menopausal status, postmenopausal hormone use	
	HPFS, Prospective Cohort, Age: 40-75 years, M/W	771/ 39 424 16.8 years			Incidence, MM,	>2 cups/day vs. never	0.92 (0.68-1.2) Ptrend:0.98		
Miura, 2014 SKI23423 Australia	NSCS, Prospective Cohort, Age: 49.3 years, M/W	323/ 1 325 11 years	Biennial follow-up questionnaires, histological reports	Validated FFQ	Incidence, BCC	≥1 cup/day vs. none	1.05 (0.73-1.52) Ptrend:0.78	Age, sex, tanning ability, treatment allocation, elastosis of neck, freckling back, history of skin cancer	Mid-points of exposure categories, number of cases per category
		196/ 1 325 11 years			Incidence, SCC		1.15 (0.69-1.92) Ptrend:0.60	Additionally adjusted for pack years of smoking	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Song, 2012 SKI23421 USA	NHS, Prospective Cohort, Age: 30-55 years, W	14 230/ 72 921 24 years	Biennial follow-up questionnaires and medical records	Validated FFQ	Incidence, BCC	>3 cups/day vs. <1 cup/month	0.98 (0.87-1.10) Ptrend:0.01	Age, BMI, family history of melanoma, hair colour, history of severe sunburn, physical activity, presence of moles, smoking status, UV index at birth, age 15, age 30, childhood reaction to sun, history of non-skin cancer, sun exposures at different age intervals	Mid-points of exposure categories
	HPFS, Prospective Cohort, Age: 40-75 years, M	8 556/ 39 976 22 years					1.00 (0.87-1.15) Ptrend:0.81		
	NHS, Prospective Cohort, Age: 30-55 years, W	1 043/ 72 921 24 years			Incidence, SCC		0.89 (0.55-1.43) Ptrend:0.63		
	HPFS, Prospective Cohort, Age: 40-75 years, M	910/ 39 976 22 years					1.44 (0.99-2.10) Ptrend:0.03		
	NHS, Prospective Cohort, Age: 30-55 years, W	403/ 72 921 24 years			Incidence, MM		0.79 (0.40-1.56) Ptrend:0.40		Superseded by Wu, 2015 (NHS, HPFS)
	HPFS,	338/					0.84 (0.39-1.82)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Prospective Cohort, Age: 40-75 years, M	39 976 22 years					Ptrend:0.64		

Figure 9 RR estimates of melanoma by levels of decaffeinated coffee intake

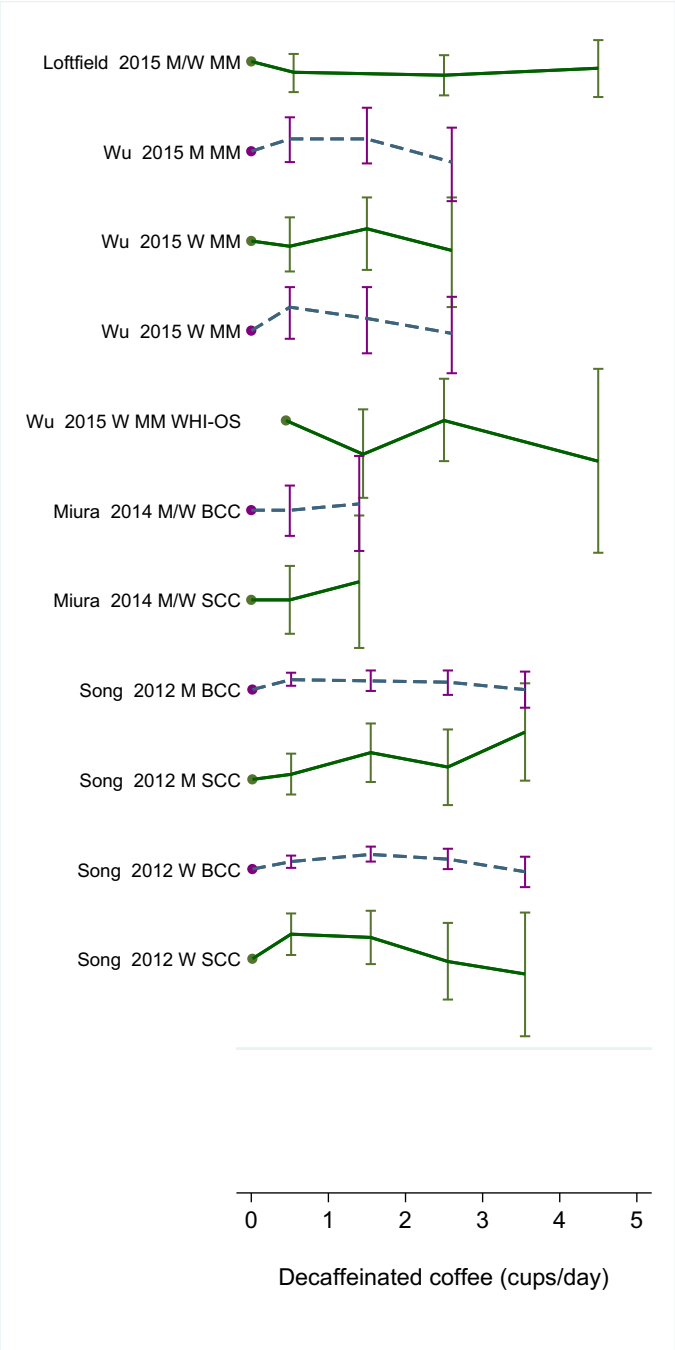


Figure 10 RR (95% CI) of melanoma for the highest compared with the lowest level of decaffeinated coffee intake

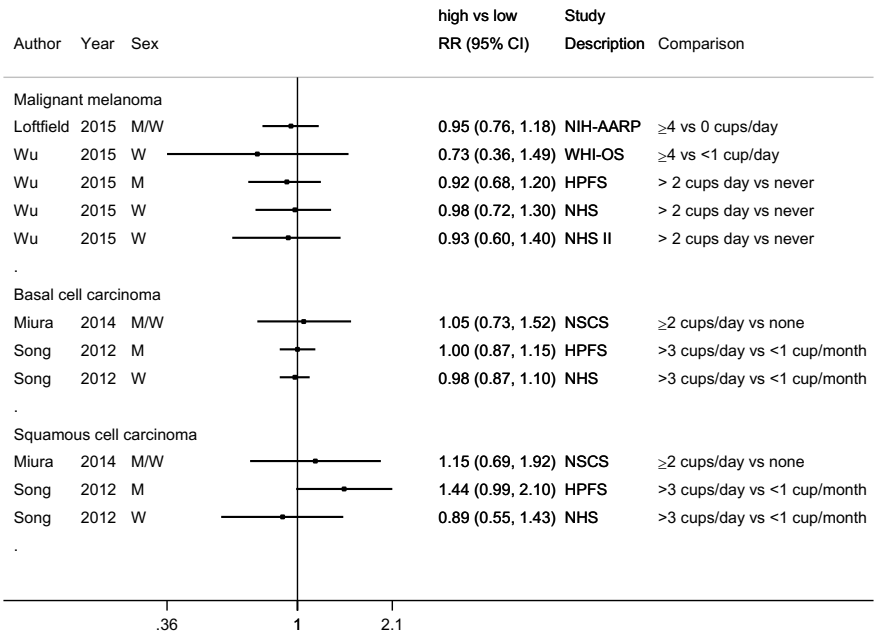


Figure 11 Relative risk of melanoma for 1 cup/day increase of decaffeinated coffee intake

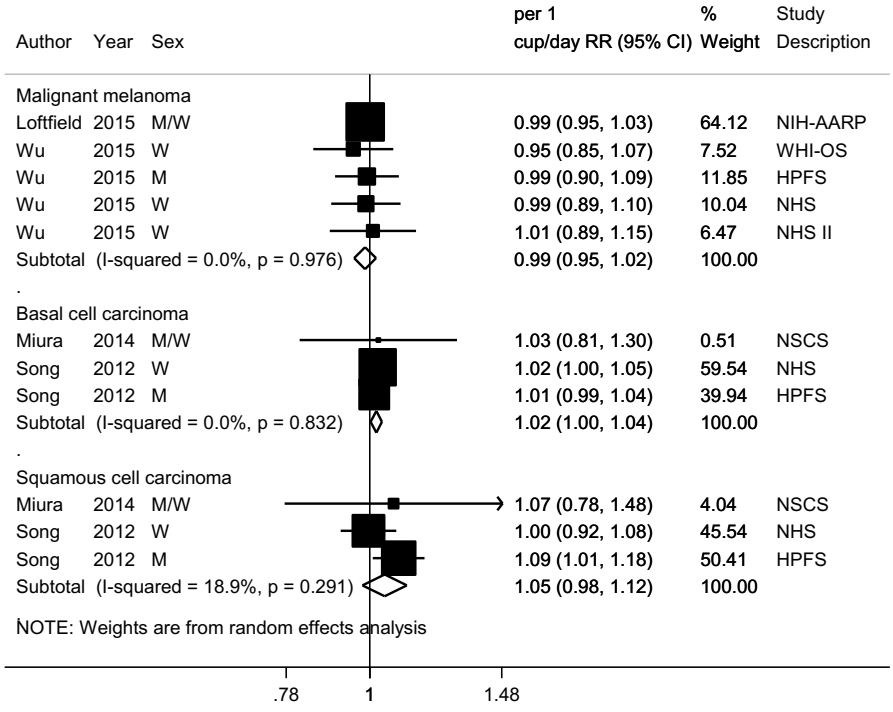


Figure 12 Funnel plot of studies included in the dose response meta-analysis of decaffeinated coffee and melanoma

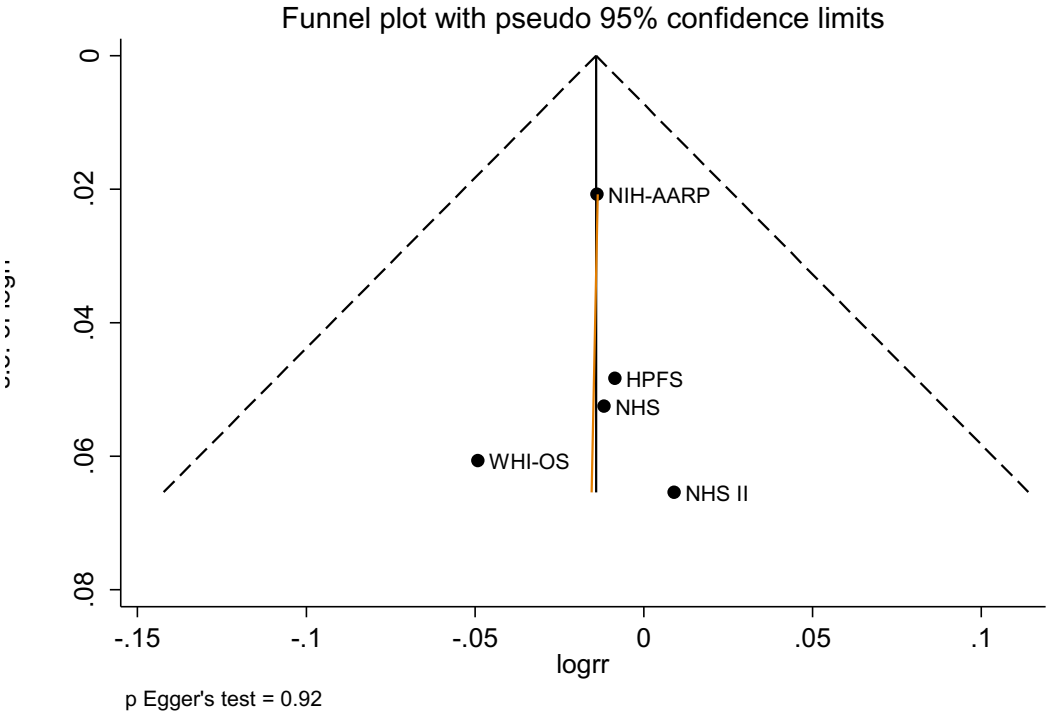
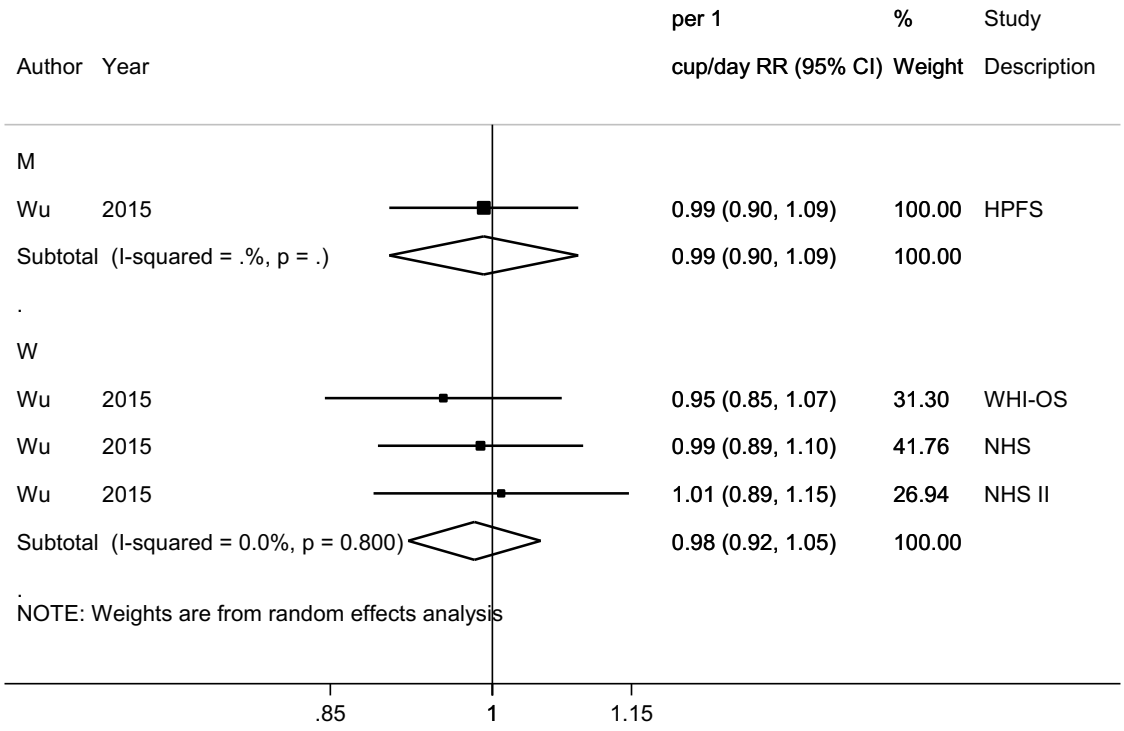


Figure 13 Relative risk of melanoma for 1 cup/day increase of decaffeinated coffee intake, by sex



3.7.1 Total alcoholic drinks

Overall summary

Seventeen studies on total alcohol intake were identified from which eight publications were identified during the CUP.

Dose-response meta-analyses were conducted on total alcohol intake and melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Not enough studies were identified to conduct dose response meta-analysis for non-melanoma skin cancer (NMSC).

Table 14 Total alcohol intake and skin cancer risk. Number of studies in the CUP SLR.

	Number
Studies identified	17 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (6 publications) melanoma risk Not enough studies for NMSC risk 7 (5 publications) BCC 3 (3 publications) SCC risk
Studies included in linear dose-response meta-analysis	6 (6 publications) melanoma risk Not enough studies for NMSC risk 9 (7 publications) BCC 3 (3 publications) SCC risk
Studies included in non-linear dose-response meta-analysis	6 (6 publications) melanoma risk Not enough studies for NMSC risk 6 (4 publications) BCC Not enough studies for SCC risk

Skin cancer

Summary

Main results:

Six out of seven studies on melanoma, the nine studies (8 publications) on BCC and the three studies on SCC could be included in the dose-response meta-analysis. Not enough studies were identified for NMSC (1 study from 1 publication).

Malignant melanoma

Total alcohol intake (as ethanol) was statistically significanlty positively associated with melanoma risk (RR: 1.08, 95% CI=1.03-1.13). High proportion of within study heterogeneity was observed (I^2: 66.2%, p=0.01). The insufficient number of studies did not allow analysis of heterogeneity source.

One population study reporting standardised incidence ratio was excluded from the meta-analysis; the study reported no association between alcoholism and melanoma (Adami, 1992).

Egger's test was statistically non-significant ($p_{Egger's}$=0.142), probably because of low number of studies. However, the assymetry of the funnel plot suggest that small studies in the left side of the funnel may be missing.

Nonlinear dose-response meta-analysis:

There was statistically significant evidence of nonlinearity (p<0.0001) in the range of nondrinkers and very low consumers. However, the dose-response was mainly flat above 10 g/day.

Non-melanoma skin cancer

Only one study was identified in CUP (Kubo, 2014). The RR of NMSC was 1.23 (95% CI 1.11- 1.36), when comparing alcohol consumption ≥7 drinks per week with non-drinking and 1.08 (95% CI 1.05- 1.11) for seven additional servings per week.

Sensitivity analysis:

The association remained statistically significant when each study was excluded in turn in influence analysis.

Basal cell carcinoma

Total alcohol intake (as ethanol) was not associated with BCC risk (RRfor 10 g/day increment: 1.04, 95% CI=0.99-1.10). High and statistically significant heterogeneity was observed (I^2: 68.3%, p-value=0.004).

Egger's test showed no evidence of publication or small study bias.

Stratified analyses by sex showed no association in men (RR: 1.03, 95% CI=0.99-1.08; I^2: 71.1, p-value heterogeneity test=0.016), whereas a statistically significant positive association was found for women (RR: 1.08, 95% CI=1.04-1.12; I^2: 43.2, p=0.152).

Sensitivity analysis:

The association became marginally significant (positive) when Milan 2003 (RR: 1.05, 95% CI=1.00-1.10) was excluded. Milan 2003 reported results on same-sex twins, and assumed that they had similar sun exposure in childhood.

Nonlinear dose-response meta-analysis:

There was statistical significant evidence of nonlinearity (p<0.0001) in the range of nondrinkers and very low consumers. However, the dose-response plateaued above 10 g/day.

Squamous cell carcinoma

Total alcohol intake (as ethanol) was not associated with risk of SCC (RR: 1.03, 95% CI=0.97-1.09). No heterogeneity was observed (I^2: 0%, p=0.578).

Egger's test was not conducted due to low number of publications.

Sensitivity analysis:

The results did not change substantially (no association) when studies were excluded in turn in influence analysis.

Study quality:

All studies used FFQ or questionnaires to assess alcohol consumption, except one study which used 7-day food diary (EPIC-Norfolk; Davies, 2002).

Two studies adjusted for different measures of skin sensitivity to sunlight and sunlight exposure (Wu, 2015d; Kubo, 2014). One study adjusted for skin sensitivity to sunlight and various measures of personal characteristics (such as degree of freckling, number of nevi) (Jensen, 2012) and one study for hair colour (Davies, 2002). Three studies adjusted for several personal characteristics (skin colour, elastosis or hair colour) and sunlight exposure (Ansems, 2008; Freedman, 2003a; Freedman, 2003b). One study in twin pairs assumed that most twins were exposed to a similar environment until the age of 16 (Milan, 2003). Three studies were minimally adjusted for age and sex (Loftfield, 2015; Asgari, 2012) or age only (Foote, 2001).

Regarding study population, two studies were prospective follow-up of participants in a randomised controlled trial, the Nambour Skin Cancer Prevention Trial on beta-carotene supplements and sunscreen creams (Ansems, 2008) and in a trial on oral vitamin A in "moderately sun-damaged" subjects with ten or more actinic keratoses (Foote, 2001). In the follow-up of the Nambour Skin Cancer Prevention Trial, risk estimates remained statistically non-significant when participants with history of skin cancer were excluded for BCC and SCC. One study on melanoma (Freedman, 2003a) included incident and mortality cases. Two studies on BCC (Ansems, 2008, Nambour Skin Cancer Study; Davies, 2002, EPIC-Norfolk) and one study on SCC (Ansems, 2008) included incident and prevalent cases.

In one study that reported data on tumour-based BCC and SCC analyses (Ansems, 2008), results were similar when analyses were person-based rather than tumour-based.

All the studies included in the dose-response analysis had "nondrinkers" as reference category. Non-drinkers were defined in different ways. In three studies on melanoma there is no description of nondrinkers (Loftfield, 2015; Asgari, 2012; Freedman, 2003a). In one study the reference category was "lifelong abstainers" - subjects who had no alcohol consumption during the previous year- and "never or almost never" before the past year (Klatsky, 2015). Kubo *et al*. defined the reference category as "less than 100 alcoholic drinks in their lifetime" (Kubo, 2014) while in Allen *et al*. "nondrinkers" included non-drinkers and former drinkers (Allen, 2009). Four studies on BCC and SCC did not describe the "nondrinkers" definition of the reference category (Wu, 2015d; Ansems, 2008; Freedman, 2003b; Fung, 2002a; Foote, 2001). One study defined never drinkers as "never" and "past" drinkers (Jensen, 2012).

Table 15 Total alcohol intake and skin cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP.

	2005 SLR	CUP
Increment unit used	Servings/day	10g/day
Malignant melanoma		
Studies (n)	2	6
Cases	731	7 367
RR (95%CI)	1.18 (0.99-1.40)	1.08 (1.03-1.13)
Heterogeneity (I^2, p-value)	0%, 0.951	66%, 0.01
P value Egger test	-	0.08
Basal cell carcinoma		
Studies (n)	2	9
Cases	1 495	3 349
RR (95%CI)	1.24 (0.65-2.34)	1.04 (0.99-1.10)
Heterogeneity (I^2, p-value)	61%, 0.109	68.3%, 0.004
P value Egger test	-	0.799
Squamous cell carcinoma		
Studies (n)	1	3
Cases	106	425
RR (95%CI)	1.69 (0.65-4.38)	1.03 (0.97-1.09)
Heterogeneity (I^2, p-value)	-	0%, 0.578
P value Egger test	-	-
Stratified and sensitivity analysis		
Malignant Melanoma		
Sex	**Men**	**Women**
Studies (n)	1	3
Cases	48	2 690
RR (95%CI)	1.17 (0.82-1.67)	1.09 (1.03-1.16)
Heterogeneity (I^2, p-value)	-	34%, 0.22
BCC		
Sex	**Men**	**Women**

Studies (n)	4	4	
Cases	10 884	22 073	
RR (95%CI)	1.03 (0.99-1.08)	1.08 (1.04-1.12)	
Heterogeneity (I^2, p-value)	71.1%, 0.016	43.2%, 0.152	
Geographic area	**Australia**	**Europe**	**North America**
Studies (n)	1	3	5
RR (95%CI)	0.94 (0.81-1.09)	1.01 (0.96-1.06)	1.10 (1.02-1.17)
Heterogeneity (I^2, p-value)	-	13.4%, 0.315	54.5%, 0.111
Exposure assessment	**FFQ**	**Questionnaire**	
Studies (n)	6	2	
RR (95%CI)	1.03 (0.98-1.07)	1.02 (0.78-1.32)	
Heterogeneity (I^2, p-value)	59.6%, 0.060	82.6%, 0.016	-
Number of cases	**<500 cases**	**500-<1000 cases**	**>1000 cases**
Studies (n)	4		5
RR (95%CI)	0.98 (0.88-1.09)		1.06 (1.00-1.12)
Heterogeneity (I^2, p-value)	16.5%, 0.309		85.6%, 0.001
Publication year	**≤2010**	**>2010**	
Studies (n)	5	4	
RR (95%CI)	1.03 (0.91-1.16)	1.03 (0.99-1.08)	
Heterogeneity (I^2, p-value)	61.9%, 0.033	81.2%, 0.021	
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**	
Studies (n)	7	2	
RR (95%CI)	1.04 (0.98-1.10)	1.08 (0.93-1.25)	
Heterogeneity (I^2, p-value)	77.8%, 0.001	0.0%, 0.432	

Table 16 Total alcohol intake and malignant melanoma risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Bagnardi, 2015	2 cohort, 12 case-control studies	6 096 cases (men and women combined)	Europe, North America, Australia	Malignant melanoma	**Light drinking** (≤12.5g/d) vs. nondrinking All studies	1.11 (0.97-1.27)	36%
					Case-control studies (12 studies)	1.06 (0.90-1.25)	32%
					Cohort studies (2 studies)	1.25 (1.13-1.38)	0%
					Men (3 studies) Women (4 studies)	1.19 (0.82-1.72) 1.25 (1.13-1.38)	0% 0%
					Moderate drinking (12.5-50g/d) vs. nondrinking All studies	1.20 (1.03-1.41)	38%
					Case-control studies (10 studies)	1.16 (0.92-1.45)	32%
					Cohort studies (2 studies)	1.27 (1.13-1.42)	0%

					Men (3 studies) Women (3 studies)	1.32 (0.90-1.92) 1.27 (1.14-1.43)	0% 0%
Rota, 2014	2 cohort studies, 14 case-control studies	6 251 cases (men and women combined)	Europe, North America, Australia and Paraguay	Malignant melanoma	**Any alcohol drinking vs. no/occasional drinking** All studies	1.20 (1.06-1.37)	55.6%, 0.003
					Case-control studies (14 studies)	1.20 (1.01-1.44)	57.5%, 0.003
					Cohort studies (2 studies)	1.26 (1.19-1.35)	0.0%, 0.657
					Men (3 studies) Women (3 studies)	1.47 (0.94-2.29) 1.26 (1.19-1.35)	45.7%, 0.159 0%, 0.665
					Light alcohol drinking vs. no/occasional drinking (≤1drink/d) All studies	1.10 (0.96-1.26)	41.8%, 0.045
					Case-control studies (12 studies)	1.06 (0.90-1.25)	31.7%, 0.129
					Cohort studies (2 studies)	1.25 (1.15-1.35)	0.0%, 0.847
					Moderate to heavy alcohol drinking vs. no/occasional drinking (>1drink/d) All studies	1.18 (1.01-1.40)	51.0%, 0.021
					Case-control studies (10 studies)	1.13 (0.90-1.41)	53.2%, 0.023
					Cohort studies (2 studies)	1.29 (1.17-1.43)	0.0%, 0.370

Table 17 Total alcohol intake and skin cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Klatsky, 2015 SKI23406 USA	KPMCP, Prospective Cohort, Age: 41 years, M/W	1 164/ 124 193 17.8 years	Cancer registry	Questionnaire	Incidence MM	≥3 drinks/day vs. Never drinkers	2.20 (1.60-3.10)	Age, sex, BMI, educational level, marital status, race/ethnicity, smoking
					Never smokers		1.80 (1.20-2.80)	Paper does not specify
Loftfield, 2015 SKI23424 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 904/ 447 357 10.5 years	Cancer registry	Validated FFQ	Incidence MM	>3 drinks/day vs. none for >5 years	1.11 (0.95-1.29)	Age, sex
Wu, 2015d SKI23407 USA	NHS, NHS II, HPFS, Prospective Cohort, M/W	28 951/ 211 462 3 740 000 person-years	Self-report	FFQ	Incidence BCC	per 10 g/day	1.06 (1.03-1.10)	Age, BMI, caffeine consumption, cumulative UV flux since baseline, ethnicity, family history of melanoma, hair colour, number of moles on arms or legs, number of severe sunburns, physical activity, skin reaction to sun as a child/adolescent, smoking status, use
		28 951/				≥30 g/day vs. None	1.22 (1.15-1.30) Ptrend:<0.0001	
		19 679/			Incidence BCC Women	≥30 g/day vs. None	1.27 (1.16-1.38) Ptrend:<0.0001	
		9 272/			Incidence BCC Men	≥30 g/day vs. None	1.18 (1.08-1.28) Ptrend:<0.0001	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								of sunscreen in summer months, average time spent in direct sunlight in summer months
Kubo, 2014 SKI23408 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	9 593/ 59 575 10.2 years	Medical records by physicians	FFQ	Incidence NMSC	≥7 drinks/week vs. Non-drinkers	1.23 (1.11-1.36) Ptrend:<0.0001	Age, BMI, education years, having a healthcare provider, health insurance, history of melanoma, history of NMSC, Langleys of exposure, physical activity, skin reaction to sun, smoking, childhood sun exposure, current summer sun exposure, use of sunscreen, last medical visit within 1 year
		9 593/				Per 7 drinks/ week	1.08 (1.05-1.11)	
		9 593/				Current drinker vs. Non-drinkers	1.12 (1.00-1.24)	
		532/			Incidence MM	≥7 drinks/week vs. Non-drinker	1.64 (1.09-2.49) Ptrend:0.0013	
		532/				Per 7 drinks/ week	1.16 (1.06-1.27)	
		532/				Current drinker vs. Non-drinkers	1.18 (0.76-1.82)	
Asgari, 2012 SKI23409 USA	VITAL, Prospective Cohort, Age: 50-76 years,	566/ 69 635 5.84 years	Cancer registry	FFQ	Incidence MM	≥2 vs. ≤0 drinks/day	1.28 (0.97-1.70) Ptrend:0.05	Age, sex

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M/W							
Jensen, 2012 SKI23410 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	2 384/ 54 766 11.4 years	Cancer and pathology registries	FFQ + questionnaire	Incidence BCC	per 10 g/d	1.01 (0.99-1.04)	Age, sex, BMI, education years, degree of freckling, number of nevi, sun sensitivity
		2 384/				≥50.1 vs. 0.1-10 g/d	1.03 (0.88-1.21)	
		1 207/			Incidence BCC Women	per 10 g/d	1.05 (1.01-1.09)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity, menopausal status, use of hormone replacement therapy at baseline
		1 207/				≥50.1 vs. 0.1-10 g/d	1.22 (0.89-1.68)	
		1 177/			Incidence BCC Men	per 10 g/d	1.01 (0.99-1.04)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity
		1 177/				≥50.1 vs. 0.1-10 g/d	1.09 (0.89-1.34)	
		192/			Incidence SCC	per 10 g/d	1.03 (0.97-1.10)	Age, sex, BMI, education years, degree of freckling, number of nevi, sun sensitivity
		192/				≥50.1 vs. 0.1-10 g/d	1.25 (0.72-2.14)	
		116/			Incidence SCC Men	per 10 g/d	1.03 (0.96-1.11)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity
		116/				≥50.1 vs. 0.1-10 g/d	1.23 (0.66-2.28)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		76/			Incidence SCC Women	per 10 g/d	1.05 (0.90-1.21)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity, menopausal status, use of hormone replacement therapy at baseline
		76/				≥50.1 vs. 0.1-10 g/d	0.56 (0.08-4.12)	
Allen, 2009 SKI22188 UK	MWS, Prospective Cohort, Age: 55 years, W	2 459/ 1 280 296 7.2 years	National health service central registers	Questionnaire	Incidence MM	≥15 vs. ≤2 drinks/week	1.17 (1.00-1.37) Ptrend:0.3	Age, BMI, physical activity, region of residence, socio-economic status, use of HRT, use of oral contraception, smoking status
		1 999/			Drinkers	Per 10g/d	1.04 (0.97-1.12)	
Ansems, 2008 SKI23411 Australia	NSCS, Prospective Cohort, Age: 49.7 years, M/W	127/ 1 360 12 942 person-years	Histology	Semi-quantitative FFQ	Tumour-based incidence SCC	26.3 g/day vs. Abstainer	0.94 (0.49-1.80) Ptrend:0.38	Age, sex, beta carotene treatment, sunscreen treatment, pack-years of smoking until 1992, self-reported skin colour, elastosis of the neck, leisure time sun exposure, skin cancer before 1992
		-/			No history of skin cancer	26.5 g/day vs. Abstainer	0.50 (0.16-1.57) Ptrend:0.17	
		-/			History of skin cancer	25.8 g/day vs. Abstainer	1.85 (0.82-4.19) Ptrend:0.16	
		267/ 1 360 12 942 person-			Tumour-based incidence BCC	26.3 g/day vs. Abstainer	1.05 (0.65-1.65) Ptrend:0.84	Age, sex, beta carotene treatment, sunscreen treatment,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		years						elastosis of the neck, occupational sun exposure, leisure time sun exposure, history skin cancer before 1992
		-/			No history of skin cancer	26.5 g/day vs. Abstainer	0.87 (0.43-1.73) Ptrend:0.74	
		-/			History of skin cancer	25.8 g/day vs. Abstainer	1.19 (0.64-2.23) Ptrend:0.57	
Freedman, 2003a SKI00519 USA	USRT, Prospective Cohort, Age: 39 years, M/W, radiologic technologists	207/ 68 588 698 028 person years	Self-report followed by pathology reports and other confirmatory medical records	Questionnaire	Incidence MM	>14 drinks/week vs. Never-drinkers	2.10 (0.90-4.80) Ptrend:0.08	Age, sex, adult sunlight exposure, alcohol consumption, decade since began to work as radiological technician, educational level, hair colour, personal history of NMSC, proxy measures for residential childhood, skin pigmentation, years smoked
		159/			Incidence MM Women	>14 drinks/week vs. Never-drinkers	2.10 (0.60-7.00) Ptrend:0.05	
		48/			Incidence MM Men	>14 drinks/week vs. Never-drinkers	2.40 (0.70-8.20) Ptrend:0.61	
Freedman, 2003b SKI00515 USA	USRT, Prospective Cohort, Age: 38 years, M/W, radiologic technologists	1 360/ 68 371 698 190 person years	Self-report followed by pathology reports and other confirmatory medical records	Questionnaire	Incidence BCC	>14 vs. 0 drinks/week	1.00 (0.70-1.60) Ptrend:0.001	Age, adult sun exposure, BMI, decade since began to work as radiological technician, educational level, ethnicity, hair colour, proxy measures for residential childhood, skin pigmentation,
		1 036/			Incidence BCC Women	>14 vs. 0 drinks/week	0.90 (0.50-1.70) Ptrend:0.01	
		324/			Incidence BCC	>14 vs. 0 drinks/week	1.20 (0.70-2.30) Ptrend:0.08	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Men			years smoked
Milan, 2003 SKI00640 Finland	Finnish Adult Twin Cohort Study, Case Cohort, M/W	184/ 13 888 15.2 years	Population registry	Questionnaire	Incidence BCC Women	Non-drinker vs. Drinker	0.73 (0.42-1.27)	Age, ethnicity, sunlight
		184/			Incidence BCC Women	per 10 g/day	0.85 (0.54-1.33)	
		149/			Incidence BCC Men	Non-drinker vs. Drinker	1.14 (0.41-3.15)	
		149/			Incidence BCC Men	per 10 g/day	0.87 (0.70-1.07)	
Davies, 2002 SKI00989 UK	EPIC-Norfolk, Nested Case Control, M/W	123/ 247 1 976	Cancer registry	Self-reported 7-day food diary	Incidence BCC	per 14.5 g/day	1.09 (0.87-1.37)	BMI, hair colour
Foote, 2001 SKI07414 USA	Arizona USA 1985-1992, Prospective Cohort, Age: 21-85 years, M/W, Moderately Sun-damaged	144/ 918 57 months	Physician referral/cancer registry/advertising	Questionnaire	Incidence BCC	≥3 vs. ≤0 drinks/week	1.47 (0.90-2.41) Ptrend:0.52	Age
		106/			Incidence SCC	≥3 vs. ≤0 drinks/week	1.31 (0.76-2.25) Ptrend:0.44	

Table 18 Total alcohol intake and skin cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Schaumberg, 2004 SKI00367 USA	PHS, Nested case-control, Age: 40-84 years, M	1 338/ 1 338	Self-report followed by review of pathology reports	Not stated	Occurence NMSC	Yes (drink alcohol) vs. No (no alcohol)	Ptrend:<0.001	Age, smoking status	No measure of association provided
Fung, 2002a SKI00891 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W, Female nurses and Male Health Professionals	6 088/ 107 975 8 years in women & 10 years in men	Ongoing or prior study	FFQ	Incidence BCC	≥30 g/day vs. Non-drinkers	1.12 (1.01-1.26) Ptrend:0.0001	Age, area of residence, childhood area of residence, BMI, beer consumption, liquor consumption, missing FFQ, smoking habits, total energy, wine consumption	Superseded by Wu 2015
		3 060/ 107 975 8 years			Incidence BCC Women	≥30 g/day vs. Non-drinkers	1.06 (0.89-1.28) Ptrend:0.001	Additionally adjusted for: ancestry, childhood sun reaction, childhood tanning ability, hair colour, lifetime blistering sunburn, sun screen use	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		3 028/ 107 975 10 years			Incidence BCC Men	≥30 g/day vs. Non-drinkers	1.16 (1.01-1.34) Ptrend:0.002	Additionally adjusted for: ancestry, eye colour, hair colour, tendency to burn in childhood, childhood sun exposure in swimsuit	
Adami, 1992 SKI22200 Sweden	Uppsala Alcoholics, Sweden, Prospective Cohort, Age: 50 years, M/W, Alcoholics	11/ 9 353 7.7 years	Cancer registry	Lifestyle grouping	Incidence Skin cancer Men	Alcoholics vs. Study population	0.80 (0.30-1.80)	Age	Inadequate categorisation
		1/			Incidence Skin cancer Women	Alcoholics vs. Study population	1.50 (0.00-8.20)		
Whittemore, 1985 SKI22091 USA	HPALS, Case Cohort, M/W, College alumni	-/ 51 977	Alumni offices and questionnaires	Questionnaire via mail	Incidence MM	Not stated	Not significant association was found	-	No measure of association provided

Figure 14 RR estimates of melanoma by levels of total alcohol intake

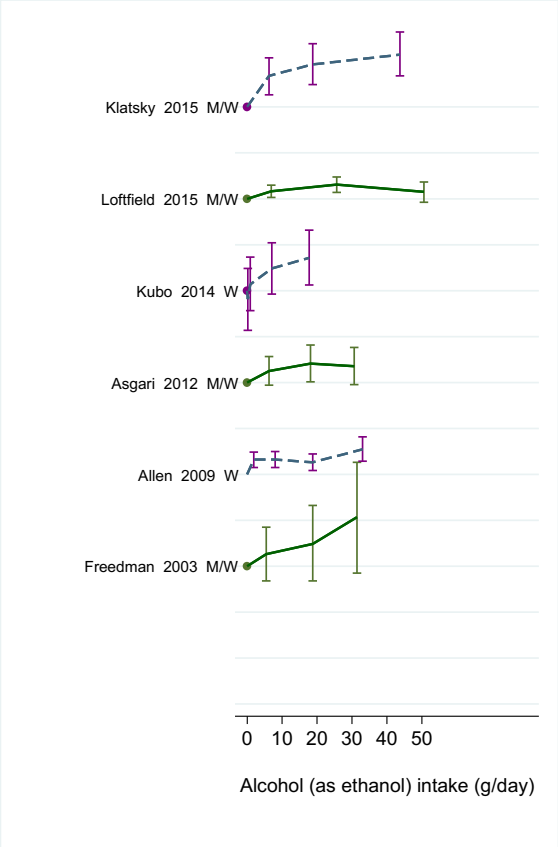


Figure 15 RR (95% CI) of melanoma for the highest compared with the lowest level of total alcohol intake

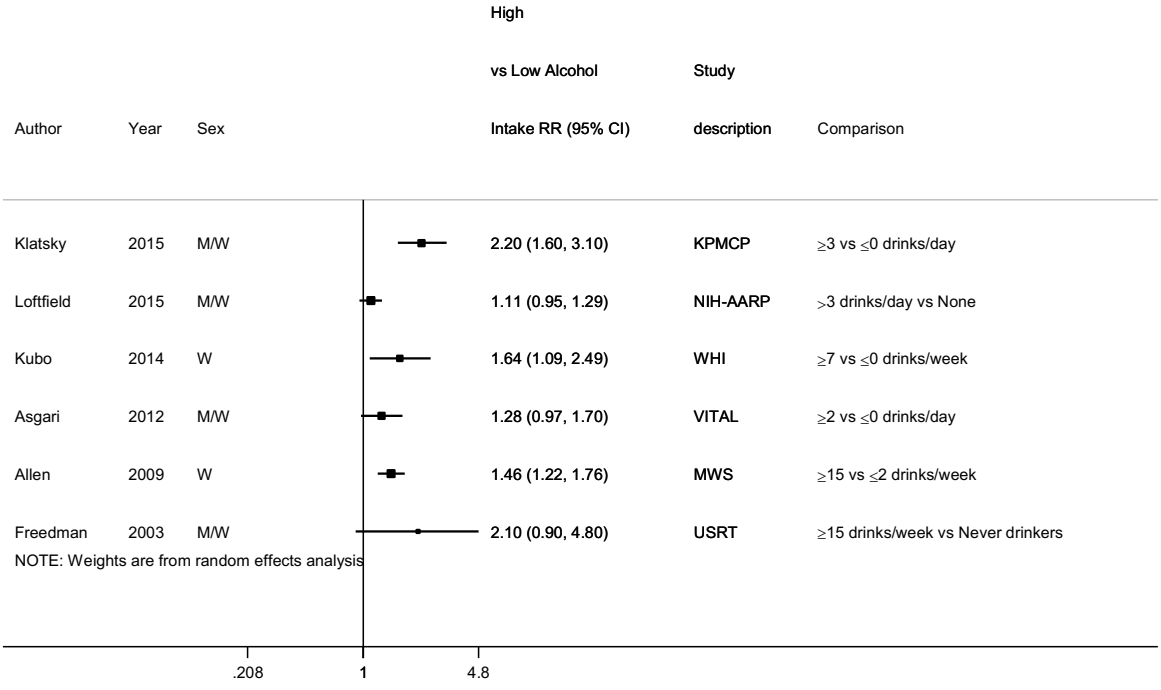


Figure 16 Relative risk of melanoma per 10g/day increase of total alcohol intake

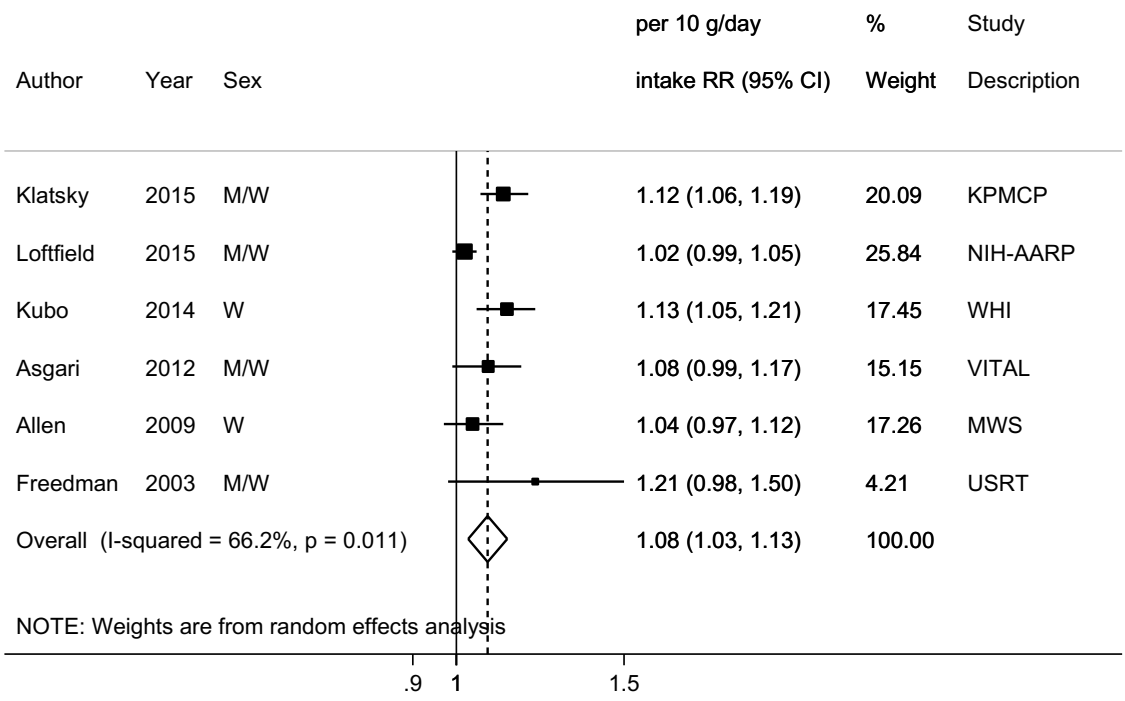


Figure 17 Funnel plot of studies included in the dose response meta-analysis of total alcohol intake and melanoma

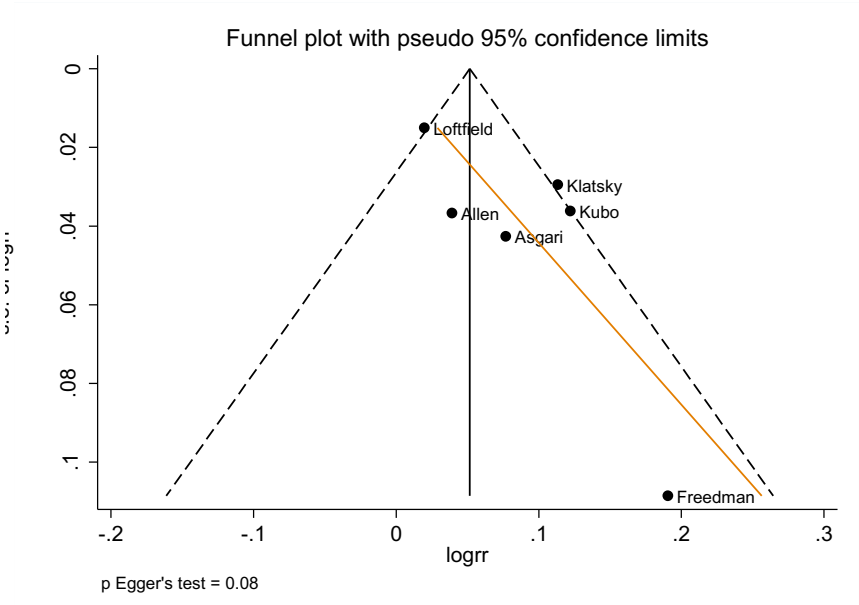


Figure 18 Nonlinear dose-response meta-analysis of total alcohol intake and melanoma

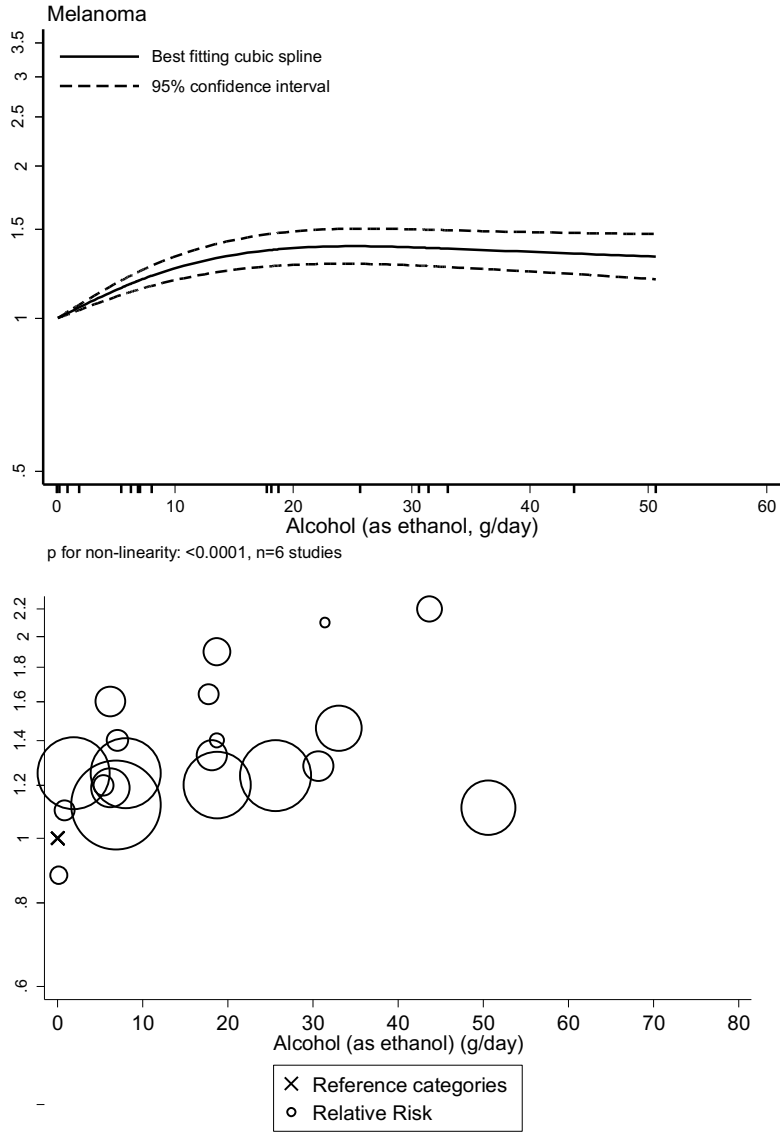


Table Relative risk of melanoma with alcohol intake using non-linear models

Ethanol (g/day)	RR (95%CI)
0	1.00
0.8	1.02 (1.02-1.03)
5.45	1.15 (1.11-1.19)
6.88	1.19 (1.14-1.24)
8.04	1.21 (1.16-1.27)
17.7	1.36 (1.27-1.47)
25.6	1.39 (1.28-1.50)
30.6	1.38 (1.27-1.50)
33.0	1.37 (1.26-1.49)

Figure 19 RR estimates of BCC by levels of total alcohol intake

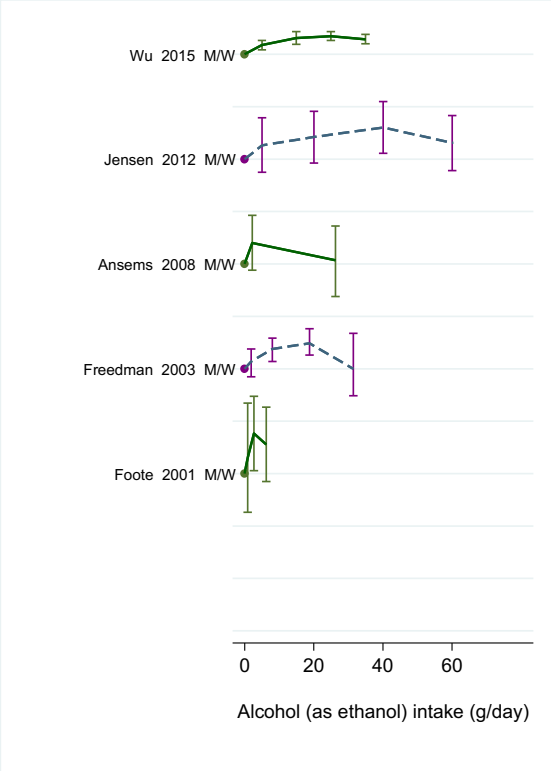
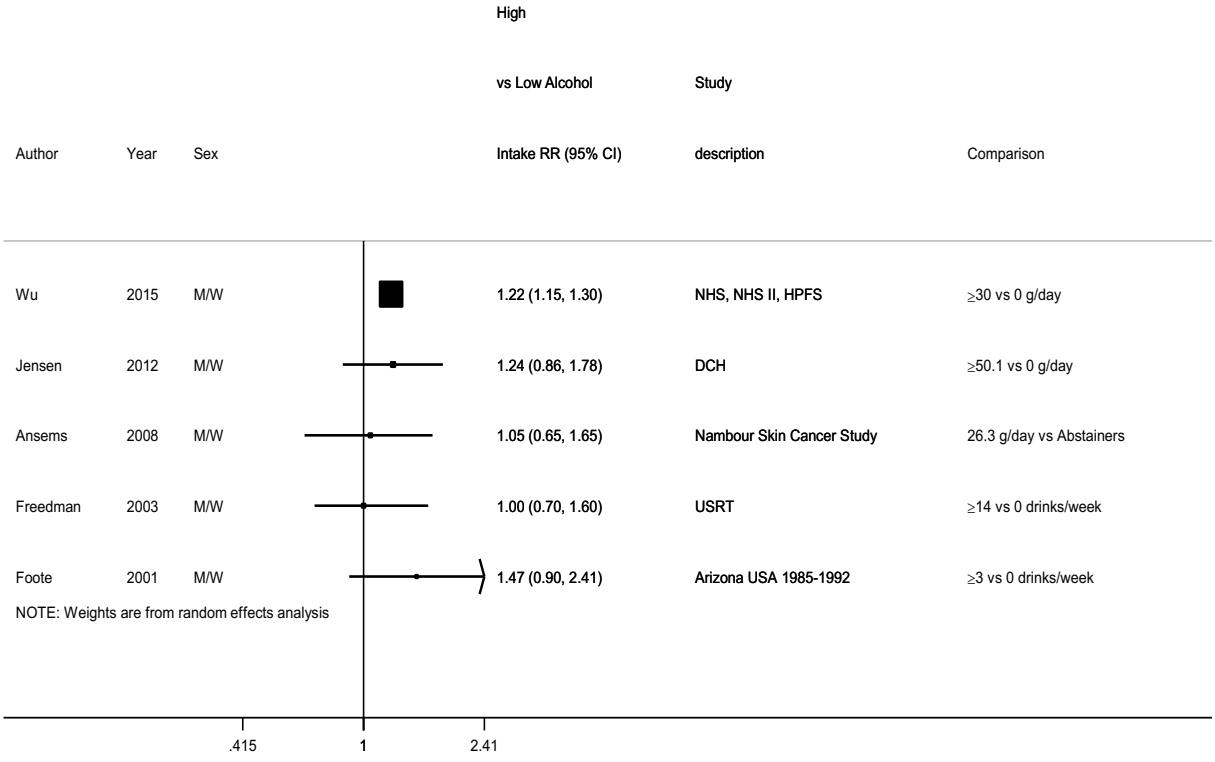


Figure 20 RR (95% CI) of BCC for the highest compared with the lowest level of total alcohol intake



Note: Hamling method was used for Jensen, 2012.

Figure 21 Relative risk of BCC per 10g/day increase of total alcohol intake

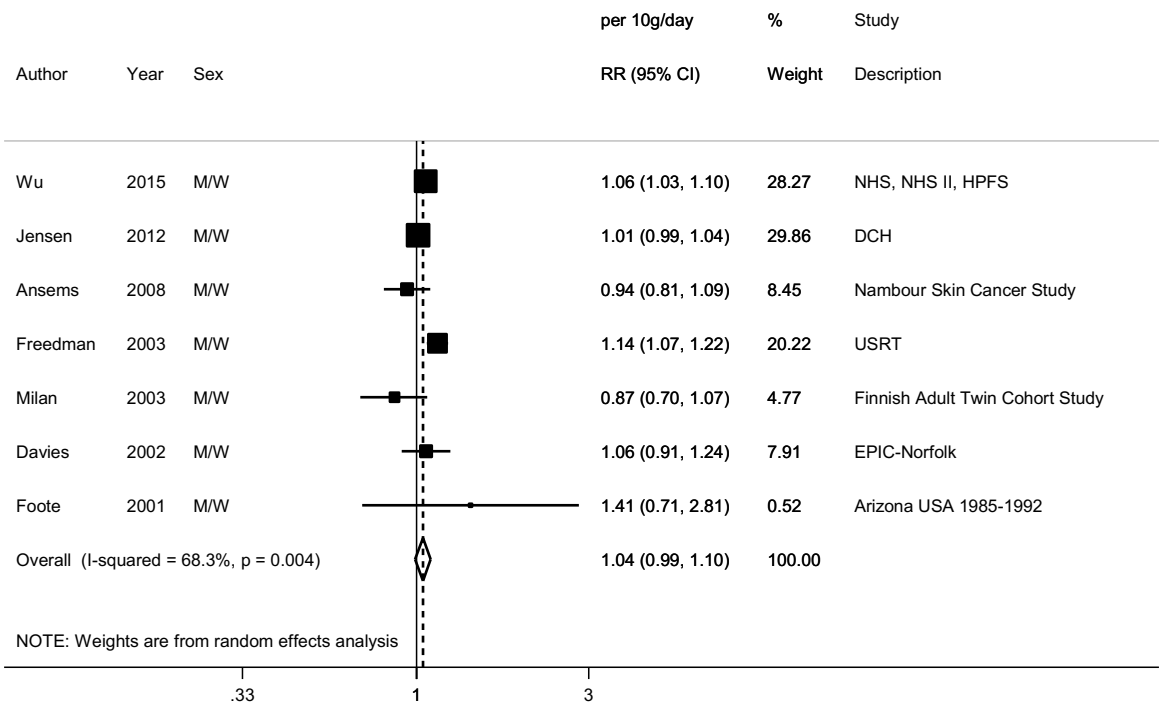


Figure 22 Funnel plot of studies in the dose response meta-analysis of total alcohol and BCC

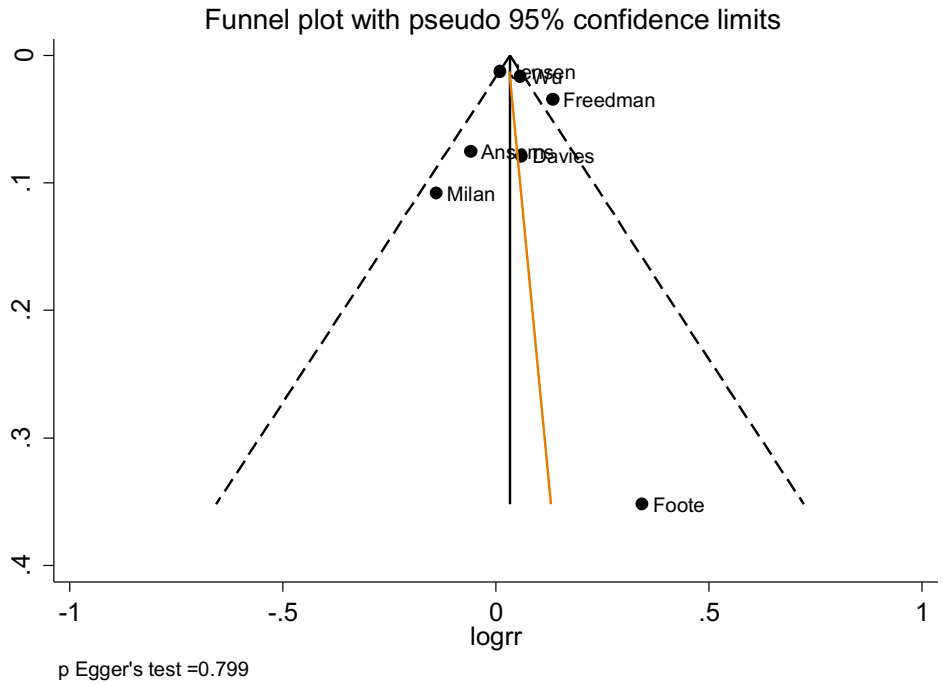


Figure 23 Relative risk of BCC per 10g/day increase of total alcohol intake, by sex

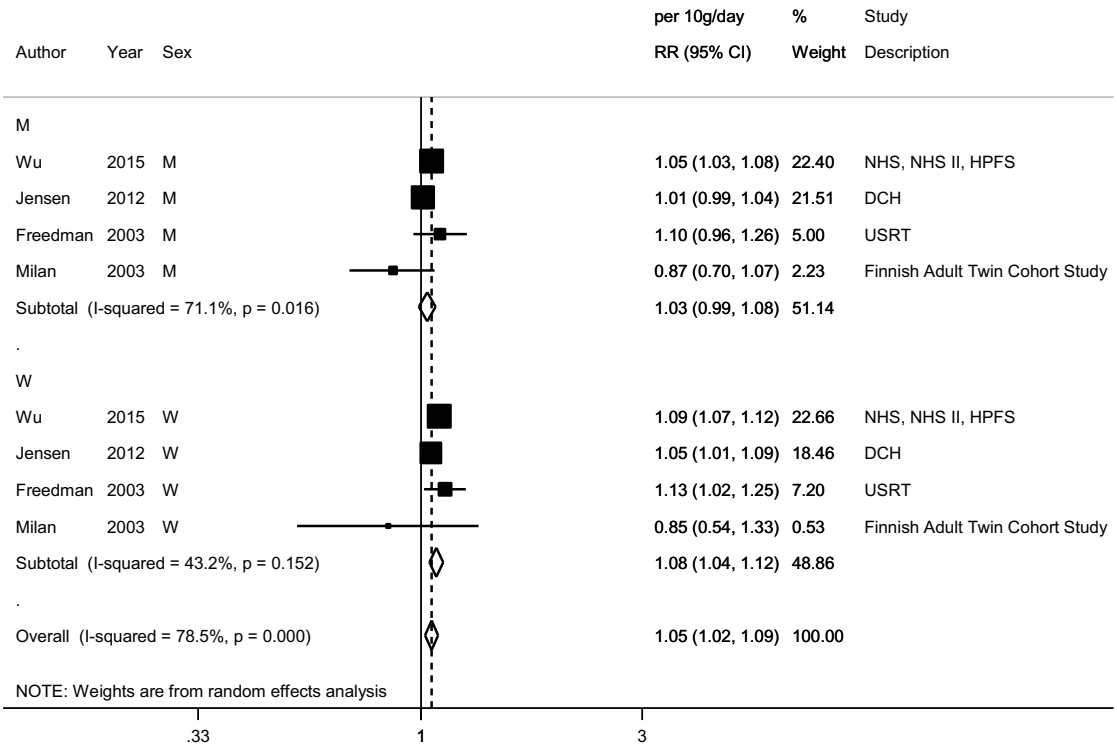


Figure 24 Relative risk of BCC per 10g/day increase of total alcohol intake, by geographic location

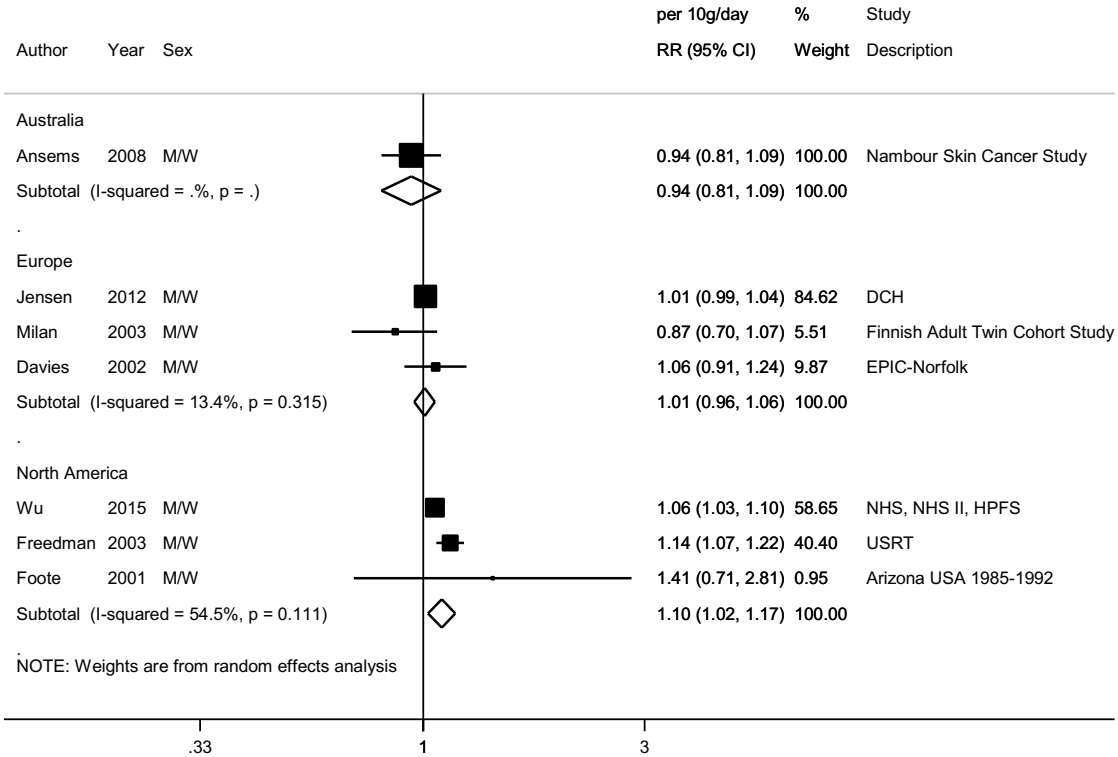


Figure 25 Nonlinear dose-response meta-analysis of total alcohol intake and BCC

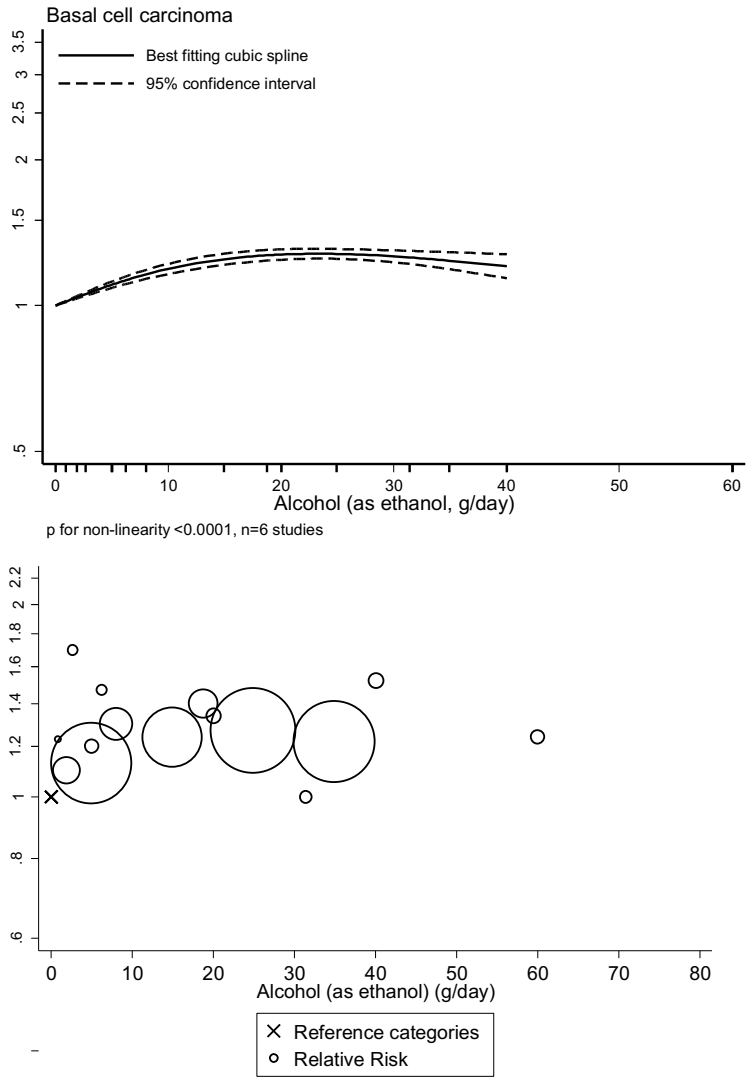


Table Relative risk of BCC with alcohol intake using non-linear models

Ethanol (g/day)	RR (95%CI)
0	1.00
1.8	1.04(1.03-1.05)
5.0	1.10(1.09-1.12)
6.2	1.13(1.11-1.15)
8.0	1.16(1.14-1.18)
15.0	1.25 (1.21-1.28)
25.0	1.28 (1.25-1.31)
31.4	1.26(1.22-1.30)

Figure 26 RR estimates of SCC by levels of total alcohol intake

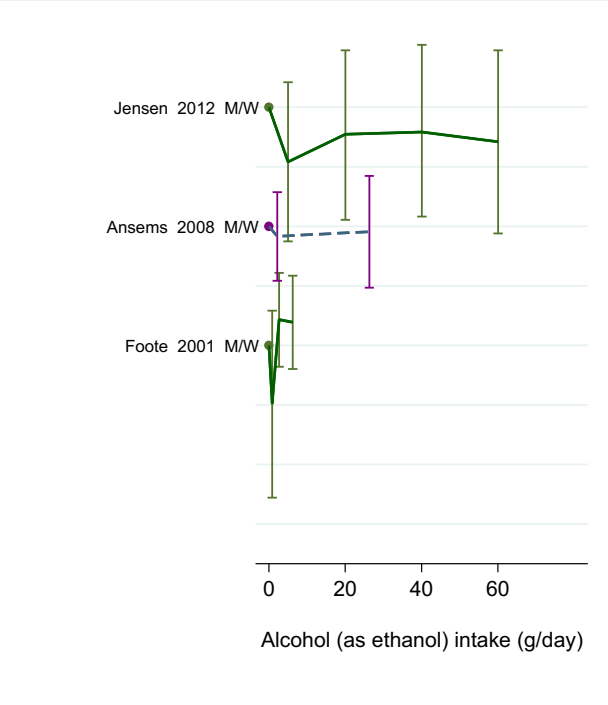
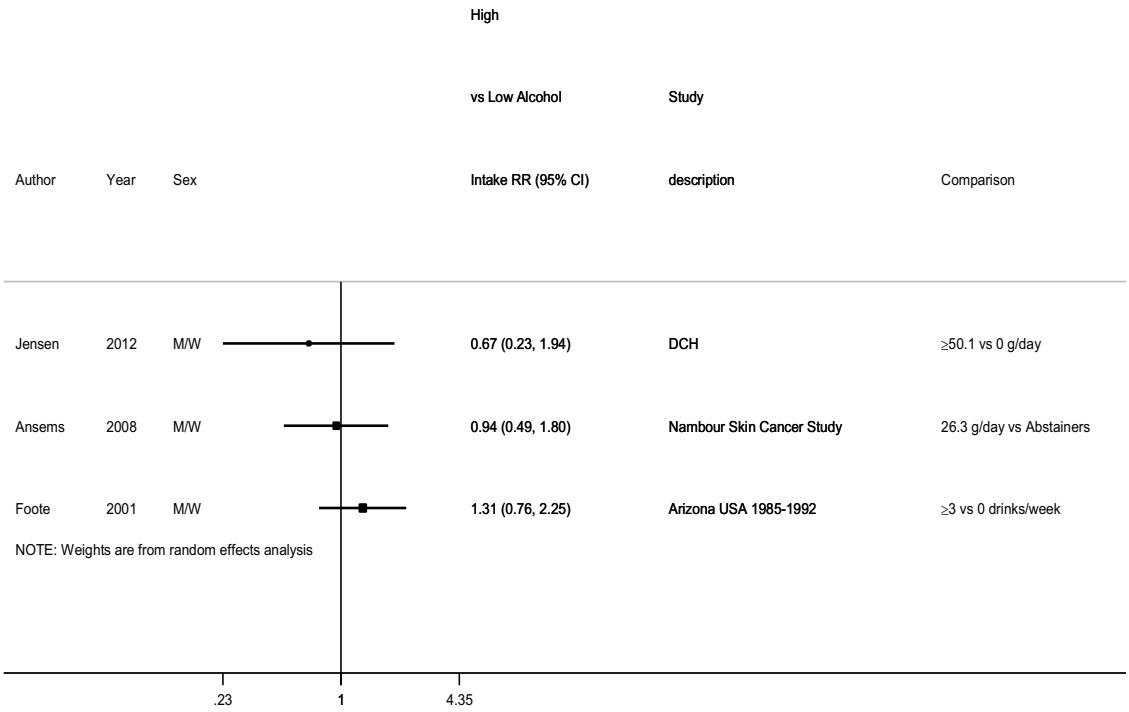
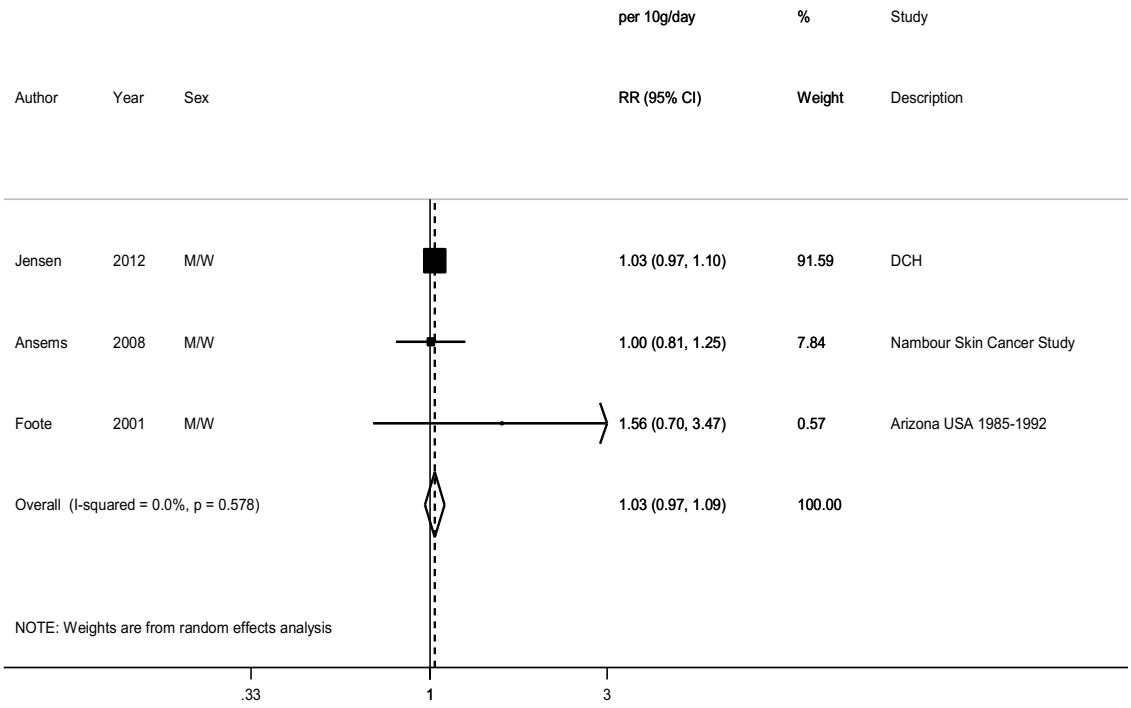


Figure 27 RR (95% CI) of SCC for the highest compared with the lowest level of total alcohol intake



Note: Hamling's method was used for Jensen, 2012.

Figure 28 Relative risk of SCC per 10g/day increase of total alcohol intake



3.7.1.1 Beer

Cohort studies

Summary

Four studies (three publications on melanoma, non-melanoma and SCC) were identified in the 2005 SLR and five new studies (six publications on melanoma, non-melanoma, SCC and BCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

Statistically non-significant (positive) associations were observed in the prospective cohort from the Kaiser Permanente (Klatsky, 2015) and the WHI-OS study in USA (Kubo, 2014).

A Norwegian prospective cohort study reported statistically non-significant inverse association of beer drinking and melanoma in men (47 cases) compared with non-beer drinkers, IRR: 0.70, 95% CI= (0.30-1.40). A positive statistically non-significant association was found for women (61 cases), IRR: 1.40, 95% CI= 0.60-3.40 (Veierod, 1997).

In a historical cohort study, Danish brewery workers (employed for at least six months between 1939 to 1963) did not have higher risk of developing melanoma (50 incident cases) compared to general Danish population, SIR: 1.12, 95% CI= 0.83-1.48 (Thygesen, 2005). An average brewery worker was consuming 77.7 g of ethanol (from beer) at work per day while an average adult Dane was consuming 163 g of from beer) per day in 1960.

Non-Melanoma skin cancer

In the WHI-OS study, current beer drinkers had a higher risk of NMSC (9 593 cases) compared to non-drinkers, RR: 1.16; 95% CI= 1.01-1.33 (Kubo, 2014).

The Danish brewery workers study reported that brewery workers had a non-statistically significant lower risk of non-melanoma skin cancer (329 cases) compared to the general Danish population, SIR: 0.90, 95% CI= 0.80-1.00 (Thygesen, 2005).

Basal cell carcinoma

A pooled analysis of the NHS, NHS II and HPFS cohorts found no association of beer consumption and BCC in men and women. No association was observed in an Australian follow-up community-based skin cancer study (Nambour Skin Cancer Study), which used randomly selected participants of a skin cancer prevention field trial (Ansems, 2008).

A large Danish prospective study found a statistically significant inverse association of beer consumption and BCC (RR for >50g/day vs. >0-10g/day: 0.70; 95% CI= 0.53-0.93, 2 220 cases). Inverse but statistically non-significant results were found per 10g/day increment (RR: 0.97; 95% CI= 0.93-1.00). In analysis by sex, the hazard ratios per 10 g/day were 0.97 (95% CI= 0.94-1.01) in men and 1.03 (95% CI= 0.94-1.12) in women (Jensen, 2012).

Squamous cell carcinoma

No association between beer drinking and SCC was observed in The Nambour Skin Cancer Study (RR >161.3g/day vs. abstainers: 0.79; 95% CI= 0.40-1.57, p-trend= 0.43) (Ansems, 2008). Results did not change substantially when participants with history of skin cancer were excluded from the analysis, however among participants with history of skin cancer a positive although statistically non-significant association was observed, RR: 1.53; 95% CI=0.61-3.82, p-trend= 0.34.

Table 19 Beer consumption and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Klatsky, 2015 SKI23406 USA	KPMCP, Prospective Cohort, Age: 41 years, M/W	- 124 193 17.8 years	Cancer registry	Questionnaire	Incidence MM	≥3 vs. ≤1 drinks/day	1.10 (0.60-2.00)	Age, sex, BMI, educational level, marital status, race/ethnicity, smoking, alcohol intake among drinkers of more than 1 drink per month
Wu, 2015d SKI23407 USA	NHS, NHS II, HPFS, Prospective Cohort, M/W	28 951/ 211 462 3 740 000 person-years	Self-report	FFQ	Incidence BCC	≥10 vs. ≤0 g/day	1.00 (0.85-1.17) Ptrend:0.71	BMI, caffeine consumption, cumulative UV flux since baseline, ethnicity, family history of melanoma, hair colour, number of moles on arms or legs, number of severe sunburns, physical activity, skin reaction to sun as a child/adolescent, smoking status, use of sunscreen in summer months, average time spent in direct sunlight in summer months, other alcoholic beverages listed in the table
		9 272/			Men	≥10 vs. ≤0 g/day	1.06 (0.97-1.15) Ptrend:0.38	
		19 679/			Women	≥10 vs. ≤0 g/day	0.97 (0.73-1.29) Ptrend:0.67	
Kubo, 2014 SKI23408 USA	WHI, Prospective Cohort, Age: 50-79 years, W,	9 593/ 59 575 10.2 years	Medical records by physicians	FFQ	Occurrence of incidence NMSC	Current drinker vs. Non-drinkers	1.16 (1.01-1.33)	Age, BMI, education years, having a healthcare provider, health insurance, history of melanoma, history of NMSC, Langleys
		532/			Incidence	Current drinker	1.18 (0.68-2.04)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Postmenopausal				MM	vs. Non-drinkers		of exposure, physical activity, skin reaction to sun, smoking, childhood sun exposure, current summer sun exposure, use of sunscreen, last medical visit within 1 year
Jensen, 2012 SKI23410 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	2 220/ 54 766 11.4 years	Cancer and pathology registries	FFQ + questionnaire	Incidence BCC	per 10 g/day	0.97 (0.93-1.00)	Age, sex, BMI, education years, degree of freckling, number of nevi, sun sensitivity, mutually adjusted for the various types of alcohol
		2 220/				≥50.1 vs. 0.1-10 g/day	0.70 (0.53-0.93)	
		1 224/			Incidence BCC Women	per 10 g/day	1.03 (0.94-1.12)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity, menopausal status, use of hormone replacement therapy at baseline, , mutually adjusted for the various types of alcohol
		1 224/				≥50.1 vs. 0.1-10 g/day	0.91 (0.29-2.83)	
		1 185/			Incidence BCC Men	per 10 g/day	0.97 (0.94-1.01)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity, mutually adjusted for the various types of alcohol
		1 185/				≥50.1 vs. 0.1-10 g/day	0.75 (0.56-1.01)	
Ansems, 2008	NSCS,	127	Histology	Semi-	Tumour-based	>161.3 g/day	0.79 (0.40-1.57)	Age, sex, beta carotene

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
SKI23411 Australia	Prospective Cohort, Age: 49.7 years, M/W	1 360 12 942 person-years		quantitative FFQ	incidence SCC	vs. Abstainers	Ptrend:0.43	treatment, sunscreen treatment, pack-years of smoking until 1992, self-reported skin colour, elastosis of the neck, leisure time sun exposure, skin cancer before 1992
		/			No history of skin cancer	>161.3 g/day vs. Abstainers	0.58 (0.19-1.77) Ptrend:0.17	
		/			History of skin cancer	>161.3 g/day vs. Abstainers	1.53 (0.61-3.82) Ptrend:0.34	
		267 1 360 12 942 person-years			Tumour-based incidence BCC	>161.3 g/day vs. Abstainers	1.36 (0.86-2.15) Ptrend:0.27	Age, sex, beta carotene treatment, sunscreen treatment, elastosis of the neck, occupational sun exposure, leisure time sun exposure, history skin cancer before 1992
		/			No history of skin cancer	>161.3 g/day vs. Abstainers	1.55 (0.80-2.99) Ptrend:0.27	
		/			History of skin cancer	>161.3 g/day vs. Abstainers	1.02 (0.52-1.97) Ptrend:0.89	
Ibiebele, 2007 SKI23445 Australia	NSCS, Prospective Cohort, Age: 20-69 years, M/W	- 1 360 11 years	Histology	FFQ	Occurrence of incidence SCC History of skin cancer	Tertile3 vs. Tertile1	1.18 (0.56-2.47)	Age, sex, skin colour, skin elastosis, smoking status, dietary supplement use, burn-tan propensity of the skin, total energy, treatment allocation
Thygesen, 2005 SKI22553 Denmark	Danish Brewery Workers' Union, Historical Cohort,	379/ 13 051	Workers union members		Incidence Skin cancer	Danish brewery workers vs. General Danish male population	0.92 (0.83-1.02)	Age
		50/			Incidence MM		1.12 (0.83-1.48)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M, Brewery workers	329/			Incidence NMSC		0.90 (0.80-1.00)	
Fung, 2002a SKI00891 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W, Female nurses and Male Health Professionals	6 088/ 107 975 8 years in women & 10 years in men	Ongoing or prior study	FFQ	Incidence BCC	≥30 g/day vs. Non-drinkers	0.90 (0.73-1.10) Ptrend:0.78	Age, area of residence, childhood area of residence, BMI, beer consumption, liquor consumption, missing FFQ, smoking habits, total energy, wine consumption
		3 028/ 107 975 10 years			Incidence BCC Men	≥30 g/day vs. Non-drinkers	0.92 (0.73-1.17) Ptrend:0.95	Additionally adjusted for: ancestry, eye colour, hair colour, tendency to burn in childhood, childhood sun exposure in swimsuit
		3 060/ 107 975 8 years			Incidence BCC Women	≥30 g/day vs. Non-drinkers	0.82 (0.53-1.27) Ptrend:0.5	Additionally adjusted for: ancestry, childhood sun reaction, childhood tanning ability, hair colour, lifetime blistering sunburn, sun screen use
Veierod, 1997 SKI17728 Norway	Norway 1977-1983, Prospective Cohort, Age: 16-56 years, M/W	61/ 50 757 12.4 years	Health screening program	FFQ	Incidence MM Men	Yes vs. No	0.70 (0.30-1.40)	Age, area of residence
		47/			Women		1.40 (0.60-3.40)	

3.7.1.2 Wine

Cohort studies

Summary

Three studies (two publications on BCC) were identified in the 2005 SLR and five new studies (five publications on melanoma, NMSC, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

A North American prospective cohort study reported a positive association between wine consumption (RR for three or more drinks/day compared to less than one drink: 1.70; 95% CI= 1.20-2.30) and melanoma (1 164 incidence cases) (Klatsky, 2015).

The WHI-OS study reported no association between wine consumption with melanoma (RR: 1.06; 95% CI= 0.69-1.65) (Kubo, 2014).

Non-melanoma skin cancer

The WHI-OS study reported statistically non-significant increased risk of NMSC in current wine drinkers (9 593 cases) compared to non- drinkers, RR: 1.11; 95% CI= 1.00-1.23 (Kubo, 2014).

Basal cell carcinoma

A large Danish prospective study reported no association between wine consumption and BCC (RR for the comparison >50g/day vs. >0-10g/day: 0.98; 95% CI= 0.74-1.29, 2 409 cases). Similar results were observed in analyses by sex (in women, RR: 0.98; 95% CI= 0.62-1.53, 1 224 cases; in men, RR: 1.04; 95% CI= 0.73-1.47, 1 185 cases). In dose-response analysis, positive association for both gender combined (RR for 10g/day increment: 1.05; 95% CI=1.02-1.08) and for men and women (RR for 10g/day: 1.04; 95% CI=1.00-1.08 and HR for 10g/day: 1.06; 95% CI=1.00-1.10, respectively) were observed (Jensen, 2012).

BCC was not associated with wine consumption in the Finnish Adult Twin Cohort (Milan, 2003).

Red or white wines

Malignant melanoma

The WHI-OS study reported statistically non-significant increased risk in current drinkers of red wine compared to non- drinkers (RR: 1.34; 95% CI=0.86-2.10) and statistically significant increased risk in current drinkers of white wine compared to non- drinkers, RR: 1.52; 95% CI=1.02-2.27 (Kubo, 2014).

Non-melanoma skin cancer

The WHI-OS study reported no association of current red wine drinking compared to no drinking alcohol (RR: 1.06; 95% CI= 0.94-1.18, Kubo, 2014) but a statistically significant increased risk in current white wine drinkers compared to non- drinkers was observed (RR: 1.16; 95% CI= 1.05-1.28; Kubo, 2014).

Basal cell carcinoma

A pooled analysis of the NHS, NHS II and HPFS cohorts found no association between red wine drinking and BCC (28 951 cases) (Wu, 2015d). The results were the same for men and women. However, white wine intake was positively associated with increased risk of BCC (RR for ≥ 10g/day of white wine vs. no alcohol: 1.22 (1.06-1.40), p-trend <0.0001; and HR per 10g/day white wine increment: 1.10; 1.06-1.15). The positive associations with white wine were statistically significant in men and women.

Statistically non-significant positive associations were observed for red and white wine in the Nambour Skin Cancer Study (RR for >4.2 g/day of red wine vs. abstainers: 1.23; 95% CI= 0.75-2.03, p-trend= 0.93; and for white wine consumption vs. abstainer, RR: 1.18; 95% CI= 0.74-1.89, p-trend= 0.47) (Ansems, 2008). The results remained statistically non-significant when participants with history of skin cancer were excluded from the analysis (Ansems, 2008).

Squamous cell carcinoma

No associations with red wine or white wine were observed in the Nambour Skin Cancer Study (Ansems, 2008).

Fortified wine

Basal cell carcinoma

A statistically non-significant positive association of sherry/port consumption with BCC was found in the Nambour Skin Cancer Study (RR for >1.2g/day vs. abstainers: 1.52; 95% CI=0.96-2.41, p-trend= 0.29 (Ansems, 2008). Similar results were found in analyses in participants with no history of skin cancer, RR: 1.46; 95% CI= 0.73-2.90, p-trend=0.66.

Squamous cell carcinoma

A statistically non-significant positive association of sherry/port consumption with SCC was found in the Nambour Skin Cancer Study (RR for >1.2g/day vs. abstainers RR: 1.41; 95% CI=0.74-2.70, p-trend= 0.36). In analyses only on participants with no history of skin cancer, statistically non-significant (inverse) association was observed (RR: 0.88; 95% CI=0.29-2.65, p-trend=0.50) (Ansems, 2008).

Table 20 Wine consumption and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Klatsky, 2015 SKI23406 USA	KPMCP, Prospective Cohort, Age: 41 years, M/W	- 124 193 17.8 years	Cancer registry	Questionnaire	Incidence MM	≥3 vs. ≤1 drinks/day	1.70 (1.20-2.30)	Age, sex, BMI, educational level, marital status, race/ethnicity, smoking, alcohol intake among drinkers of more than 1 drink per month
Wu, 2015d SKI23407 USA	NHS, NHS II, HPFS, Prospective Cohort, M/W	28 951/ 211 462 3 740 000 person-years	Self-report	FFQ	Incidence BCC	White wine ≥10 vs. ≤0 g/day	1.22 (1.06-1.40) Ptrend:<0.0001	BMI, caffeine consumption, cumulative UV flux since baseline, ethnicity, family history of melanoma, hair colour, number of moles on arms or legs, number of severe sunburns, physical activity, skin reaction to sun as a child/adolescent, smoking status, use of sunscreen in
		28 951/				Red wine ≥10 vs. ≤0 g/day	0.99 (0.89-1.10) Ptrend:0.67	
		9 272/			Men	White wine ≥10 vs. ≤0 g/day	1.10 (0.96-1.25) Ptrend:0.08	
						Red wine ≥10 vs. ≤0 g/day	1.00 (0.86-1.17) Ptrend:0.94	
		19 679/			Women	White wine ≥10 vs. ≤0 g/day	1.30 (1.15-1.46) Ptrend:<0.0001	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						Red wine ≥10 vs. ≤0 g/day	0.98 (0.85-1.14) Ptrend:0.51	summer months, average time spent in direct sunlight in summer months, other alcoholic beverages listed in the table
Kubo, 2014 SKI23408 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	9 593/ 59 575 10.2 years	Medical records by physicians	FFQ	Occurrence of incidence NMSC	Current drinker vs. Non-drinkers	1.11 (1.00-1.23)	Age, BMI, education years, having a healthcare provider, health insurance, history of melanoma, history of NMSC, Langleys of exposure, physical activity, skin reaction to sun, smoking, childhood sun exposure, current summer sun exposure, use of sunscreen, last medical visit within 1 year
		9 593/			Occurrence of incidence NMSC	Red wine Current drinker vs. Non-drinkers	1.06 (0.94-1.18)	
		9 593/			Occurrence of incidence NMSC	White wine Current drinker vs. Non-drinkers	1.16 (1.05-1.28)	
		532/			Incidence MM	Current drinker vs. Non-drinkers	1.06 (0.69-1.65)	
		532/			Incidence MM	White wine Current drinker vs. Non-drinkers	1.52 (1.02-2.27)	
		532/			Incidence MM	Red wine Current drinker vs. Non-drinkers	1.34 (0.86-2.10)	
Jensen, 2012	DCH,	2 409/	Cancer and	FFQ +	Incidence	per 10 g/d	1.05 (1.02-1.08)	Age, sex, BMI,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
SKI23410 Denmark	Prospective Cohort, Age: 50-64 years, M/W	54 766 11.4 years	pathology registries	questionnaire	BCC			education years, degree of freckling, number of nevi, sun sensitivity, mutually adjusted for the various types of alcohol
		2 409/				≥50.1 vs. 0.1-10 g/d	0.98 (0.74-1.29)	
		1 224/			Incidence BCC Women	per 10 g/d	1.06 (1.00-1.10)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity, menopausal status, use of hormone replacement therapy at baseline, , mutually adjusted for the various types of alcohol
		1 224/				≥50.1 vs. 0.1-10 g/d	0.98 (0.62-1.53)	
		1 185/			Incidence BCC Men	per 10 g/d	1.04 (1.00-1.08)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity, mutually adjusted for the various types of alcohol
		1 185/				≥50.1 vs. 0.1-10 g/d	1.04 (0.73-1.47)	
Ansems, 2008 SKI23411	NSCS, Prospective	127 1 360	Histology	Semi-quantitative FFQ	Tumour-based incidence	White wine >8.4 g/day vs.	1.20 (0.62-2.32) Ptrend:0.45	Age, sex, beta carotene treatment,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Australia	Cohort, Age: 49.7 years, M/W	12 942 person-years			SCC	Abstainers		sunscreen treatment, pack-years of smoking until 1992, self-reported skin colour, elastosis of the neck, leisure time sun exposure, skin cancer before 1992
		/			No history of skin cancer		0.93 (0.33-2.68) Ptrend:0.71	
		/			History of skin cancer		1.90 (0.79-4.55) Ptrend:0.08	
		267 1 360 12 942 person-years			Tumour-based incidence BCC	White wine >8.4 g/day vs. Abstainers	1.18 (0.74-1.89) Ptrend:0.47	Age, sex, beta carotene treatment, sunscreen treatment, elastosis of the neck, occupational sun exposure, leisure time sun exposure, history skin cancer before 1992
		/			No history of skin cancer		0.95 (0.47-1.92) Ptrend:0.93	
		/			History of skin cancer		1.31 (0.68-2.52) Ptrend:0.42	
		127 1 360 12 942 person-years			Tumour-based incidence SCC	Fortified wine >1.2 g/day vs. Abstainers	1.41 (0.74-2.70) Ptrend:0.37	Age, sex, beta carotene treatment, sunscreen treatment, pack-years of smoking until 1992, self-reported skin colour, elastosis of the neck, leisure time sun exposure, skin cancer before
		/			No history of skin cancer		0.88 (0.29-2.65) Ptrend:0.50	
		/			History of skin cancer		2.46 (1.06-5.72) Ptrend:0.05	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								1992
		267 1 360 12 942 person-years			Tumour-based incidence BCC	Fortified wine >1.2 g/day vs. Abstainers	1.52 (0.96-2.41) Ptrend:0.29	Age, sex, beta carotene treatment, sunscreen treatment, elastosis of the neck, occupational sun exposure, leisure time sun exposure, history skin cancer before 1992
		/			No history of skin cancer		1.46 (0.73-2.90) Ptrend:0.66	
		/			History of skin cancer		1.58 (0.85-2.95) Ptrend:0.33	
		127 1 360 12 942 person-years			Tumour-based incidence SCC	Red wine >4.2 g/day vs. Abstainers	0.64 (0.30-1.36) Ptrend:0.37	Age, sex, beta carotene treatment, sunscreen treatment, pack-years of smoking until 1992, self-reported skin colour, elastosis of the neck, leisure time sun exposure, skin cancer before 1992
		/			No history of skin cancer		0.22 (0.05-1.07) Ptrend:0.25	
		/			History of skin cancer		1.50 (0.60-3.79) Ptrend:0.72	
		267 1 360 12 942 person-years			Tumour-based incidence BCC	Red wine >4.2 g/day vs. Abstainers	1.23 (0.75-2.03) Ptrend:0.93	Age, sex, beta carotene treatment, sunscreen treatment, elastosis of the neck,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		/			No history of skin cancer		0.72 (0.32-1.60) Ptrend:0.13	occupational sun exposure, leisure time sun exposure, history skin cancer before 1992
		/			History of skin cancer		1.65 (0.84-3.23) Ptrend:0.17	
Milan, 2003 SKI00640 Finland	Finnish Adult Twin Cohort Study, Case Cohort, M/W	149/ 13 888 15.2 years	Population registry	Questionnaire	Incidence BCC Men	>1 vs. <1 glasses/week	0.96 (0.58-2.01)	Age, ethnicity, sunlight
						>2 times/month vs. Rarely/never	0.87 (0.55-1.96)	
		184/			Incidence BCC Women	>1 vs. <1 glasses/week	1.11 (0.66-1.98)	
						>2 times/month vs. Rarely/never	1.30 (0.76-2.23)	
Fung, 2002a SKI00891 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W, Female nurses and Male Health Professionals	6 088/ 107 975 8 years in women & 10 years in men	Self-report	FFQ	Incidence BCC	Red wine ≥15 vs. non-drinkers g	0.79 (0.45-1.39) Ptrend:0.23	Age, area of residence, childhood area of residence, BMI, beer consumption, liquor consumption, missing FFQ, smoking habits, total energy, wine consumption
						White wine ≥15 vs. non-drinkers g	1.24 (0.97-1.60) Ptrend:0.01	
		3 028/ 107 975 10 years			Incidence BCC Men	Red wine ≥15 vs. non-drinkers g	1.00 (0.67-1.49) Ptrend:0.64	Additionally adjusted for: ancestry, eye colour,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						White wine ≥15 vs. non-drinkers g	1.07 (0.79-1.45) Ptrend:0.24	hair colour, tendency to burn in childhood, childhood sun exposure in swimsuit
		3 060/ 107 975 8 years			Incidence BCC Women	Red wine ≥15 vs. non-drinkers g	0.56 (0.29-1.08) Ptrend:0.004	Additionally adjusted for: ancestry, childhood sun reaction, childhood tanning ability, hair colour, lifetime blistering sunburn, sun screen use
						White wine ≥15 vs. non-drinkers g	1.39 (1.11-1.73) Ptrend:0.0002	

3.7.1.3 Spirits

Cohort studies

Summary

Two studies (one publication on BCC) were identified in the 2005 SLR and five new studies (five publications on melanoma, non-melanoma, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

A large prospective cohort study carried out in North America reported no statistically significant association (positive) of liquor consumption and melanoma (RR for three or more with less than one drink/day: 1.20; 95% CI=0.70-2. 10; 1 164 cases) (Klatsky, 2015).

The WHI-OS study reported an increased risk of melanoma in current liquor drinkers compared to non- drinkers, RR: 1.65; 95% CI=1.07-2.55, 532 cases (Kubo, 2014).

Non-melanoma skin cancer

The WHI-OS study reported an increased risk of NMSC in current liquor drinkers compared to non- drinkers, RR: 1.26; 95% CI=1.13-1.41, 9 593 cases (Kubo, 2014)

Basal cell carcinoma

The pooled analysis of the NHS, NHS II and HPFS cohorts found a positive statistically significant association between BCC and liquor consumption (RR per 10g/day increment: 1.05; 95% CI= 1.03-1.07, 13 737 cases and HR for ≥10g/day vs. no alcohol consumption: 1.17; 95% CI=1.12-1.23, p-trend < 0.000) that was similar in men and women (Wu, 2015d).

A large Danish prospective study reported statistically non-significant but increased BCC among heavy spirit drinkers (>50g/day) compared to light spirit drinkers (>0 to ≤10 g/day) overall and by sex. In dose-response analyses, the HR for 10 g/day increment was: 1.11; 95% CI= 1.02-1.21 for men and women combined, 1.16; 95% CI=1.05-1.29 in men and 1.04; 95% CI=0.88-1.23 in women (Jensen, 2012).

Spirits consumption was not associated with BCC in the Nambour Skin Cancer Study (Ansems, 2008).

Squamous cell carcinoma

Spirits consumption was statistically non-significantly inversely associated with BCC in the Nambour Skin Cancer Study (Ansems, 2008).

Table 21 Spirit consumption and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Klatsky, 2015 SKI23406 USA	KPMCP, Prospective Cohort, Age: 41 years, M/W	- 124 193 17.8 years	Cancer registry	Questionnaire	Incidence MM	≥3 vs. ≤1 drinks/day	1.20 (0.70-2.10)	Age, sex, BMI, educational level, marital status, race/ethnicity, smoking, alcohol intake among drinkers of more than 1 drink per month
Wu, 2015d SKI23407 USA	NHS, NHS II, HPFS, Prospective Cohort, M/W	28 951/ 211 462 3 740 000 person-years	Self-report	FFQ	Incidence BCC	≥10 vs. ≤0 g/day	1.17 (1.12-1.23) Ptrend:<0.0001	BMI, caffeine consumption, cumulative UV flux since baseline, ethnicity, family history of melanoma, hair colour, number of moles on arms or legs, number of severe sunburns, physical activity, skin reaction to sun as a child/adolescent, smoking status, use of sunscreen in summer months, average time spent in direct sunlight in summer months, other alcoholic beverages listed in the table
		9 272/			Men	≥10 vs. ≤0 g/day	1.15 (1.07-1.23) Ptrend:0.002	
		19 679/			Women	≥10 vs. ≤0 g/day	1.19 (1.12-1.27) Ptrend:<0.0001	
Kubo, 2014 SKI23408 USA	WHI, Prospective Cohort, Age: 50-79 years,	9 593/ 59 575 10.2 years	Medical records by physicians	FFQ	Occurrence of incidence NMSC	current drinker vs. non-drinkers	1.26 (1.13-1.41)	Age, BMI, education years, having a healthcare provider, health insurance, history of melanoma, history of NMSC, Langleys of exposure,
		532/			Incidence	current drinker	1.65 (1.07-2.55)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	W, Postmenopausal				MM	vs. non-drinkers		physical activity, skin reaction to sun, smoking, childhood sun exposure, current summer sun exposure, use of sunscreen, last medical visit within 1 year
Jensen, 2012 SKI23410 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	2 409/ 54 766 11.4 years	Cancer and pathology registries	FFQ + questionnaire	Incidence BCC	per 10 g/d	1.11 (1.02-1.21)	Age, sex, BMI, education years, degree of freckling, number of nevi, sun sensitivity, mutually adjusted for the various types of alcohol
		2 409/				≥50.1 vs. 0.1-10 g/d	1.95 (0.49-7.82)	
		1 224/			Women	per 10 g/d	1.04 (0.88-1.23)	Age, BMI, education years, degree of freckling, number of nevi, sun sensitivity, menopausal status, use of hormone replacement therapy at baseline, , mutually adjusted for the various types of alcohol
		1 224/				≥50.1 vs. 0.1-10 g/d	3.09 (0.43-22.09)	
		1 185/			Men	per 10 g/d	1.16 (1.05-1.29)	Ag , BMI, education years, degree of freckling, number of nevi, sun sensitivity, mutually adjusted for the various types of alcohol
		1 185/				≥50.1 vs. 0.1-10 g/d	1.77 (0.25-12.66)	
Ansems, 2008	NSCS,	127	Histology	Semi-quantitative	Tumour-based	>2.1 g/day vs.	0.68 (0.68-1.35)	Age, sex, beta carotene

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
SKI23411 Australia	Prospective Cohort, Age: 49.7 years, M/W	1 360 12 942 person-years		FFQ	incidence SCC	Abstainers	Ptrend:0.27	treatment, sunscreen treatment, pack-years of smoking until 1992, self-reported skin colour, elastosis of the neck, leisure time sun exposure, skin cancer before 1992
		/			No history of skin cancer	>2.1 g/day vs. Abstainers	0.36 (0.11-1.24) Ptrend:0.20	
		/			History of skin cancer	>2.1 g/day vs. Abstainers	1.33 (0.57-3.12) Ptrend:0.91	
		267 1 360 12 942 person-years	Histology	Semi-quantitative FFQ	Tumour-based incidence BCC	>2.1 g/day vs. Abstainers	1.12 (0.70-1.79) Ptrend:0.31	Age, sex, beta carotene treatment, sunscreen treatment, elastosis of the neck, occupational sun exposure, leisure time sun exposure, history skin cancer before 1992
		/			No history of skin cancer	>2.1 g/day vs. Abstainers	1.04 (0.52-2.07) Ptrend:0.31	
		/			History of skin cancer	>2.1 g/day vs. Abstainers	1.15 (0.61-2.17) Ptrend:0.90	
Fung, 2002a SKI00891 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W, female nurses and male health professionals	6 088 107 975 8 years in women & 10 years in men	Ongoing or prior study	FFQ	Incidence BCC	≥30 vs. non-drinkers g	1.12 (0.88-1.42) Ptrend:0.003	Age, area of residence, childhood area of residence, BMI, beer consumption, liquor consumption, missing FFQ, smoking habits, total energy, wine consumption
		3 060/ 107 975 8 years			Women	≥30 g/day vs. non-drinkers	0.97 (0.77-1.23) Ptrend:0.13	Additionally adjusted for: ancestry, childhood sun reaction, childhood tanning ability, hair colour, lifetime

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								blistering sunburn, sun screen use
		3 028/ 107 975 10 years			Men	≥30 vs. non-drinkers g	1.25 (1.06-1.47) Ptrend:0.01	Additionally adjusted for: ancestry, eye colour, hair colour, tendency to burn in childhood, childhood sun exposure in swimsuit

3.7.1.4 Other alcoholic drinks

Cohort studies

One study on melanoma was identified in the 2005 SLR. No meta-analysis was conducted

Malignant melanoma

A Norwegian prospective study reported an IRR of 0.6; 95% CI=0.30-1.20 in men (47 cases) and 1.70; 95% CI=0.90-3.20 in women (61 cases) when comparing consumption of wine/liquor with no consumption (Veierod, 1997).

4 Food production, preservation, processing and preparation

4.1.2.7.2 Arsenic in drinking water

Note: Arsenic and inorganic arsenic compounds had been classified as "carcinogenic to humans" (Group 1) by the WHO International Agency for Research on Cancer Monograph Working Group. The judgement is supported by sufficient evidence from ecologic studies. The arsenic-associated skin tumours include SCC and BCC.

(In: A Review of Human Carcinogens Part C: Arsenic, metals, fibres and dusts, 2009, Lyon, France, at http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C.pdf . Tables of ecologic and case-control studies on arsenic from drinking water and skin cancer risks are in Appendix 4. Studies on environmental or occupational exposure to arsenic are not included)

Cohort studies

Summary

Two studies (two publications on skin cancer and melanoma) were identified in the 2005 SLR and one study (one publication on melanoma and NMSC) was identified in the CUP.

No meta-analysis was conducted.

Skin cancer

A prospective study conducted in arseniasis-hyperendemic areas in Taiwan reported a statistically significantly positive association of arsenic concentration in drinking water and skin cancer risk, comparing 0.71-1.10 vs. 0 mg/L, RR: 8.69, 95% CI= (1.08-65.50), p-trend=0.06, 26 cases (Hsueh, 1997).

Malignant melanoma

A historical cohort study on mortality from melanoma of the skin was conducted in Utah, USA (Lewis, 1999). The study reported a SMR: 0.83, 95% CI= (0.17-2.43) in men (3 cases) and SMR: 1.82, 95% CI= (0.50-4.66) in women (4 cases), comparing ≥5 000 vs. <1 000 ppb-years.

A prospective cohort study conducted in Denmark (DCH), where concentrations of arsenic in drinking water are low (median 0.7µg/L) reported a non-significant inverse association of

arsenic in drinking water and melanoma risk (147 cases), IRR: 0.80, 95% CI= (0.59-1.08) per 1 μg/L in time-weighted average exposure (Baastrup, 2008).

Non-melanoma skin cancer

In the Danish cohort study, no association was reported with NMSC risk (1 010 cases), IRR: 0.99, 95% CI= (0.94-1.06) per μg/L in time-weighted average exposure (Baastrup, 2008).

Table 22 Arsenic and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Cohort studies								
Baastrup, 2008 SKI22196 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	147/ 56 378 10 years	Danish cancer registry	Time weighted average exposure Questionnaire	Incidence, MM	Per 1 µg/litre	0.80 (0.59-1.08)	Area of enrolment, education, skin reaction to sun, suntanned during summer
		1 010/			Incidence, NMSC		0.99 (0.94-1.06)	Area of enrolment, education, skin reaction to sun, suntanned during summer, occupation
		147/		Cumulative exposure	Incidence, MM	Per 5 mg	0.96 (0.89-1.04)	Area of enrolment, education, skin reaction to sun, suntanned during summer
		1 010/			Incidence, NMSC		0.99 (0.97-1.01)	Area of enrolment, education, skin reaction to sun, suntanned during summer, occupation
Lewis, 1999 SKI14438 USA	Utah, USA 1900-1945, Historical Cohort, Age: 70 years,	3/ 4 058	Church residency lists	Arsenic in drinking water Church records	Men	SMR (O/E)	0.83 (0.17-2.43)	Age, contemporary date
		4/ 4 058			Mortality, MM, women		1.82 (0.50-4.66)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M/W, Mormons							
Hsueh, 1997 SKI02322 Taiwan	Taiwan 1989-1992, Prospective Cohort, Age: 30-years, M/W	26/ 654	Area residency lists	**Average arsenic concentration in drinking water** Interview	Incidence, skin cancer	0.71-1.1 vs. ≤0 mg/litre	8.69 (1.08-65.50) Ptrend:<0.01	Age, sex, educational level
				Cumulative arsenic exposure	Incidence, skin cancer	>17.7 vs. ≤0 mg/litre-year	7.58 (0.95-60.33) Ptrend:<0.01	

Case-control studies

Hsu, 2015 Taiwan	Population-based case-control study in 3 villages in South-west Taiwan (recruited from 1989 to 1996)	57 patients with Bowen's diseases, 8 BCC, 5 with SCC and 210 age and gender matched controls		Arsenic in well water in the village multiplied by years lived in the village	ppm-years <10 10-19.9 20+	Cumulative exposure (ppm/year)	1 (ref) 3.55 (1.14-11.06) 5.25 (1.72-16.05)	Age, gender

5 Dietary constituents

5.5.1.1 Retinol in blood

Cohort studies

Summary

Six studies (eight publications on skin cancer, melanoma, SCC and BCC) were identified in the 2005 SLR and no new studies were identified in the CUP (Table 26).

No meta-analysis was conducted.

Skin cancer

In a nested case-control study conducted in UK (43 cases of melanoma) (Wald, 1986) and in a North-American study (18 cases) (Kark, 1981) retinol in blood was not related to skin cancer risk (RR not reported in the publications).

Malignant melanoma

A non- significant inverse association between circulating retinol and melanoma was reported in the Washington County study (RR: 0.40, 95% CI= 0.10-1.60 for the highest vs. lowest comparison, 30 cases) (Breslow, 1995) and in a Finnish cohort study (unadjusted RR:0.80, per one standard deviation increase in retinol, ptrend=0.60, 10 cases) (Knekt, 1991).

Basal cell carcinoma

No statistically significant associations of circulating retinol with BCC were reported in the Washington County study (RR: 3.30, 95% CI= 0.90-11.60 for the highest vs. lowest comparison, 32 cases) (Breslow, 1995), and in the Finnish cohort study (FMCHES) (RR: 0.50, 95% CI= 0.10-2.10 in women (29 cases) and men (38 cases) (RR: 1.70, 95% CI= 0.50-5.10) for the comparison of highest vs. lowest quantiles) (Knekt, 1990a). In the Evans County, Georgia, Heart Study mean blood retinol at baseline was lower in the people without cancer than in the 12 cases identified during follow-up but no relative risk estimate or p value were reported (Kark, 1981).

Squamous cell carcinoma

No statistically significant associations were reported in the Skin Cancer Prevention Study (RR: 1.16, 95% CI= 0.60-2.23, for >830 vs. ≤610 ng/ml, 129 cases) (Karagas, 1997) and in the Washington County study (RR: 1.80, 95% CI= 0.60-5.80 for the highest vs. lowest comparison, 37 cases) (Breslow, 1995).

5.5.1.1 Retinol in diet

Cohort studies

Summary

Two studies (three publications on melanoma and BCC) were identified in the 2005 SLR and two studies (two publications on melanoma, BCC and SCC) were identified in the CUP.

One meta-analysis was identified (Zhang, 2014) including six case-control and two cohort studies. The summary RR estimate for the highest compared with the lowest level of retinol in diet was 0.84 (95% CI=0.69-1.02).

Malignant melanoma

In the VITAL cohort study (527 cases), a statistically non-significant inverse association was reported, (RR: 0.85, 95% CI= 0.62-1.16, comparing >638.4 vs. ≤280.5 μg/day) (Asgari, 2012). No association was reported in the Nurses' Health Study (414 cases) (RR: 1.07, 95% CI= 0.74-1.55, comparing ≥850 vs. <300 μg/day) (Feskanich, 2003).

Basal cell carcinoma

In a follow-up study of participants in an Australian cancer prevention trial, a statistically non-significant inverse association with dietary retinol was observed (RR: 0.79, 95% CI= (0.49-1.30), comparing 1066 vs. 247 μg/day). The analysis was tumour-based (321 BCC tumours in 149 participants) (Heinen, 2007). Statistically non-significant associations of opposite direction were reported in participants without history of skin cancer (n=658), RR: 1.10, 95% CI= (0.47-2.50) and with history of skin cancer (n=311), RR: 0.69, 95% CI= (0.39-1.20), respectively.

In the Nurses' Health Study, dietary retinol intake was positively associated with BCC (5 392 cases) (RR: 1.20, 95% CI= (1.10-1.30), for 6 378 vs. 1 185 IU/day) in an analysis adjusted for important potential confounders including hair colour, eye colour, ancestry, current state of residence and at younger age, tendency to burn in childhood and childhood sun exposure in swimsuit (Fung, 2002b). Women with higher intakes of retinol appeared to be leaner, used sunscreen more often, smoked less, and lived in states with higher ambient sun radiation and although the analyses were multivariable adjusted, residual confounding by sun exposure and sun sensitivity cannot be ruled out.

Squamous cell carcinoma

In a follow-up of participants in an Australian cancer prevention trial, statistically non-significant positive association was observed (RR: 1.20, 95% CI= (0.70-2.10), comparing 1 066 vs. 247 μg/day. The analyses were tumour-based (221 tumours in 116 participants) (Heinen, 2007). Similarly, statistically non-significant positive associations were reported in participants with no skin cancer history (RR: 2.10, 95% CI= 0.60-7.30, 646 cases) and in participants with skin cancer history (RR: 1.10, 95% CI= (0.60-2.00, 294 cases) comparing the highest and the lowest tertiles).

Table 23 Retinol in diet and skin cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Zhang, 2014	2 cohort and 6 case-control studies	2 776	USA, Italy	Melanoma	Highest vs lowest	0.84 (0.70-1.01)	20%, p=0.27

5.5.1.1 Total retinol intake

Cohort studies

Summary

Two studies (four publications on melanoma, BCC and SCC) were identified in the 2005 SLR and one study (one publication on melanoma) was identified in the CUP (Table 26).

One meta-analysis was identified (Zhang, 2014). The summary RR estimate for the highest compared with the lowest level of retinol in one case-control and two cohort studies was 0.84 (95% CI = 0.69-1.02). The two cohort studies are reviewed below.

Malignant melanoma

In the VITamins And Lifestyle (VITAL) cohort study (516 cases), total retinol intake from diet and supplements was inversely but statistically not significantly related to melanoma (RR: 0.84, 95% CI= 0.64-1.10, comparing >1 771.4 vs. ≤514.2 μg/day) (Asgari, 2012). Similar results were reported in two cohorts of nurses (NHS and NHS II, 414 cases) (RR: 0.85, 95% CI= 0.63-1.16, comparing ≥1 800 vs. <400 μg/day) (Feskanich, 2003). Both studies were multivariable adjusted including skin sensitivity to sunburn and severe sunburns in young age.

Basal cell carcinoma

Total retinol intake was not associated with BCC in the Nurses' Health Study (771 cases) (RR: 0.98, 95% CI= 0.78-1.22, comparing 7131 vs. 819 IU/day) (Hunter, 1992) and in the Health Professional Follow-up Study (3190 cases) (RR: 0.99, 95% CI= 0.84-1.16, comparing 12 533 vs. 1 053 IU/day) (van Dam, 2000).

Squamous cell carcinoma

In a pooled analysis of the Nurses' Health Study and Health Professional Follow-up Study (674 cases) a statistically non-significant inverse association with SCC was observed, RR: 0.85, 95% CI= 0.67-1.09, comparing highest vs. lowest intakes) (Fung, 2003). The RR estimates was 0.76; 95% CI=0.55–1.05; p trend= 0.16 in women and 0.98 (95% CI: 0.68–1.41); p-trend= 0.75 in women and men respectively for the highest vs. lowest comparisons.

Table 24 Retinol in diet and supplement and skin cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Zhang, 2014	2 cohort and 1 case-control study	1 184	USA	Melanoma	Highest vs lowest	0.84 (0.69-1.02)	0%, p=0.98
	2 cohort studies	980	USA			0.84 (0.69-1.03)	0%

5.5.1.1 Retinol in supplement

Randomised controlled trials

Summary

Two RCTs (three publications on BCC and SCC) were identified in the 2005 SLR and no new studies were identified in the CUP (Table 26).

In the SKICAP trial, 525 subjects with a history of at least four basal cell carcinomas and/or cutaneous squamous cell carcinomas were entered into a randomized, double-blind, placebo-controlled trial to receive oral retinol (25 000 IU), isotretinoin *(5-10* mg), or a placebo supplementation daily for 3 years. The three intervention groups had very similar distributions of all characteristics at randomization. The primary end points for the trial were time to first new SCC or BCC. There were no differences in compliance between the three groups. Over 95% of the participants reported taking at least 50% of the total number of capsules, and over 80% of the participants reported taking at least 75% of the total number of capsules. Attrition rates were high in all groups. The proportion of people with side effects was higher in the isotretinoin-treated group, but the overall degree of toxicity was modest.

In the SKICAP-AK trial, 2297 subjects with moderate skin cancer risk (history of more than 10 actinic keratoses and at most 2 squamous cell carcinoma or basal cell carcinoma skin cancers were randomly assigned to receive oral retinol (25,000 IU) or placebo supplementation daily for up to *5* years. Baseline characteristics were similar between the two groups. The primary end points for the trial were time to first new SCC or BCC. Median follow-up time was 3.8 years. Capsule count adherence (at least 85% of subjects taking at least three quarters of their capsules) and clinical adverse symptoms were very similar between the two groups (approximately 1% higher in the retinol group than in the control group) (Moon, 1997a).

The results of the largest trial (SKICAP-AK) showed a protective effect of retinol supplementation for preventing new SCC tumours but not BCC in moderate risk subjects. The smaller trial (SKICAP) did not show any effect of retinol supplementation on incidence of new BCC or SCC tumours.

Basal cell carcinoma

In the SKICAP trial, time to first occurrence of BCC did not differ between those who received the retinol, isotretinoin or placebo (Levine, 1997; Moon, 1997b). Participants on retinol had new 106 tumours (33.2% of the total); those who were given isotretinoin developed 103 tumours (32.2% of the total); and those treated with a placebo had 110 tumours (34.4% of the total).

In the SKICAP-AK trial, 417 subjects had a first new BCC. There was no difference between retinol and placebo groups (RR: 1.06, 95% CI= 0.86-1.32, P=0.36). The cumulative probability of a first new BCC in *5* years was 0.22 for the retinol group and 0.21 for the placebo group (Moon, 1997a).

Squamous cell carcinoma

In the SKICAP trial, retinol treatment had no effect on SCC incidence; no risk estimate was reported (Levine, 1997; Moon, 1997b). Retinol-treated participants accounted for 41 SCC (32.8% of the total); isotretinoin-treated participants had 40 tumours (32% of the total); and those on placebo capsules had 41 tumours (32.8% of the total).

In the SKICAP-AK trial, retinol supplementation was effective in reducing first new SCC (RR: 0.68, 95% CI= 0.51-0.92, P=0.04) compared to placebo. Of the 249 subjects with a first new SCC, 113 **c**ases were diagnosed in the retinol group and 136 in the placebo group (Moon, 1997a).

Cohort studies

No studies were identified in the 2005 SLR and one study (one publication on melanoma) was identified in the CUP (Table 26).

One meta-analysis was identified (Zhang, 2014). The summary RR estimate of one case-control and one cohort study was 0.87 (95% CI = 0.51-1.04).

Malignant melanoma

In the VITAL cohort study (554 cases), the risk of melanoma was lower in current retinol supplement users compared to non-users (RR: 0.60, 95% CI= 0.41-0.89). There was no association with former supplement use. In analysis by intake level, the association was marginally significant for high dose (>1 200 µg/day –higher than in a standard multivitamin) compared to non-use (RR: 0.74, 95% CI= 0.55-1.00) (Asgari, 2012) and no association at the intermediate level (19.3–1,200 µg per day). The inverse association was driven by a risk reduction in women (RR: 0.27; 95% CI= 0.11–0.66, 6 user and 188 non user cases). There was no statistically significant association in men (RR: 0.83; 95% CI= 0.54–1.27; 22 users and 318 non user cases). The reduction in melanoma risk was stronger in sun-exposed anatomic sites.

Table 25 Retinol in supplement and skin cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Zhang, 2014	1 cohort and 1 case-control study	844	USA	Melanoma	Highest vs. lowest	0.87 (0.51-1.47)	55.2%,p=0.11
Bath-Hextall, 2007	2 randomised control trials (Levine, 1997 SKICAP; Moon, 1997 SKICAP-AK)	2 822	USA	Incident BCC	Highest vs. lowest	1.07 (0.91-1.25)	0%
				Incident SCC		0.92 (0.57-1.49)	0%

Table 26 Total, dietary or supplemental retinol and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Asgari, 2012 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	516/ 69 635 5.84 years	SEER cancer registry	**Total** 120-item FFQ	Incidence, MM	>1 771.4 vs. ≤514.2 µg/day	0.84 (0.64-1.10) Ptrend:0.33	Age, gender, education, BMI, alcohol, freckles between the ages 10-20, ≥3 severe sunburns between ages 10-20, red or blond hair between the ages 10-20, reaction to 1 h in strong sunlight, family history of melanoma, history of NMSC, mole removed, macular degeneration
		527/		**Dietary**		>638.4 vs. ≤280.5 µg/day	0.85 (0.62-1.16) Ptrend:0.72	
		554/		**Supplement** (includes multivitamin sources)		>1 200 µg/day vs. non-user	0.74 (0.55-1.00) Ptrend:0.28	
		350/			Men		0.77 (0.53-1.12) Ptrend:0.60	
		204/			Women		0.71 (0.43-1.16) Ptrend:0.29	
		534/		**Individual supplement use**	Incidence, MM	Current vs. non-user	0.60 (0.41-0.89)	
		340/			Men		0.83 (0.54-1.27)	
		194/			Women		0.27 (0.11-0.66)	
Heinen, 2007 Australia	NSCS, Follow-up of a trial on skin cancer, Age: avg. between 53-65,	116 (221 tumours)/ 1 001 8 years	Questionnaires, confirmed through histological reports	**Dietary** 129-item semi-quantitative FFQ	Tumour-based incidence, SCC	1 066 vs. 247 µg/day	1.20 (0.70-2.10) Ptrend:0.47	Additionally adjusted for tanning ability of skin
		646 participants			No skin cancer		2.10 (0.60-7.30)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M/W				history			
		294 participants			With skin cancer history		1.10 (0.60-2.00)	
		149 (321 tumours)			Tumour-based incidence BCC		0.79 (0.49-1.30) Ptrend:0.33	Age, sex, energy intake, skin colour, elastosis of the neck, number of painful sunburns, smoking, treatment allocation, use of dietary supplements, history of skin cancer
		658 participants			No skin cancer history		1.10 (0.47-2.50)	
		311 participants			With skin cancer history		0.69 (0.39-1.20)	
Feskanich, 2003 SKI00696 USA	NHS and NHSII, Prospective Cohort, Age: 25-77 years, W	414/ 162 078	Medical records	**Total** FFQ	Incidence, MM	≥1 800 vs. <400 µg/day	0.85 (0.63-1.16) Ptrend:0.52	Age, follow-up cycle, area of residence, BMI, family history of specific cancer, hair colour, height, menopausal status, number of moles, number of sunburns, oral contraceptive use, parity, post-menopausal hormone use, skin reaction
				Dietary		≥850 vs. <300 µg/day	1.07 (0.74-1.55) Ptrend:0.99	Additionally adjusted for multivitamin use and vitamin A supplement use

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Fung, 2003 SKI00818 USA	NHS and HPFS pooled	674/ 129 811	Self-report confirmed by medical records	**Total** FFQ	Incidence, SCC	Q5 vs. Q1	0.85 (0.67-1.09) Ptrend:0.23	Age, area of residence, area of residence, BMI, beer consumption, liquor, missing FFQ, smoking habits, total energy, wine
	NHS , Prospective Cohort, Age: 30-75 years, M/W, female nurses	369/ 85 944 14 years max			Incidence, SCC, women	8 677 vs. 1 185 IU/day	0.76 (0.55-1.05) Ptrend:0.16	Ancestry, childhood sun reaction, childhood tanning ability, hair colour, lifetime blistering sunburn, sun screen use
	HPFS, Prospective Cohort, Age: 30-75 years, M/W, male health professionals	305/ 43 867 10 years max			Incidence, SCC, men	11 021 vs. 1 131 IU/day	0.98 (0.68-1.41) Ptrend:0.75	Childhood sun exposure in swimsuit, eye colour, tendency to burn in childhood
Fung, 2002b SKI01012 USA	NHS, Prospective Cohort, Age: 30-55 years, W,	5 392/ 85 836 8 years	Not stated	**Dietary** (cumulative average intake) FFQ	Incidence, BCC	6378 vs. 1185 IU/day	1.20 (1.10-1.30) Ptrend:0.0009	Age, ancestry, area of residence, BMI, beer consumption, childhood sun exposure, energy intake, eye colour, hair colour, liquor, missing FFQ, red wine,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	female nurses							smoking habits, tendency to burn in childhood, white wine
Van Dam, 2000 SKI01672 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, health professionals	3 190/ 43 217	Self-reported	**Total** FFQ	Incidence, BCC	12 533 vs. 1 053 IU/day	0.99 (0.84-1.16) Ptrend:0.55	Age, 2 year follow-up periods, carotenes, folate, frequency of physical examinations, hair colour, major ancestry, mean solar radiation, smoking habits, vitamin C, vitamin D, vitamin E, energy intake, BMI
Karagas, 1997 SKI02443 USA	SKICAP, Nested Case Control, Age: 35-84 years, M/W, History > 1 BCC or SCC	117/ 337 5 years	Questionnaire every 4 months and annual dermatological examination	**Plasma retinol** measured using HPLC	Incidence, SCC	>830 vs. ≤610 ng/ml	1.16 (0.60-2.23) Ptrend:0.31	Age, sex, study centre (matching factors), adjusted for smoking habits
		129/379			Any SCC		1.43 (0.77-2.64)	
Levine, 1997 SKI02273 USA	SKICAP, Randomised Control Trial, Age: 21-85 years, M/W, history of>/=4 BCC/SCC	110 (placebo)106 (treatment)/ 173 (treatment), 174 (placebo) 3 year intervention	Examination by dermatologist every 6 months	**Supplementation** with 25 000 units of retinol daily	Incidence, BCC	Treatment vs. placebo	-	Age, sex, number of moles and freckles, number of prior skin cancers, skin type, sun exposure
		41 (placebo) 41(treatment)/			SCC			

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		173 (treatment), 174 (placebo group)						
Moon, 1997a SKI02274 USA	SKICAP-AK, Randomised Control Trial, Age: 21-84 years, M/W, History >= 10 actinic keratoses and <=2 SCC/BCC	113 (treatment), 136 (placebo)/ 1 140 (placebo), 1 157 (treatment) up to 5 years intervention	Examination by dermatologist at least once per year	**Supplementation** with 25 000 units of retinol daily	Incidence, SCC	Treatment vs. placebo	0.68 (0.51-0.92)	Age, sex, moles and freckles, prior skin cancer, skin burns in sun, sun exposure
		417 total cases/			BCC		1.14 (0.91-1.43)	
Moon, 1997b SKI02405 USA	SKICAP-AK, Randomised Control Trial, Age: 63 years, M/W, History >= 10 actinic keratoses and <=2 SCC/BCC;	/1 140 (placebo), 1 157 (treatment) 5 year intervention	Pathology review	**Supplementation** with 25 000 IU of retinol daily	Incidence, BCC	The 5 year probability of first cancer	0.21 for both the retinol and the placebo group	Age, gender, number of prior skin cancers and number of nevi, sun exposure, skin type, sensitivity to sunburn
					SCC		0.10 for the retinol and 0.15 for the placebo group	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	SKICAP-S/B (SKICAP), subjects with history of ≥4 prior skin cancers	/174 (placebo), 173 (treatment) 3 year intervention					No effect on BCC or SCC incidence	
Breslow, 1995 SKI02677 USA	Maryland USA 1974-1975, Nested Case Control, Age: 18- years, M/W	30/ 25 620	-	**Serum** retinol measured using HPLC	Incidence, MM	Q 3 vs. Q 1	0.40 (0.10-1.60) Ptrend:0.23	Adjustment for smoking, education, hours since last meal did not substantially change results
		32			BCC		3.30 (0.90-11.60)	
		37			SCC		1.80 (0.60-5.80) Ptrend:0.35	
Hunter, 1992 SKI03249 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	771/ 73 366	Self-reports confirmed by medical records	**Dietary** FFQ	Incidence, BCC	5190 vs. 683 IU/day	1.07 (0.85-1.33) Ptrend:0.28	Area of residence, BMI, childhood tendency to sunburn, contemporary date, hair colour, lifetime severe and painful sunburn, UV exposure
				Total		7131 vs. 819 IU/day	0.98 (0.78-1.22) Ptrend:0.42	
Knekt, 1991 SKI03576 Finland	FMCHES, Nested Case Control, Age: 15- years, M/W	10/ 28	Finnish cancer registry	**Serum retinol** measured using HPLC	Incidence, MM	Per one standard unit (standard deviation)	0.80 Ptrend:0.60	Unadjusted

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Knekt, 1990a SKI22124 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	38/110	Finnish cancer registry	**Serum retinol**	Incidence, BCC, Men, after excluding first two years of follow-up	Lowest vs. higher quintiles	1.70 (0.50-5.10)	Smoking
		29/81			Women		0.50 (0.10-2.10)	
Wald, 1986 SKI22127 UK	BUPA, Nested Case Control, Age: 35-64 years, M	43/	National Health Service records	**Serum retinol** measured using HPLC	Incidence, skin cancer	(mean exposure)	-	-
Peleg, 1984 SKI23392 USA	Evans County Study, Nested Case Control, Age: 15- years, M/W	3 102	-	**Serum retinol**	Incidence, skin cancer	(mean exposure)	-	-
Kark, 1981 SKI22128 USA	Evans County Study, Case Cohort, Age: 15- years, M/W	18/ 3 102	Follow-up examinations	**Serum retinol**	Incidence, skin cancer	(mean exposure)	-	Age, sex, ethnicity
		12/			Incidence, BCC	(mean exposure)	-	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Wald, 1980 SKI04913 UK	BUPA, Nested Case Control, Age: 35-64 years, M	45/	Health screening programme	**Serum retinol**	Incidence, skin cancer	(mean exposure)	-	-

5.5.1.2 Beta-carotene in blood

Cohort studies

Summary

Eight studies (10 publications on skin cancer, melanoma, NMSC, BCC and SCC) were identified in the 2005 SLR and no new studies (one publication on BCC and SCC) were identified in the CUP (Table 28).

No meta-analysis was conducted.

Skin cancer

In a small study (16 cases) conducted in arseniasis hyperendemic villages in Taiwan, there was an inverse association between serum levels of beta-carotene and subsequent skin cancer (RR for >0.18 vs. ≤0.14 μg/ml: 0.01, 95% CI= (0.00-0.37) (Hsueh, 1997). In a case-control nested in a prospective study conducted in UK (BUPA), skin cancer cases had 8% lower mean serum beta-carotene concentrations than unaffected controls (Wald, 1988).

Malignant melanoma

In a meta-analysis of two cohort studies in the 2005 SLR, the summary RR for each 1 μg/100 ml increment was 0.90, 95% CI= 0.78-1.03, I^2=73%, p=0.06 (Breslow, 1995; Knekt, 1991).

No new cohort studies were identified in the CUP.

Basal cell carcinoma

In a nested case-control study in an Australian community based prospective study on skin cancer, serum beta-carotene levels were not associated with subsequent BCC (RR: 1.15, 95% CI= 0.88-1.50 for each quartile increment, 90 cases) and RR: 1.07, 95% CI= 0.59-1.96, comparing 1.1 vs. 0.3 μmol/L, 77 cases) (McNaughton, 2005, van der Pols, 2009).

In the Isotretinoin-BCC trial that included participants with history of at least two BCC, serum beta-carotene levels were not related to subsequent BCC (RR: 1.01, 95% CI= 0.71-1.44, comparing T3 vs. T1) (Dorgan, 2004).

No association was also reported in a North American study (RR: 1.30, 95% CI= 0.40-4.00) (Breslow, 1995) and a Finnish study (RR: 3.10, 95% CI= 0.90-10.60 in men 0.40, 95% CI= 0.10-1.70 in women, for the highest vs. lowest comparisons) (Knekt, 1990a).

Squamous cell carcinoma

In the 2005 SLR, the summary RR for 1 μg/100 ml increment of serum beta-carotene was 0.99, 95% CI= (0.98-1.00) combining two cohorts (Karagas, 1997, Dorgan, 2004). The SKICAP study (Karagas, 1997) included participants with a history of at least one BCC or SCC and the ISOBCC trial included participants with a history of at least two BCC (Dorgan, 2004). Another study not included in the dose-response meta-analysis reported a statistically non-significant positive association (RR: 1.40, 95% CI= 0.50-4.00 for the highest vs. lowest comparison) (Breslow, 1995).

No association was also observed in the Australian community based prospective study on skin cancer (RR: 0.92, 95% CI= 0.47-1.81, comparing 1.1 vs. 0.3 μmol/L, 59 cases) (van der Pols, 2009).

Non-melanoma skin cancer

In a nested case-control study within the Physicians' Health Study trial, baseline plasma beta-carotene concentration was not associated with NMSC risk, RR: 0.97, 95% CI= 0.69-1.37, for ≥23.29 vs. ≤7.28 μg/dL among subjects assigned to placebo (Schaumberg, 2004). (See results of the Physicians' Health Study (Frieling, 2000) trial of beta-carotene supplementation under 5.5.1.2. Beta-carotene in supplements).

5.5.1.2 Beta-carotene in diet

Cohort studies

Summary

Two studies (two publications on BCC) were identified in the 2005 SLR and one new study (one publication on melanoma) was identified in the CUP (Table 28).

No meta-analysis was conducted.

Malignant melanoma

In the VITamins And Lifestyle (VITAL) cohort study (519 cases), beta-carotene in diet was not related to melanoma risk (RR: 1.15, 95% CI= 0.87-1.53, comparing >5 648.5 vs. ≤2 138.8 μg/day) (Asgari, 2012).

Basal cell carcinoma

In the Australian community prospective study (NSCS, 90 cases), dietary beta-carotene was statistically non-significantly positively associated with incidence of BCC, RR: 2.16, 95% CI= 0.87-5.36, comparing highest vs. lowest quartiles of intake (McNaughton, 2005).

Beta-carotene in diet was not related to BCC in the EPIC-Norfolk study (RR: 1.06, 95% CI= 0.84-1.34, for each 1 210 μg/day increment, 109 cases), (Davies, 2002).

5.5.1.2.2 Beta-carotene in diet and supplement

Cohort studies

Summary

Three studies (four publications on melanoma, BCC and SCC) were identified in the 2005 SLR and one new study (one publication on melanoma) was identified in the CUP (Table 28).

No meta-analysis was conducted.

Malignant melanoma

Total beta-carotene intake was not associated with melanoma (RR: 1.13, 95% CI= 0.86-1.49, comparing >9 358.2 vs. ≤3 515 μg/day in the VITamins And Lifestyle (VITAL) cohort study (519 cases) (Asgari, 2012), and in the Nurses' Health studies (NHS and NHS II, 414

cases; RR: 1.22, 95% CI= 0.86-1.74, comparing ≥6 000 vs. <2 400 μg/day) (Feskanich, 2003).

Basal cell carcinoma

Beta-carotene intake from diet and supplements was not associated with incidence of BCC (RR: 1.21, 95% CI= 0.48-3.09, comparing highest vs. lowest quartiles of intake) in an Australian cohort study (McNaughton, 2005). In the Nurses' Health Study (5 392 cases), the cumulative average dietary intake of beta-carotene was positively associated with incidence of BCC (RR: 1.10, 95% CI= (0.99-1.20) for highest vs. lowest quintile, with a statistically significant linear dose-response trend (P_{trend}=0.02) (Fung, 2002b).

Squamous cell carcinoma

A statistically non-significant positive associations between total beta-carotene intake and SCC were observed in men in the HPFS (RR: 1.42, 95% CI: 0.93–2.16, p-trend= 0.88, 305 cases) and women in the NHS (RR: 1.10, 95% CI= 0.79–1.54, p-trend= 0.31, 369 cases) comparing highest vs. lowest quintile. The pooled summary was RR: 1.21, 95% CI= 0.94-1.58 (Fung, 2003).

5.5.1.2 Beta-carotene in supplement

Randomised controlled trials

Summary

Four RCTs (seven publications on melanoma, NMSC, BCC and SCC) were identified in the 2005 SLR and no new RCTs were identified in the CUP (Table 28).

In the Physician's Health Study, a randomized, double-blind, placebo-controlled trial with a two-by-two factorial design, male physicians between 40-84 years of age and without history of skin cancer (except NMSC) and cardiovascular disease were assigned to 50 mg beta-carotene or beta-carotene placebo on alternate days.

In the Nambour Skin Cancer Prevention Trial, community residents were randomly assigned to daily sunscreen use or daily supplementation with 30 mg of beta-carotene over an average period of 4.5 years. 27% of the subjects had a history of skin cancer.

In the Women's Health Study, a randomised double-blind trial, apparently healthy female health professionals, aged 45 or older without history of cancer (except NMSC) were assigned to 50 mg beta-carotene supplementation on alternate days or placebo over a median duration of 2.1 years.

In the Beta Carotene Trial based in California USA, participants were assigned to 50 mg beta-carotene supplementation daily or placebo over a period of five years. Participants had a history of NMSC (persons with at least 1 BCC or SCC).

Malignant melanoma

After an average of 12.9 years of supplementation in the PHS trial, no effect was observed (RR: 0.90, 95% CI= 0.60-1.20) (Cook, 2000).

No effect of beta-carotene supplementation on melanoma risk was observed in the WHS (19 and 21 cases in the treated and placebo groups respectively, p value not reported) (Lee, 1999).

Non-melanoma skin cancer

In the PHS trial, 12 years with beta-carotene supplementation (50 mg every other day) had no effect on the risk of non-melanoma skin cancer (RR: 0.98; 95% CI=0.92-1.05, 3607 events). There was no evidence of trend for beneficial or adverse effect, and results were similar regardless of smoking status (Frieling, 2000).

No effect of beta-carotene supplementation (50 mg/day) was observed in the Beta Carotene Trial, California, in people with antecedents of NMSC (RR: 1.04, 95% CI= 0.89-1.21) (Greenberg, 1990). The relative rates were 1.44, 95% CI= 0.99-2.09 in current smokers and 0.97, 95% CI= 0.82-1.15 in non-current smokers.

Basal cell carcinoma

In the 2005 SLR, the summary OR based on the three RCTs (Frieling, 2000; Green, 1999; Greenberg, 1990) was 1.00 (95% CI= 0.94-1.07).

In the PHS trial, beta-carotene supplementation had no effect on BCC (RR: 0.99; 95% CI= 0.92-1.06) and the relative rates were similar in never smokers (RR: 1.02, 95% CI= 0.93-1.13), current smokers (RR: 1.07, 95% CI= 0.85-1.35) and past smokers (RR: 0.93, 95% CI= 0.84-1.04) (Frieling, 2000).

Squamous cell carcinoma

In the 2005 SLR, the summary OR based on the three RCTs (Frieling, 2000; Green, 1999; Greenberg, 1990) was 1.07 (95% CI= 0.89-1.30). In the PHS trial (Frieling, 2000), beta-carotene supplementation had no effect on SSC (RR: 0.97, 95% CI= 0.84-1.13) and the relative rates were similar in never smokers (RR: 0.96, 95% CI= 0.77-1.20), past smokers (RR: 0.95, 95% CI= 0.76-1.19) and current smokers (RR: 1.08, 95% CI= 0.69-1.68).

Cohort studies

Summary

No studies were identified in the 2005 SLR and one study (two publications on melanoma) was identified in the CUP (Table 28).

No meta-analysis was conducted.

Malignant melanoma

In the VITAL cohort study with 556 cases and 5.84 years of follow-up, beta-carotene supplementation use (RR: 0.95, 95% CI= 0.64-1.40, comparing current vs. non-users) and levels of supplementation (RR: 1.08, 95% CI= 0.86-1.36, comparing intake of >600 μg/day vs. no use of beta-carotene supplements) were not associated with melanoma (Asgari, 2012). Long-term intake of ≥3000 μg/day of beta-carotene from supplements was statistically non-significantly inversely associated with melanoma risk when compared to no use (RR: 0.87, 95% CI= 0.48-1.56) (VITAL, Asgari, 2009).

Table 27 Beta-carotene in supplement and skin cancer risk. Results of meta-analysis of RCTs published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Druesne-Pecollo, 2010	3	98	USA, France	Melanoma	Treatment vs. placebo No restriction (all studies)	0.98 (0.65-1.46)	0.22
	2	58			Combined with other antioxidants	1.03 (0.61-1.75)	0.09
	2	73			With doses of 20-30 mg/day	0.81 (0.51-1.27)	0.59
	2	33			Majority of men	0.62 (0.31-1.25)	0.70
	3	65			Majority of women	1.14 (0.68-1.89)	0.07
	4	4 447	Australia, USA, UK, France	NMSC	No restriction (all studies)	0.99 (0.93-1.05)	0.52
	2	3 870			Alone	0.99 (0.93-1.06)	0.17
	2	577			Combined with other antioxidants	0.98 (0.83-1.15)	0.55
	3	4 315			With doses of 20-30 mg/day	0.99 (0.93-1.05)	0.36
	3	4 119			Majority of men	0.97 (0.91-1.03)	0.46
	2	395			Majority of women	1.18 (0.97-1.45)	0.53

	3	3 482	Australia, USA, France	BCC	No restriction	1.00 (0.93-1.07)	0.82
	2	3 367			Alone	0.99 (0.93-1.06)	0.74
	2	3 367			With doses of 20-30 mg/day	0.99 (0.93-1.06)	0.74
	2	3 230			Majority of men	0.99 (0.92-1.06)	0.45
	2	252			Majority of women	1.13 (0.88-1.44)	0.23
	3	773		SCC	No restriction	0.99 (0.86-1.14)	0.31
	2	760			Alone	1.00 (0.87-1.15)	0.20
	2	760			With doses of 20-30 mg/day	1.00 (0.87-1.15)	0.20
	2	701			Majority of men	0.97 (0.84-1.12)	0.77
	2	72			Majority of women	1.27 (0.80-2.03)	0.24

Note: Of the four studies included in the NMSC meta-analyses, two studies are included in the CUP review under 5.5.1.2 Beta-carotene supplementation (Green, 1999; Frieling, 2000) and two are included under 5.5.18 Multivitamins supplement (Hercberg, 2007; Heart protection study collaborative group, 2002)

Table 28 Total, circulating or supplemental beta-carotene and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Asgari, 2012 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	519/ 63 576 5.84 years	SEER cancer registry	120-item FFQ, **Total**	Incidence, MM	>9 358.2 vs. ≤3 515 µg/day	1.13 (0.86-1.49) Ptrend:0.47	Age, gender, education, BMI, alcohol, freckles between the ages 10-20, ≥3 severe sunburns between ages 10-20, red or blond hair between the ages 10-20, reaction to 1 h in strong sunlight, family history of melanoma, history of NMSC, mole removed, macular degeneration; total and dietary beta-carotene also adjusted for energy intake
		527/		**Dietary**		>5 648.5 vs. ≤2 138.8 µg/day	1.15 (0.87-1.53) Ptrend:0.46	
		556/		**Supplement** (includes multivitamin sources)		>600 µg/day vs. non-user	1.08 (0.86-1.36) Ptrend:0.36	
		532/		**Individual supplement use**		Current vs. non-user	0.95 (0.64-1.40)	
Asgari, 2009 USA	VITAL, Prospective Cohort Study, Age: 50-76 M/W	453/ 69 671	SEER cancer registry	**Supplement** Self-administered questionnaire	Incidence, MM	≥3 000 vs. >0-≤600 µg/day (10-year average)	0.87 (0.48-1.56) Ptrend:0.38	Age, gender, education, 1st degree family history of melanoma, personal history of NMSC, ever had moles

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								removed, freckles between ages 10-20 years, had ≥3 severe sunburns between ages 10-20 years, natural red/blond hair between ages 10-20 years, reaction to 1-hour in strong sunlight
van der Pols, 2009 SKI23427 Australia	NSCS, Nested Case Control, M/W	77 cases from placebo group only/ 562 8 years	Biennial follow-up questionnaires, histological reports	**Serum** Beta-carotene was analysed by HPLC using the method of Sowell et al., 1994	BCC (person-based incidence)	1.1 vs. 0.3 µmol/L	1.07 (0.59-1.96)	Age, sex, alcohol intake, pack years of smoking, time spent outdoors on weekends, history of skin cancer
		59 cases/ 544			SCC (person-based incidence)		0.92 (0.47-1.81) Ptrend:0.78	
McNaughton, 2005 SKI22177 Australia	NSCS, Nested Case Control, Age: 55 years M/W	90 (49 from placebo and 41 beta-carotene group/ 180	Through participants, their doctors and pathology laboratories	**Diet + supplements** 129-item semi-quantitative FFQ	Incidence, BCC	Q 4 vs. Q 1	1.21 (0.48-3.09)	Age, sex, supplement use, total energy intake
						Linear trend	1.09 (0.81-1.45)	
				Dietary		Q 4 vs. Q 1	2.16 (0.87-5.36)	
						Linear trend	1.23 (0.93-1.64)	
				Serum		Q 4 vs. Q 1	1.21 (0.52-2.81)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
				Beta-carotene was analysed by HPLC using the method of Sowell et al., 1994		Linear trend	1.15 (0.88-1.50)	Age, sex
Dorgan, 2004 SKI00325 USA	ISOBCC Trial, Prospective Cohort, Age: 40-75 years, M/W, History >=2 BCC	221/ 302 5 years maximum	Dermatological examination at each visit	**Serum** Beta-carotene was analysed by HPLC	Incidence, BCC	20.38+(M), 26.58 (W) vs. <10.5 (M), <14.65 (W) µg/dL	1.01 (0.71-1.44) Ptrend:0.94	Age, sex, BMI, clinic site, HDL, LDL, number of prior BCCs, skin type, solar damage, treatment group
		85/ 302			SCC		1.47 (0.81-2.68) Ptrend:0.06	Additionally adjusted for the number of prior SCC
Schaumberg, 2004 SKI00367 USA	PHS, Nested case-control within the trial, Age: 40-84 years, M	1 338/ 2 676 12 years	BCC was self-reported and SCC was self-reported and confirmed through pathology reports	**Serum** beta-carotene was analysed by HPLC	Incidence, NMSC Among subjects assigned to placebo	≥23.29 vs. ≤7.28 µg/dL	0.97 (0.69-1.37) Ptrend:0.84	Age, alcohol consumption, BMI, exercise, randomised aspirin assignment, smoking habits
		305/			Incidence, NMSC	Treatment (50 mg beta-carotene) vs. placebo in subjects with the lowest	0.88 (0.63-1.22) Ptrend:0.33	
		Cases of BCC and SCC with baseline plasma			BCC		0.87 (0.61-1.24)	
					SCC		0.81 (0.30-2.23)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		beta-carotene ≤7.28 µg/dL not available				baseline beta-carotene concentration, ≤7.28 µg/dL		
Feskanich, 2003 SKI00696 USA	NHS and NHSII, Prospective Cohort, Age: 25-77 years, W	414/ 162 078	Medical records	**Total** FFQ	Incidence, MM	≥6 000 vs. <2 400 µg/day	1.22 (0.86-1.74) Ptrend:0.96	Age, follow-up cycle, area of residence, BMI, family history of specific cancer, hair colour, height, menopausal status, number of moles, number of sunburns, oral contraceptive use, parity, post-menopausal hormone use, skin reaction
Fung, 2003 SKI00818 USA	NHS and HPFS pooled	674/ 129 811	Self-report confirmed by medical records	**Total** FFQ	Incidence, SCC	Q5 vs. Q1	1.21 (0.94-1.58) Ptrend:0.43	Age, area of residence, area of residence, BMI, beer consumption, liquor, missing FFQ, smoking habits, total energy, wine

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	HPFS, Prospective Cohort, Age: 30-75 years, M/W, male health professionals	305/ 43 867 10 years max			Men	8 750 vs. 2 186 µg/day	1.42 (0.93-2.16) Ptrend:0.88	Childhood sun exposure in swimsuit, eye colour, tendency to burn in childhood
	NHS , Prospective Cohort, Age: 30-75 years, M/W, female nurses	369/ 85 944 14 years max			Women	7 277 vs. 2 009 µg/day	1.10 (0.79-1.54) Ptrend:0.31	Ancestry, childhood sun reaction, childhood tanning ability, hair colour, lifetime blistering sunburn, sun screen use
Davies, 2002 SKI00989 UK	EPIC-Norfolk, Nested Case Control, Age: 65 (W), 67.8 (M) years M/W	109/ 1 976	Cancer registry	**Dietary** Self-reported 7-day food diary	Incidence, BCC	Per 1 210 µg/day	1.06 (0.84-1.34)	BMI, hair colour, dietary components
Fung, 2002b SKI01012 USA	NHS, Prospective Cohort, Age: 30-55 years, W,	5 392/ 85 836 8 years	Not stated	**Total** FFQ (cumulative average intake)	Incidence, BCC	7277 vs. 2009 µg/day	1.10 (0.99-1.20) Ptrend:0.02	Age, ancestry, area of residence, BMI, beer consumption, childhood sun exposure, energy intake, eye colour,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	female nurses							hair colour, liquor, missing FFQ, red wine, smoking habits, tendency to burn in childhood, white wine
Cook, 2000 USA	PHS, Randomised Control Trial, Age: 40-84 years, M	77 (placebo), 68 (treatment)/ 22 071 12.9 years	Self-report confirmed by medical records	**Supplementation** with 50 mg beta-carotene or placebo on alternate days	Incidence, MM	Treatment vs. placebo	0.90 (0.60-1.20)	Age, randomization assignment in the aspirin component of the trial
Frieling, 2000 SKI01657 USA	PHS, Randomised Control Trial, Age: 40-84 years, M	1821 (placebo), 1786 (treatment) /10 943 (placebo), 10 941 (treatment)	Self-report confirmed by medical records	**Supplementation** with 50 mg beta-carotene or placebo on alternate days	Incidence, NMSC	Treatment vs. placebo	0.98 (0.92-1.05)	Age, randomization assignment in the aspirin component of the trial
		871 (placebo), 875 (treatment)			Never smokers		1.02 (0.93-1.12)	
		778 (placebo), 729 (treatment)/			Past smokers		0.93 (0.84-1.03)	
		166 (placebo), 178 (treatment)/			Current smokers		1.06 (0.86-1.30)	
		1598 (placebo), 1574 (treatment)			BCC		0.99 (0.92-1.06)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		774 (placebo), 782 (treatment)/			Never smokers		1.02 (0.93-1.13)	
		679 (placebo), 636 (treatment)/			Past smokers		0.93 (0.84-1.04)	
		140 (placebo), 152 (treatment)/			Current smokers		1.07 (0.85-1.35)	
		352 (placebo), 340 (treatment)			SCC		0.97 (0.84-1.13)	
		161 (placebo), 152 (treatment)/			Never smokers		0.96 (0.77-1.20)	
		154 (placebo), 147 (treatment)/			Past smokers		0.95 (0.76-1.19)	
		37 (placebo), 41 (treatment)/			Current smokers		1.08 (0.69-1.68)	
Green, 1999 SKI08437 Australia	Nambour Skin Cancer Prevention Trial, Randomised Control Trial, Age: 20-69 years, M/W	93 (placebo), 102 (treatment)/ 1 647 4.5 years	Dermato-pathologist examination	**Supplementation** with 30 mg beta-carotene or placebo daily	Person-based incidence, BCC	Treatment vs. placebo	1.04 (0.73-1.27)	Unadjusted; adjustment for age changed results only slightly
		285 (placebo), 268 (treatment)/			Tumour-based incidence		0.89 (0.64-1.10)	
		28 (placebo), 40 (treatment)/			Person-based incidence, SCC		1.35 (0.84-2.19)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		50 (placebo), 63 (treatment)/			Tumour-based incidence		1.19 (0.89-1.41)	
Lee, 1999 SKI23382 USA	WHS, Randomised Control Trial, Age: 45- years, W	21 (placebo), 19 (treatment)/ 2.1 years treatment and additional 2 years of follow-up	Self-report confirmed by medical records	**Supplementation** with 50 mg beta-carotene or placebo on alternate days	Incidence, MM	Treatment vs. placebo	No statistically significant difference	Age, treatment group
Hsueh, 1997 SKI02322 Taiwan	Taiwan 1989-1992, Nested Case Control, Age: 30- years, M/W	16/ 77	Clinical diagnoses confirmed by biopsy	**Serum** beta-carotene measured using HPLC	Incidence, arsenic-induced skin cancer	>0.18 vs. ≤0.14 µg/ml	0.01 (0.00-0.37)	Age, sex, alcohol consumption, cumulative arsenic exposure, serum cholesterol and triglyceride levels, smoking habits
Karagas, 1997 SKI02443 USA	SKICAP, Nested Case Control, Age: 35-84 years, M/W, History > 1 BCC or SCC	117/ 337 5 years	Questionnaire every 4 months and annual dermatological examination	**Plasma** beta-carotene measured using HPLC	Incidence, first SCC	>265 vs. ≤100 ng/ml	0.71 (0.34-1.47) Ptrend:0.46	Age, sex, study centre (matching factors), adjusted for smoking habits
		129/ 379			Any SCC		0.73 (0.38-1.41) Ptrend:0.37	
Hennekens, 1996 SKI02632	PHS, Randomised	73 (placebo), 64 (treatment)/	Self-report confirmed by	**Supplementation** with 50 mg beta-	Incidence, MM	Treatment vs. placebo	No statistically significant	-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Control Trial, Age: 40-84 years, M	11 035(placebo), 11 036 (treatment) 12 years	medical records	carotene or placebo on alternate days			difference	
Breslow, 1995 SKI02677 USA	Maryland USA 1974-1975, Nested Case Control, Age: 18- years, M/W	30/ 90	Cancer registry	**Serum** beta-carotene measured using HPLC	Incidence, MM	Q 3 vs. Q 1	0.80 (0.20-2.30)	Matched by age, sex, race; adjustment for smoking, education, hours since the last meal did not substantially change the results
		32/96			BCC		1.30 (0.40-4.00) Ptrend:0.72	
		37/111			SCC		1.40 (0.50-4.00) P-trend:NA	
Comstock, 1991 SKI03597 USA	Maryland, USA 1974, Case Cohort, Age: 18- years, M/W	20/ 60	Cancer registry	**Serum** beta-carotene measured using HPLC	Incidence, MM	Low vs. high	1.90 Ptrend:0.16	Matched by age, race, sex, month blood was donated, time between blood drawing and the previous meal
		21/ 63			BCC		1.10 Ptrend:0.24	
Knekt, 1991 SKI03576 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	10/ 28	Finnish cancer registry	**Serum** beta-carotene measured using HPLC	Incidence, MM	Per one standard deviation increase	0.03 Ptrend:<0.01	Matched by age, sex, municipality
Greenberg, 1990 SKI03685	Beta Carotene Trial 1983-89,	340 (placebo), 362 (treatment)/	Annual skin examinations,	**Supplementation** with 50 mg of beta-	Incidence, NMSC	Treatment vs. placebo	1.04 (0.89-1.21)	Age, sex, age at first skin cancer,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Randomised Control Trial, Age: -85 years, M/W History >=1 BCC or SCC	892 (placebo), 913 (treatment) 5 year intervention	dermatology reports	carotene or placebo daily for five years				centre location, plasma beta carotene, plasma retinol, previous skin cancer, skin type, smoking habits
		317 (placebo), 334 (treatment)/			Had at least one new BCC		1.04 (0.89-1.21)	
		59 (placebo), 73 (treatment)/			SCC		1.22 (0.87-1.72)	
					Incidence, NMSC women		0.94 (0.68-1.31)	
					Men		1.06 (0.90-1.26)	
					Incidence, NMSC Non-smokers		0.97 (0.82-1.15)	
					Smokers		1.44 (0.99-2.09)	
Knekt, 1990a SKI22124 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	38/ 110	Finnish cancer registry	**Serum** beta-carotene measured using HPLC	Incidence, BCC, Men, after excluding first two years of follow-up	Lowest vs. higher quintiles	3.10 (0.90-10.60)	Smoking habits

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		29/81			Women		0.40 (0.10-1.70)	
Wald, 1988 SKI22138 UK	BUPA study, Nested Case Control, Age: 35-64 years, M	56/ 163	National Health Service records	**Serum** beta-carotene measured using HPLC	Incidence, skin cancer	(mean exposure)	-	-

5.5.2.3 Lycopene in diet

Cohort studies

Summary

Three studies (two publications on skin cancer, melanoma and BCC) were identified in the 2005 SLR and one new study (two publications on melanoma, SCC and BCC) was identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

In the VITAL cohort study (527 cases), no association was reported (RR: 1.15, 95% CI= 0.86-1.53, comparing >8 680.9 vs. ≤3 163.6 µg/day) (Asgari, 2012). In the NHS and NHS II, no association was found (RR not shown in the publication) (Feskanich, 2003).

Basal cell carcinoma

In a community based prospective study on skin cancer in Australia, lycopene in diet was not related to BCC (RR=0.98, 95% CI= 0.61-1.60, comparing 6 744 vs. 1 945 µg/day) (Heinen, 2007). The analysis was tumour-based (321 BCC tumours in 149 participants). In analysis stratified by NMSC history, the RR was 0.82, 95% CI= 0.45-1.50 in people with skin cancer history, and 1.20, 95% CI= 0.53-2.80 in those without previous NMSC (Heinen, 2007).

Similar results were observed in a previous nested case-control study in the same cohort. The RR estimate in the highest compared to the lowest quartile of intake was 0.64, 95% CI= 0.26-1.56 (McNaughton, 2005).

Squamous cell carcinoma

In a community based prospective study on skin cancer in Australia, lycopene in diet was not related to SCC risk (RR=0.84, 95% CI= 0.48-1.50, comparing 6 744 vs. 1 945 µg/day) (Heinen, 2007). The analysis was tumour-based. In analysis stratified by NMSC history, the RR was 0.78, 95% CI= 0.42-1.50 in people with skin cancer history, and 1.10, 95% CI= 0.35-3.60 in those without previous NMSC (Heinen, 2007).

Table 29 Lycopene in diet and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Asgari, 2012 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	527/ 69 635 5.84 years	SEER cancer registry	120-item FFQ	Incidence, MM	>8 680.9 vs. ≤3 163.6 µg/day	1.15 (0.86-1.53) Ptrend:0.31	Age, gender, education, BMI, alcohol, freckles between the ages 10-20, ≥3 severe sunburns between ages 10-20, red or blond hair between the ages 10-20, reaction to 1 h in strong sunlight, family history of melanoma, history of NMSC, mole removed, macular degeneration, energy intake
Heinen, 2007 Australia	NSCS, Follow-up of a trial on skin cancer, Age: avg. between 53-65, M/W	149 (321 tumours)/ 1 001 8 years	Questionnaires, confirmed through histological reports	129-item semi-quantitative FFQ	Tumour-based incidence BCC	6 744 vs. 1 945 µg/day	0.98 (0.61-1.60) Ptrend:0.94	Age, sex, energy intake, skin colour, elastosis of the neck, number of painful sunburns, smoking, treatment allocation, use of dietary supplements, history of skin cancer
		658 participants			No skin cancer history		1.20 (0.53-2.80) Ptrend:0.64	
		311 participants			With skin cancer history		0.82 (0.45-1.50) Ptrend:0.52	
		116 (221 tumours			Tumour-based incidence, SCC		0.84 (0.48-1.50) Ptrend:0.56	Additionally adjusted for tanning ability of skin
		646			No skin cancer		1.10 (0.35-3.60)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		participants			history		Ptrend:0.87	
		294 participants			With skin cancer history		0.78 (0.42-1.50) Ptrend:0.45	
McNaughton, 2005 SKI22177 Australia	NSCS, Nested Case Control, Age: 55 years M/W	90/ 180	Through participants, their doctors and pathology laboratories	129-item semi-quantitative FFQ	Incidence, BCC	Q 4 vs. Q 1	0.64 (0.26-1.56)	Age, sex, supplement use, total energy intake
						Linear trend	0.85 (0.65-1.13)	
Feskanich, 2003 SKI00696 USA	NHS and NHSII, Prospective Cohort, Age: 25-77 years, W	414/ 162 078	Medical records	FFQ	Incidence, MM	-	-	-

5.5.2.5 Lutein and zeaxanthin in diet

Cohort studies

Summary

Three studies (two publications on skin cancer, melanoma and BCC) were identified in the 2005 SLR and one new study (two publications on melanoma, BCC and SCC) was identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

No association was reported in the VITAL cohort study (527 cases) (RR: 1.27, 95% CI= 0.95-1.70, comparing >3,683.8 vs. ≤1 449.2 µg/day of lutein and zeaxanthin (Asgari, 2012). No association was found in the NHS and NHS II (RR nor shown in the publication) (Feskanich, 2003).

Basal cell carcinoma

In a community based prospective study on skin cancer in Australia, lutein and zeaxanthin in diet was not related to SCC risk (RR=1.10, 95% CI= 0.71-1.80, comparing 2 945 vs. 1 974 µg/day) (Heinen, 2007). The analysis was tumour-based (321 BCC tumours in 149 participants). In analysis stratified by NMSC history, the RR was 1.40, 95% CI= 0.65-2.90 in people with skin cancer history, and 0.87, 95% CI= 0.48-1.60 in those without previous NMSC (Heinen, 2007).

Similar results were observed in a previous nested case-control study in the same cohort. The RR estimate of first incident BCC in the highest compared to the lowest quartile of intake was 1.65, 95% CI= 0.69-3.95 (McNaughton, 2005).

Squamous cell carcinoma

No association was reported in the Australian cohort study (RR: 0.65, 95% CI= 0.38-1.1, comparing 2 945 vs. 1 974 µg/day, 221 tumours in 116 participants) (Heinen, 2007). In analysis stratified by NMSC history, the RR was 0.94, 95% CI= 0.24-3.60 in those without skin cancer history, and RR: 0.47, 95% CI= 0.25–0.89 in those with skin cancer history at baseline (Heinen, 2007).

Table 30 Lutein and zeaxanthin in diet and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Asgari, 2012 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	527/ 69 635 5.84 years	SEER cancer registry	120-item FFQ	Incidence, MM	>3 683.8 vs. ≤1 449.2 µg/day	1.27 (0.95–1.70) Ptrend: 0.07	Age, gender, education, BMI, alcohol, freckles between the ages 10-20, ≥3 severe sunburns between ages 10-20, red or blond hair between the ages 10-20, reaction to 1 h in strong sunlight, family history of melanoma, history of NMSC, mole removed, macular degeneration, energy intake
Heinen, 2007 Australia	NSCS, Follow-up of a trial on skin cancer, Age: avg. between 53-65, M/W	149 (321 tumours)/ 1 001 8 years	Questionnaires, confirmed through histological reports	129-item semi-quantitative FFQ	Tumour-based incidence BCC	2 945 vs. 1 974 µg/day	1.1 (0.71–1.8) Ptrend: 0.61	Age, sex, energy intake, skin colour, elastosis of the neck, number of painful sunburns, smoking, treatment allocation, use of dietary supplements, history of skin cancer
		658 participants			No skin cancer history		1.4 (0.65–2.9) Ptrend: 0.40	
		311 participants			With skin cancer history		0.87 (0.48–1.6) Ptrend: 0.67	
		116 (221 tumours)			Tumour-based incidence, SCC		0.65 (0.38-1.1) Ptrend: 0.13	Additionally adjusted for tanning ability of skin
		646 participants			No skin cancer history		0.94 (0.24-3.60) Ptrend: 0.99	
		294 participants			With skin cancer history		0.47 (0.25–0.89) Ptrend: 0.02	
McNaughton,	NSCS,	90/	Through		Incidence,	Q 4 vs. Q 1	1.65 (0.69-3.95)	Age, sex, supplement use,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
2005 SKI22177 Australia	Nested Case Control, Age: 55 years M/W	180	participants, their doctors and pathology laboratories	129-item semi-quantitative FFQ	BCC	Linear trend	1.25 (0.95-1.65)	total energy intake
Feskanich, 2003 SKI00696 USA	NHS and NHSII, Prospective Cohort, Age: 25-77 years, W	414/ 162 078	Medical records	FFQ	Incidence, MM	-	-	-

5.5.10 Vitamin D in blood

Cohort studies

Overall summary

Eight publications from 11 studies that examined 25-hydroxyvitamin D in blood were identified. These included a pooled study of three Danish cohorts (Monica10, Inter99, and Health2006) (Skaaby, 2014). All were new studies identified during the CUP.

Dose-response meta-analyses on circulating vitamin D and melanoma, non-melanoma skin cancer (NMSC), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) were conducted.

Table 31 Vitamin D in blood and skin cancer risk. Number of studies in the CUP SLR.

	Number
Studies identified	11 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	6 (4 publications) melanoma risk 6 (4 publications) NMSC risk 5 (4 publications) BCC 4 (3 publications) SCC risk
Studies included in linear dose-response meta-analysis	6 (4 publications) melanoma risk 6 (4 publications) NMSC risk 4 (3 publications) BCC 3 (2 publications) SCC risk
Studies included in non-linear dose-response meta-analysis	Not enough studies

Skin cancer

Summary

Main results:

The six studies (4 publications) identified on melanoma and NMSC were included in the dose-response meta-analysis, and 4 out of 5 studies (4 publications) on BCC, and 3 out of 4 studies (3 publications) on SCC. The tests for publication bias were not conducted and funnel plots are not shown due to low number of studies contributing relative risks estimates for each cancer site.

Malignant melanoma

Circulating vitamin D was statistically significantly positively associated with melanoma risk (RR: 1.61, 95% CI= 1.01-2.58). There was statistical significant evidence of heterogeneity.

Visual inspection of the forest plot indicates that the inconsistency is mainly driven by one study from Denmark (Afzal, 2013) that reported a positive association.

There was no evidence of difference of association by sex (Skaaby, 2014; Afzal, 2013).

Sensitivity analyses:

The positive association was no longer statistically significant when each study was excluded in turn in influence analysis.

Non-melanoma skin cancer

Circulating vitamin D was statistically non-significantly positively associated with NMSC risk (RR: 1.23, 95% CI= 0.91-1.67). High and statistically significant heterogeneity was observed. Visual inspection of the forest plot showns that only one study in elderly men showed a statistically significant inverse association (Tang, 2010). In this study, NMSC cases were ascertained by self-report and not confirmed by histology. In influence analysis, the association became statistically significant and positive when this study was excluded from the analysis (RR: 1.42, 95% CI= 1.09-1.86).

The pooled analysis of three Danish cohorts was a study on serum 25-Hydroxyvitamin-D levels and risk of different cancers. The only statistically significant positive association with cancer observed in the study was for NMSC (Skaaby, 2014) and it was statistically non-significant in participants with BMI < 25 kg/m^2.

Stratified analyses were not conducted due to low number of studies. In the pooled analysis (Skaaby, 2014), similar positive associations were reported in men (RR: 1.04, 95% CI= 0.90-1.21) and women (RR: 1.07, 95% CI= 0.93-1.23).

Basal cell carcinoma

Circulating vitamin D was statistically significantly positively associated with BCC (RR: 1.40, 95% CI= 1.19-1.66). Moderate heterogeneity was observed. In influence analysis, the association remained statistically significant when each study was excluded in turn from the analysis.

One study excluded from the dose-response meta-analysis reported a marginally positive association (RR: 1.7, 95% CI=1.00-2.9, comparing ≥15 vs. ≤14 ng/ml) (Eide, 2011).

Squamous cell carcinoma

Circulating vitamin D was positively but statistically non-significantly associated with SCC risk (RR: 1.57, 95% CI= 0.64-3.88). High and statistically significant heterogeneity was observed.

One study excluded from the dose-response meta-analysis reported statistically non-significant positive association (RR: 1.7, 95% CI= 0.7-1.40, comparing ≥15 vs. ≤14 ng/ml) (Eide, 2011).

Nonlinear dose-response meta-analysis:

Nonlinear dose-response meta-analyses were not conducted due to low number of studies with adequate data.

Study quality:

Two studies originated from clinical trials. The Australian study originated from a skin cancer prevention trial of daily sunscreen use and beta-carotene supplementation (van der Pols, 2013). Vitamin D status was not associated with allocation to sunscreen and beta-carotene treatment groups in the trial. The ATBC was a randomized controlled trial of alpha-tocopherol or beta-carotene investigating incidence of cancer in male smokers (Major, 2012). Supplemental vitamin D intakes were minimal among the ATBC Study participants and blood levels were relatively low compared to US populations.

The level of adjustment for skin type and sunlight exposure varied between the studies. Only two studies adjusted for some measure of skin sensitivity to sunlight and sunlight exposure (van der Pols, 2013; Liang, 2012); two studies adjusted for season (Skaaby, 2014; Afzal, 2013); one study adjusted for season of blood draw and outdoor walking activity (Tang, 2010); one study adjusted for sun exposure surrogates (Asgari, 2010), one study adjusted for propensity to sunburn (Major, 2012). One study was minimally adjusted for age and sex (Eide, 2011).

In one study (Tang, 2010) an inverse asociation of vitamin D status and NMSC was observed. The study was in highly educated men of 65 years of age or more (Tang, 2010). Cases of NMSC were ascertained by subject self-report; this is the only study in the review in which skin cancer was not confirmed by histology.

Several studies provided some evidence that the increased risk of skin cancers with increasing levels of circulating vitamin D might be explained by higher levels of vitamin D with higher UV exposure. In Afzal, 2013, the association was stronger for melanoma in sun-exposed sites (head and extremities, 40 cases) (RR per 10nmol/l was 1.58; 95% CI: 1.25–2.00) whereas it was weaker (RR: 1.24; 95% CI: 0.93–1.66) for relatively unexposed sites (trunk and other sites, 38 cases). Increasing levels of plasma 25-OH-vitD were associated with decreasing BMI, increased intensity of leisure-time activity, and with regular cycling or running. In the Australian study (van der Pols, 2013), vitamin D status was associated with indicators of UV exposure (longer time spent outdoors in the 6 months preceding blood collection and during follow-up). However, in a study in white men who sought osteoporosis or low-bone-density–related advice from 1997 to 2001 in the HFHS outpatient clinic, there was a statistically significant (positive) association of higher vitamin D status and NMSC that was of similar magnitude for the cancers in the less UV exposed body sites (Eide, 2011).

Table 32 Vitamin D in blood and skin cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR* and 2016 CUP.

	CUP	
Increment unit used	30 nmol/l	
	Malignant melanoma	**Non-melanoma skin cancer**
Studies (n)	6	6
Cases	242	1 377
RR (95%CI)	1.61 (1.01-2.58)	1.23 (0.91-1.67)
Heterogeneity (I^2, p-value)	71%, 0.02	91%, <0.0001
P value Egger test	-	-
	Basal cell carcinoma	**Squamous cell carcinoma**
Studies (n)	4	3
Cases	1 030	251
RR (95%CI)	1.40 (1.19-1.66)	1.57 (0.64-3.88)
Heterogeneity (I^2, p-value)	43%, 0.15	88%, <0.0001
P value Egger test	-	-

*No studies were identified in the 2005 SLR.

Table 33 Vitamin D in blood and skin cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Caini, 2014	3 cohort, 1 case-control study	392	Germany, Finland, Denmark, Australia	Cutaneous melanoma	Highest vs. lowest	1.46 (0.60-3.53)	54%
	2 cohort studies	768	USA, Denmark	NMSC		1.64 (1.02-2.65)	81%
	5 cohort studies	1221	USA, Australia	BCC		1.82 (1.38-2.40)	0%
	4 cohort studies	328	USA,	SCC		1.68 (0.44-6.39)	81%

Table 34 Vitamin D in blood and skin cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Skaaby, 2014 SKI23412 Denmark	Pooled study: Monica10, Inter99, Health2006, Age: 18-71 years, M/W	NMSC 369; Cutaneous melanoma 55/ 12 204 11.3 years	Cancer registry	IDS-SYS 25-Hydroxy Vitamin D method (Monica10); HPLC (Inter99); Cobas e411(Health 2006)	Incidence, NMSC All	per 10 nmol/l	1.06 (1.02-1.10)	Adjusted for study, sex, education, season during which blood was drawn, physical activity, smoking habits, alcohol intake, intake of fish, and BMI	RR rescaled to 30 nmol/l increment
						Q 4 vs. Q 1	1.43 (1.05-1.93)		
					Men	per 10 nmol/l	1.06 (1.00-1.12)		
					Women	per 10 nmol/l	1.06 (1.00-1.12)		
					Incidence, MM All	per 10 nmol/l	1.06 (0.95-1.17)		
						Q 4 vs. Q 1	1.18 (0.56-2.48)		
					Men	per 10 nmol/l	1.04 (0.90-1.21)		
					Women	per 10 nmol/l	1.07 (0.93-1.23)		
Afzal, 2013 SKI23413 Denmark	CCHS, Prospective Cohort, Age: 20-100 years, M/W	590/ 10 060 20.5 years	Danish cancer registry	DiaSorin LIAISON 25 (OH) vitamin D TOTAL assay	Incidence, NMSC	≥50 vs. ≤25 nmol/l	5.04 (2.78-9.16)	Age, sex, BMI, income, occupational physical activity, calendar month of blood draw, cumulative tobacco consumption, physical intensity of leisure-time activities, running and cycling habits	RR rescaled to 30 nmol/l increment
						≥100 vs. ≤25 nmol/l	5.28 (1.66-16.80)		
						per 10 nmol/l	1.23 (1.14-1.32)		
		78/			Incidence, MM	≥50 vs. ≤25 nmol/l	4.72 (0.96-23.30)		
						≥100 vs. ≤25 nmol/l	9.58 (2.37-38.70)		
						per 10 nmol/l	1.45 (1.22-1.73)		
van der Pols,	NSCS,	300 BCC; 176	Questionnaires	LIAISON	Incidence,	per 50 nmol/l	1.35 (0.94-1.93)	Age, sex,	RR rescaled to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
2013 SKI23414 Australia	Prospective analysis in adults who had participated in a skin cancer prevention trial (1992–1996) of daily sunscreen use and beta-carotene supplementation Age: 54 years, M/W	SCC; 17 melanoma/ 1 191 11 years	and skin examination with histological confirmation (100%)	25(OH)D assay	BCC	≥75 vs. ≤74 nmol/l	1.51 (1.10-2.07)	propensity to sunburn, skin colour, treatment allocation, elastosis neck, family history of skin cancer, freckling back, personal history of skin cancer before 1996, usual time spent outdoors	30 nmol/l increment
						≥50 vs. ≤49 nmol/l	1.38 (0.95-2.00)		
						≥75 vs. < 50 nmol/l	1.74 (1.13-2.67)		
					Incidence, SCC	per 50 nmol/l	0.68 (0.42-1.11)		
						≥75 vs. ≤74 nmol/l	0.67 (0.44-1.03)		
						≥50 vs. ≤49 nmol/l	0.78 (0.50-1.23)		
						≥75 vs. <50 nmol/l	0.61 (0.35-1.06)		
					Incidence, MM	≥75 vs. ≤74 nmol/l	2.71 (0.98-7.48)		
						per 50 nmol/l	2.70 (0.83-8.77)		
						≥50 vs. ≤49 nmol/l	1.53 (0.42-5.56)		
						≥75 vs. 50-74 nmol/l	2.75 (0.68-11.17)		
Liang, 2012 SKI23415 USA	NHS and NHS II, Nested Case	510/ 4056 controls	Biennial follow-up questionnaires	Radioimmunoassay or chemiluminescence	Incidence, BCC NHS and NHS II	Q 4 vs. Q 1	2.07 (1.52-2.80) Ptrend:<0.0001	Age at blood collection, cohort, hair colour,	

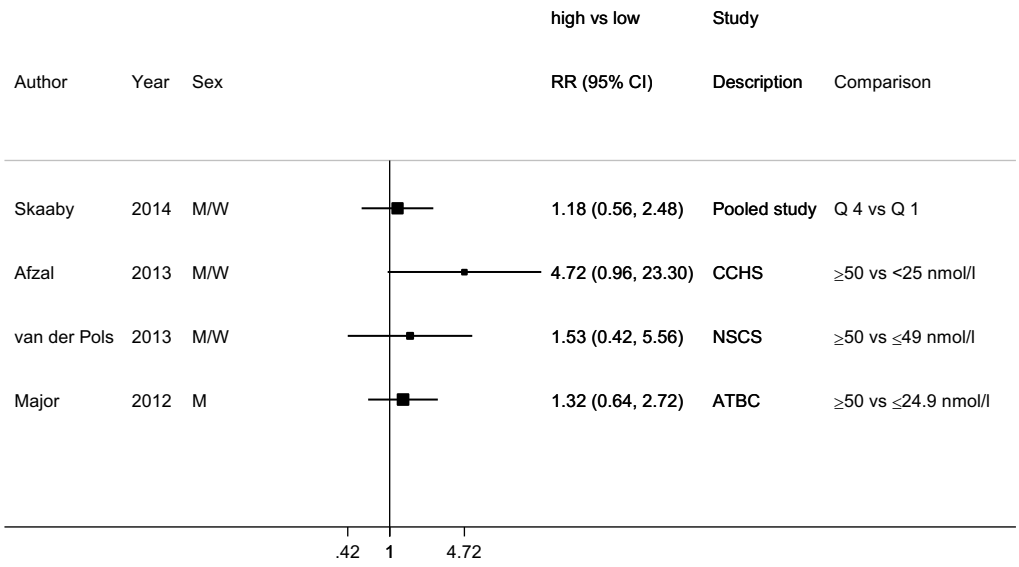
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Control, W	387/ 1641 controls	and medical records	immunoassay	NHS	≥34.3 vs. ≤20.4 ng/ml	2.28 (1.58-3.29) Ptrend:<0.0001	laboratory batch, number of sunburns, propensity to sunburn, season of blood draw, UVB flux, NHS and NHS II combined adjusted for cohort	ng/ml converted to nmol/l, midpoints of exposure quantiles
		123/ 2415 controls			NHS II	≥31.5 vs. ≤19.6 ng/ml	1.93 (1.10-3.37) Ptrend:0.01		
		281/ 2119 controls			NHS and NHS II combined, spring and fall	≥34.3 vs. ≤20.4 ng/ml	2.97 (1.90-4.63) Ptrend:<0.0001		
		158/ 954 controls			NHS and NHS II combined, summer	≥34.3 vs. ≤20.4 ng/ml	0.93 (0.51-1.71) Ptrend:0.81		
		145/ 965 controls			NHS and NHS II combined, winter	≥34.3 vs. ≤20.4 ng/ml	2.53 (1.36-4.72) Ptrend:0.006		
		75/ 4056 controls			Incidence, SCC NHS and NHS II combined	≥31.5 vs. ≤19.6 ng/ml	3.77 (1.70-8.36) Ptrend:0.0002		
		67/ 1641 controls			NHS	≥34.3 vs. ≤20.4 ng/ml	3.96 (1.68-9.34) Ptrend:0.0004		
		8/ 2415 controls			NHS II	≥31.5 vs. ≤19.6 ng/ml	4.95 (0.41-59.28) Ptrend:0.15		
Major, 2012 SKI23417 Finland	ATBC, Nested Case Control,	92/ 276 controls 18.2 years	Finnish cancer registry	LIAISON 25-OH Vitamin D Total Assay	Incidence, MM	≥50 vs. ≤24.9 nmol/l	1.32 (0.64-2.72)	Age at randomization, cholesterol, date	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 50-69 years, Men Smokers							of blood draw, height, propensity to sunburn, weight	
Eide, 2011 SKI23418 USA	HFHS, Prospective Cohort, Age: 65.9 years, M/W	240/ 3 223 9.8 years	Pathology reports	Radioimmunoassay	Incidence, NMSC	≥15 vs. ≤14 ng/ml	1.80 (1.10-2.90)	Age, sex	
						≥31 vs. ≤18 ng/ml	1.60 (1.10-2.30) Ptrend:0.02		Ng/ml converted to nmol/l, midpoints of exposure categories
		191/			Incidence, BCC	≥15 vs. ≤14 ng/ml	1.70 (1.00-2.90)		Only two exposure levels, only included in the high vs. low figure
		77/			Incidence, SCC	≥15 vs. ≤14 ng/ml	1.70 (0.70-4.00)		
Asgari, 2010 SKI23419 USA	KPNC, Nested Case Control, Age: 54.9 years, M/W	220/ 220 controls 8.74	Pathology reports	DiaSorin LIAISON 25(OH) Vitamin D Total Assay	Incidence, BCC	≥30 vs. ≤9.9 (clinical tertiles) ng/ml	3.61 (1.00-13.10) Ptrend:0.03	BMI, educational level, history of cancer, smoking status, x-ray, sun exposure surrogates (hours of exercise and leisure activities,	ng/ml converted to nmol/l, RR rescaled to 30 nmol/l increment used
						Per 1 ng/ml	1.02 (1.00-1.05)		
						≥29.79 vs. ≤14.69 (quintiles) ng/ml	2.09 (0.95-4.58)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								occupational UV, occupational sun exposure level)	
Tang, 2010 SKI23420 USA	MrOS, Nested Case Control, Age: 65- years, M, Elderly	178/ 930 controls	Self-reported	LCmass spectroscopy	Incidence, NMSC	≥32 vs. ≤31.9 ng/ml	0.59 (0.34-1.01)	Age, BMI, cigarette smoking, clinic site, season of blood draw, outdoor walking activity	ng/ml converted to nmol/l, midpoints of exposure categories
						≥29.9 vs. ≤29.8 ng/ml	0.60 (0.37-0.98)		
						29.9-58.3 vs. ≤15.9 ng/ml	0.54 (0.31-0.96) Ptrend:0.044		

RR estimates of melanoma by levels of vitamin D in blood: One study on melanoma (Major, 2012) reported risk estimates by levels of circulating vitamin D. Only RR for highest vs. lowest comparisons or for continuous increments are shown in other studies. Therefore a figure of RR estimates of cutaneous melanoma by levels of circulating vitamin D in each study is not provided in this section.

Figure 29 RR (95% CI) of melanoma for the highest compared with the lowest level of vitamin D in blood



Note: The upper CI (23.3) is out of the Figure 29 for Afzal, 2013

Figure 30 Relative risk of melanoma for 30 nmol/l increase of vitamin D in blood

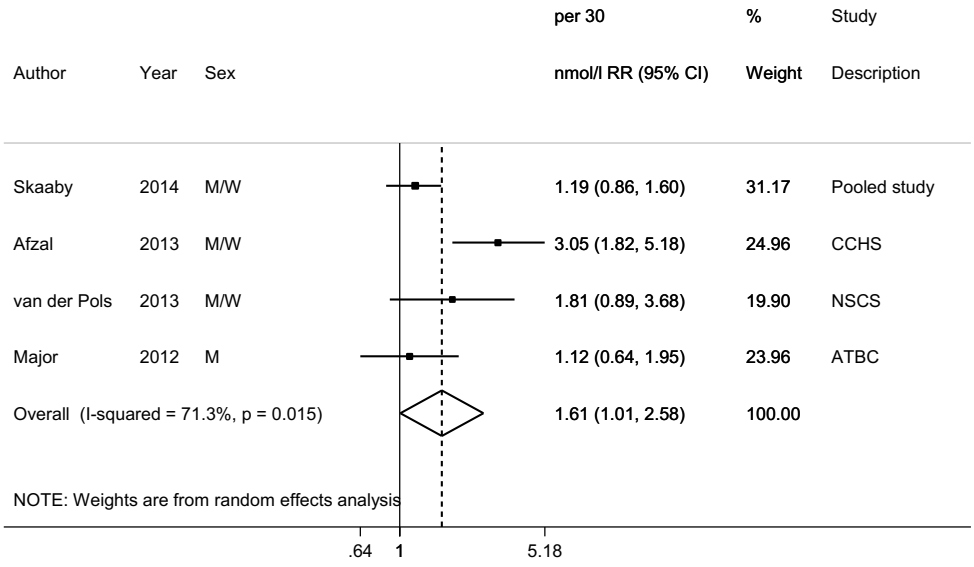


Figure 31 RR estimates of NMSC by levels of vitamin D in blood

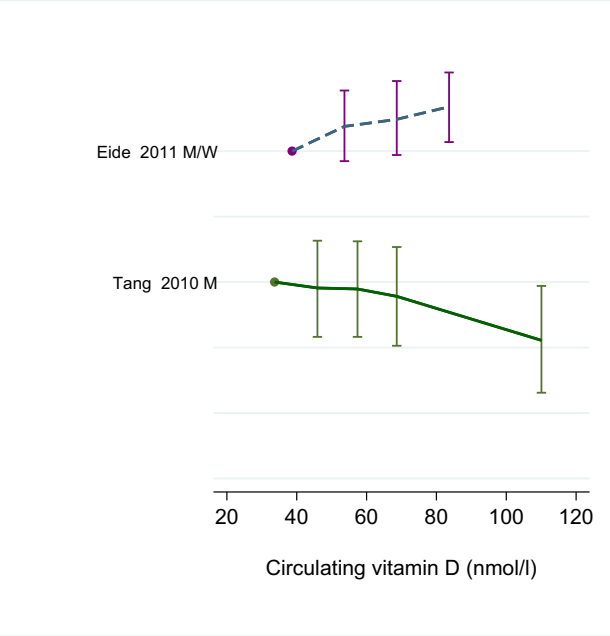


Figure 32 RR (95% CI) of NMSC for the highest compared with the lowest level of vitamin D in blood

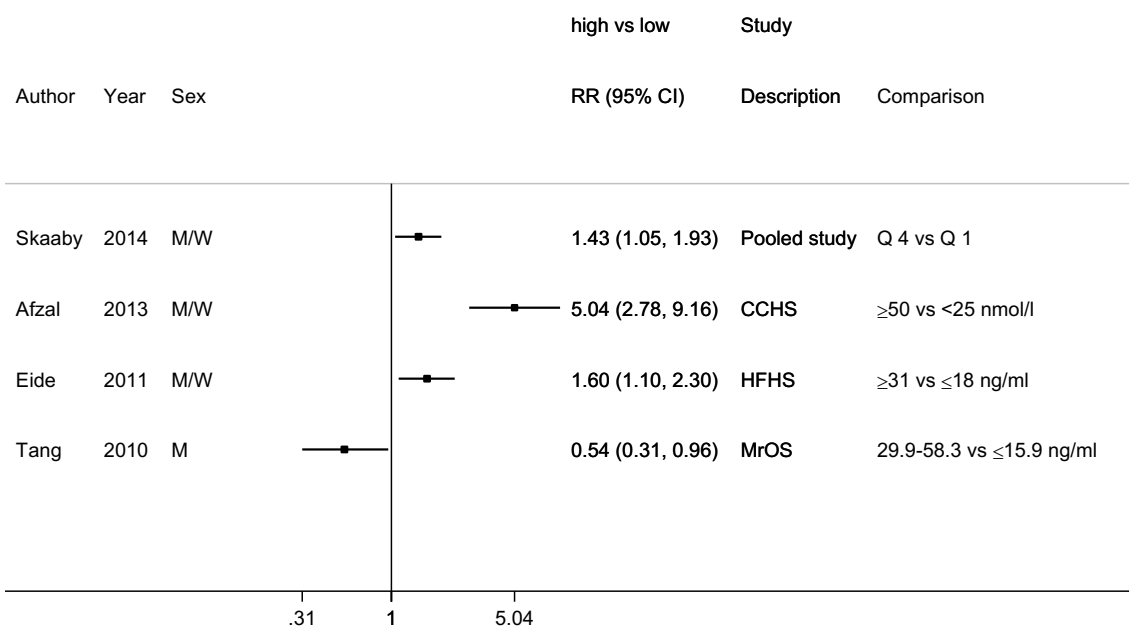


Figure 33 Relative risk of NMSC for 30 nmol/l increase of vitamin D in blood

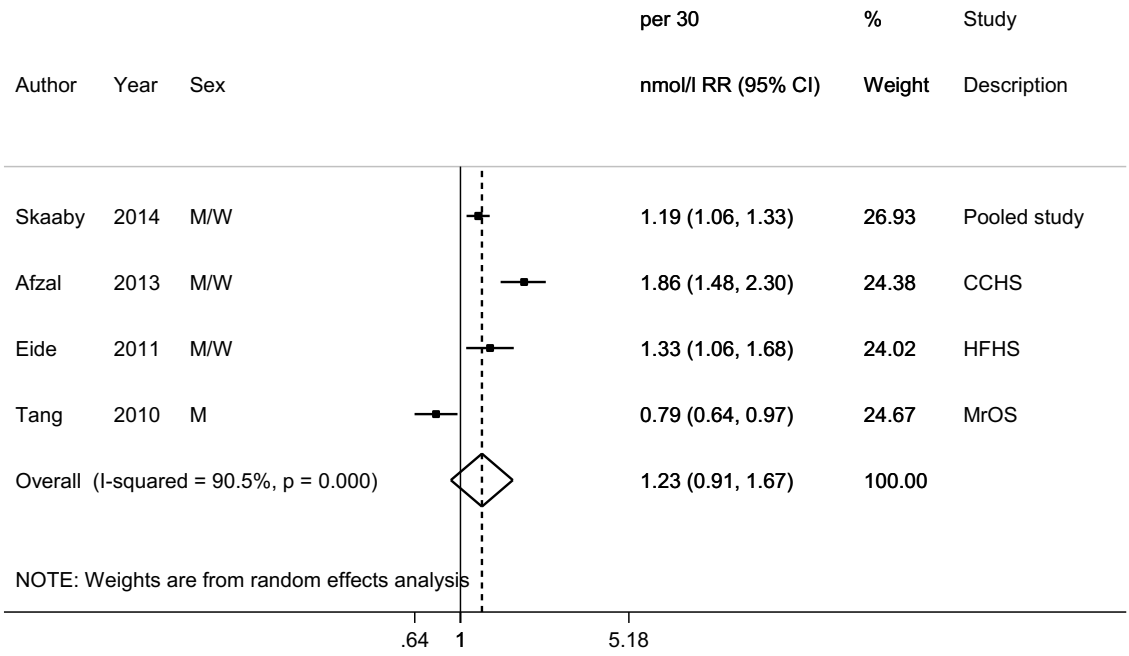


Figure 34 RR estimates of BCC by levels of vitamin D in blood

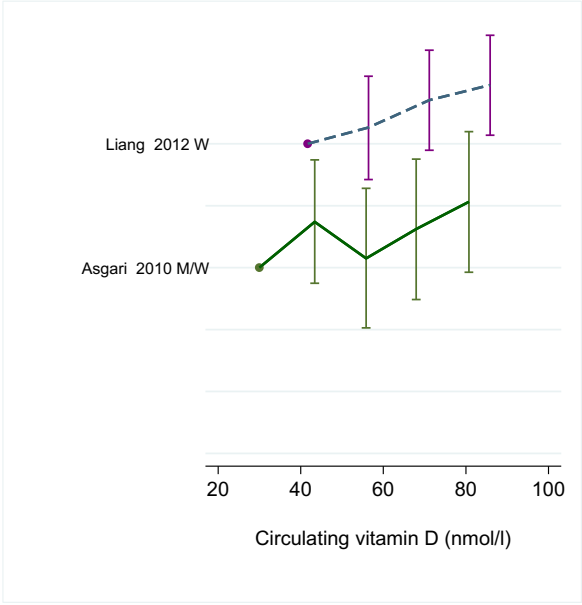


Figure 35 RR (95% CI) of BCC for the highest compared with the lowest level of vitamin D in blood

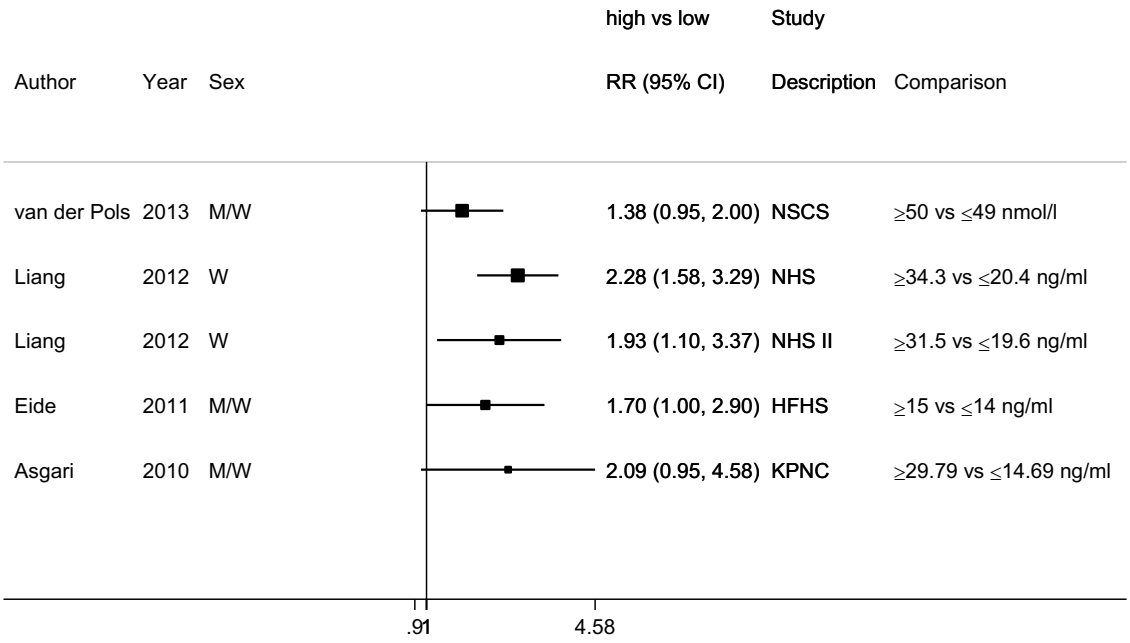
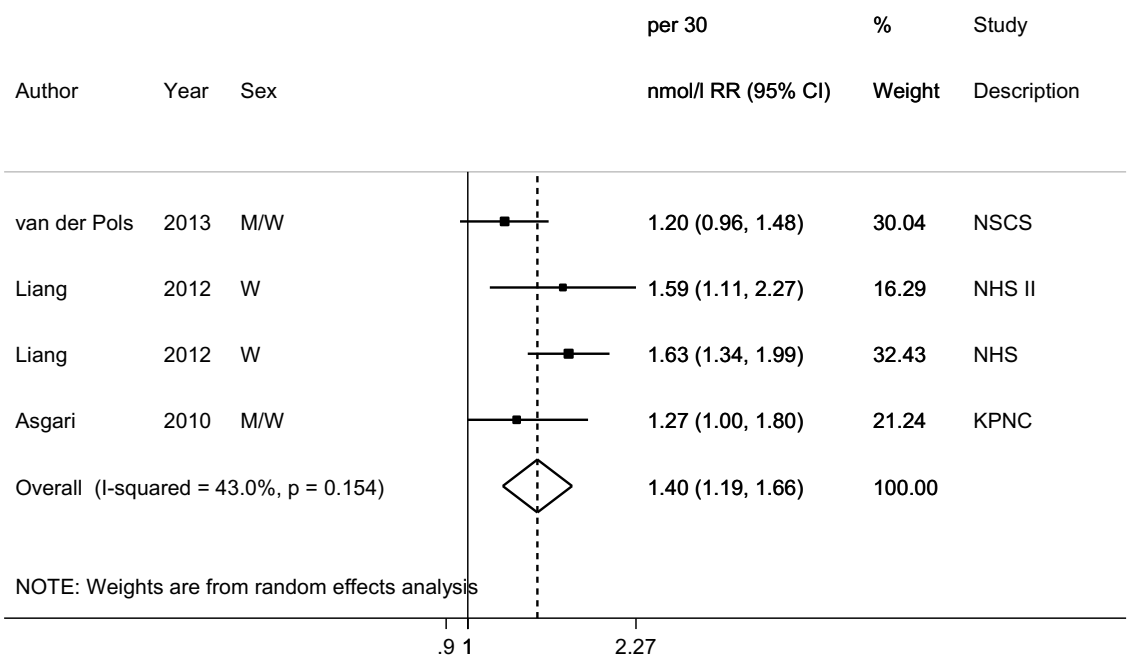


Figure 36 Relative risk of BCC for 30 nmol/l increase of vitamin D in blood



RR estimates of SCC by levels of vitamin D in blood: One study on SCC (Liang, 2012) reported risk estimates by levels of circulating vitamin D. Only RR for highest vs. lowest comparisons or for continuous increments are shown in other studies. Therefore a figure of RR estimates of SCC by levels of circulating vitamin D in each study is not provided in this section.

Figure 37 RR (95% CI) of SCC for the highest compared with the lowest level of vitamin D in blood

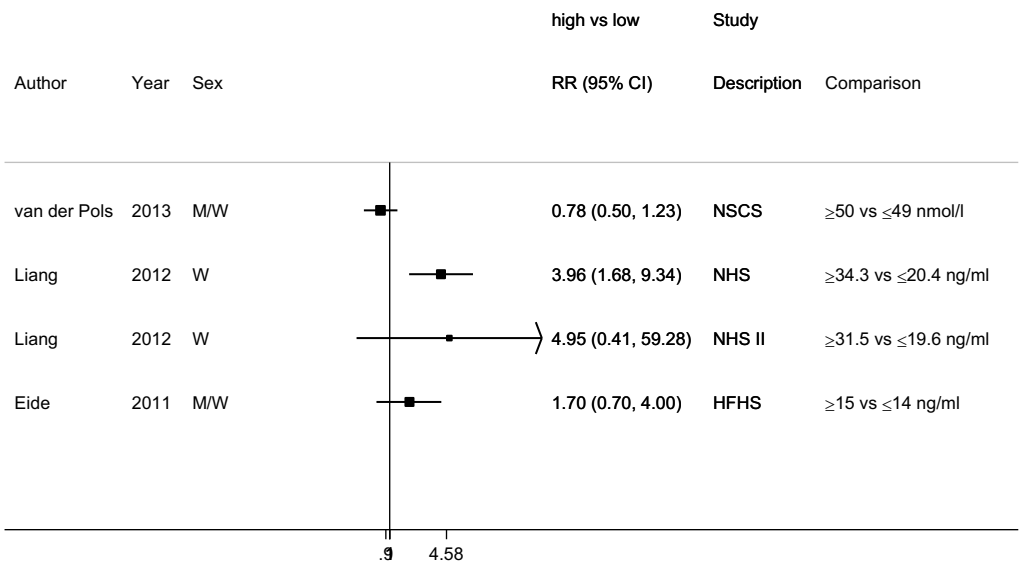
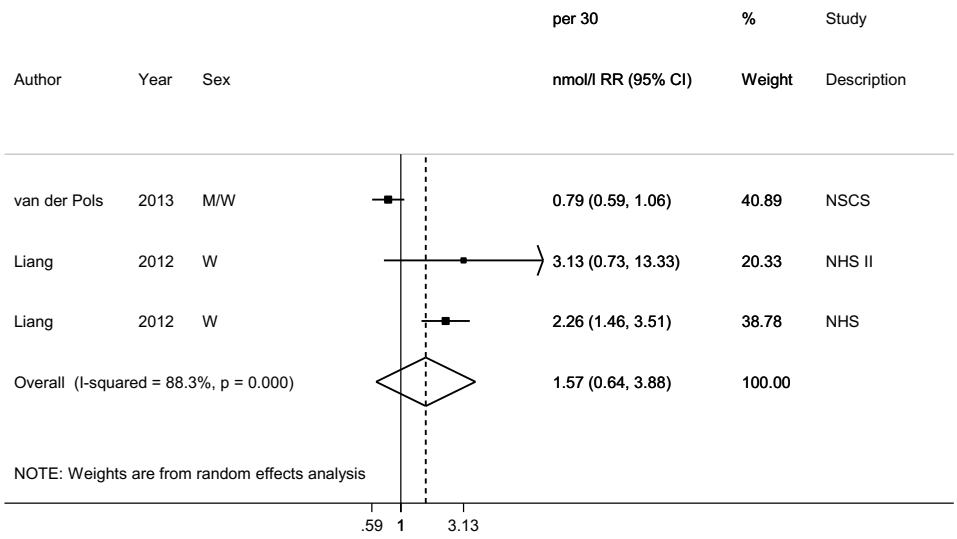


Figure 38 Relative risk of SCC for 30 nmol/l increase of vitamin D in blood



5.5.10 Vitamin D in diet

Cohort studies

Summary

Two studies (two publications on BCC) were identified in the 2005 SLR and one study (one publication on melanoma) was identified in the CUP (Table 36).

No meta-analysis was conducted.

Malignant melanoma

In the VITAL cohort study, a statistically non-significant positive association was reported (RR: 1.31, 95% CI= 0.94-1.82, comparing >7.1-53 vs. 0.3 μg/day)(Asgari, 2009).

Basal cell carcinoma

In the EPIC-Norfolk cohort study (109 cases), a statistically non-significant positive association was reported (RR: 1.07, 95% CI= 0.85-1.35 for an increment of 2.08 μg/day) (Davies, 2002). Similar association was reported in the Nurses' Health Study (771 cases) (RR: 1.02, 95% CI= 0.81-1.27, comparing 288.5 vs. 45.2 IU/day) (Hunter, 1992).

5.5.10 Vitamin D in diet and supplement

Cohort studies

Summary

Two studies (two publications on BCC) were identified in the 2005 SLR and one study (one publication on melanoma) was identified in the CUP (Table 36).

No meta-analysis was conducted.

Malignant melanoma

In the VITAL cohort study, no association was reported (RR: 1.05, 95% CI= 0.79-1.40, comparing >14-58 vs. 0-5.1 μg/day) (Asgari, 2009).

Basal cell carcinoma

In the 2005 SLR, the summary OR for 10 μg/day increment was 1.08, 95% CI=1.00-1.17 combining two cohorts (van Dam, 2000 HPFS; Hunter, 1992, NHS).

Table 35 Vitamin D in diet and supplement and skin cancer risk. Results of meta-analysis published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analysis							
Caini, 2014	1 RCT, 1 cohort study, 3 case-control studies	1 678	USA, Italy	Cutaneous melanoma	Highest vs. lowest	1.03 (0.95-1.13)	0%
	1 RCT, 3 cohort studies	4 246	USA, UK	NMSC		0.86 (0.63-1.13)	56%

5.5.10 Vitamin D in supplement

Cohort studies

Summary

No studies were identified in the 2005 SLR and one study (one publication on melanoma) was identified in the CUP (Table 36).

No meta-analysis was conducted.

Malignant melanoma

In the VITAL cohort study, melanoma risk was not associated with 10-year use of individual vitamin D supplements (RR: 1.08, 95% CI= 0.82-1.43 compared with no use) or with 10-year average intake from individual and multivitamin supplements (RR: 1.13, 95% CI= 0.89-1.43, comparing >9.9-30 μg/day vs. none) (Asgari, 2009).

5.5.10 Vitamin D and calcium in supplement

Randomised controlled trial

Summary

No RCTs were identified in the 2005 SLR and one RCT (ad hoc analyses on melanoma and NMSC) was identified in the CUP.

In the Women's Health Initiative calcium/vitamin D randomised controlled trial, postmenopausal women age 50 to 79 years were randomly assigned to receive 1,000 mg of elemental calcium plus 400 IU of vitamin D3 (CaD) daily or placebo for a mean follow-up period of 7 years. NMSC and melanoma were ascertained by annual self-report; melanoma skin cancers were confirmed by medical record review, including pathology reports.

Malignant melanoma

Supplementation of calcium and vitamin D3 did not affect the risk of melanoma (RR: 0.86; 95% CI 0.64- 1.16; 82 cases in the active group and 94 in the placebo group). In subgroup analysis, supplemented women who reported a history of NMSC had lower risk of melanoma than women in the placebo group (RR: 0.43; 95% CI 0.21 - 0.90) but this effect was not seen in women without history of NMSC (RR: 1.02; 95% CI 0.73 to 1.41) ($P_{interaction}$= 0.038) (Tang, 2011; Brunner, 2011).

Non-melanoma skin cancer

Supplementation of calcium and vitamin D3 did not have an effect on self-reported NMSC (RR: 1.02; 95%CI, 0.95- 1.07; 1683 cases in the calcium/vitamin D3 group and 1,655 cases in the placebo group). There was no effect on any of the subgroups examined (by age, BMI, total vitamin D intake, solar radiation, history of cancer, history of melanoma, or history of NMSC (Tang, 2011).

Table 36 Vitamin D, vitamin D (and calcium) and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Randomized controlled trials								
Brunner, 2011 USA	WHI Randomised Control Trial, Age: 50-79 years, W, postmenopausal	60 (placebo), 54 (treatment)/ 18 106 (placebo), 18 176 (treatment)	Self-reported medical history annually verified by medical records	**Supplementation** with 1 000 mg of elemental calcium, 400 IU vitamin D3 or placebo daily for 7 years	Incidence, MM	Treatment vs. placebo	0.91 (0.63-1.32)	Age, treatment assignment
						Treatment vs. placebo (adherent women)	1.09 (0.68-1.73)	
Tang, 2011 USA	WHI Randomised Control Trial, Age: 50-79 years, W, postmenopausal	94 (placebo), 82 (treatment)/ 18 106(placebo), 18 176(treatment)	Self-reported medical history annually verified by medical records, pathology reports	**Supplementation** with 1 000 mg of elemental calcium, 400 IU vitamin D3 or placebo daily for 7 years	Incidence, MM	Treatment vs. placebo	0.86 (0.64-1.16)	Age, treatment assignment
		24 (placebo), 10 (treatment)/			With history of NMSC		0.43 (0.21-0.90)	
		70 (placebo), 72 (treatment)/			No history of NMSC		1.02 (0.73-1.41)	
		1 655 (placebo), 1 683 (treatment)/			NMSC	Treatment vs. placebo	1.02 (0.95-1.07)	
Cohort studies								
Asgari, 2009 USA	VITAL, Prospective	441/ 68 611	Cancer registry	**Total** FFQ	Incidence, MM	>14-58 vs. 0-5.1 µg/day	1.05 (0.79-1.40) Ptrend:0.56	Age, gender, education, 1[a]

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Cohort, Age: 50-76 years, M/W	420/		**Dietary**		>7.1-53 vs. 0-3 µg/day	1.31 (0.94-1.82) Ptrend:0.05	degree family history melanoma, personal history of NMSC, ever had moles removed, freckles between ages 10 and 20 years, had ≥3 severe sunburns between ages 10 and 20 years, natural red/blond hair between ages 10 and 20 years, and reaction to 1-h in strong sunlight; dietary and total intakes additionally adjusted for total energy intake
		450/		**Supplement use,** 10-year use of individual supplements		Former/current vs. none	1.08 (0.82-1.43)	
		450/		10-year average intake from individual and multivitamin supplements		>9.9-30 µg/day vs. none	1.13 (0.89-1.43) Ptrend:0.36	
Davies, 2002 SKI00989 UK	EPIC-Norfolk, Nested Case Control, Age: 65 (W), 67.8 (M),	109/ 356	East Anglian Cancer Registry	**Dietary** Validated self-reported 7-day food diary	Incidence, BCC	Per 2.08 µg/day	1.068 (0.845-1.348)	BMI, red hair colour, dietary component

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M/W							
van Dam, 2000 SKI01672 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, health professionals	3 190/ 43 217	Family members, co-workers, postal authorities, National Death Index	**Total** Validated 131-item FFQ	Incidence, BCC	752 vs. 98 IU/day	1.10 (0.94-1.30) Ptrend:0.63	2 year follow-up periods, carotenes, folate, frequency of physical examinations, hair colour, major ancestry, mean solar radiation, retinol, smoking habits, vitamin C, vitamin E
Hunter, 1992 SKI03249 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	771/ 73 366	Self-report verified by medical records	**Dietary** Semi-quantitative FFQ	Incidence, BCC	288.5 vs. 45.2 IU/day	1.02 (0.81-1.27) Ptrend:0.57	Age, area of residence, BMI, childhood tendency to sunburn, contemporary date, hair colour, lifetime number severe sunburns, UV exposure
				Total		601.2 vs. 53.6 IU/day	1.08 (0.86-1.35) Ptrend:0.18	

5.5.18 Multivitamins supplement

Randomised controlled trials

Summary

No studies were identified in the 2005 SLR and three studies (four publications on skin cancer, melanoma, NMSC, BCC, SCC) were identified in the CUP.

No meta-analysis was conducted due to insufficient number of studies. The study characteristics and results are described and tabulated.

Skin cancer

SU.VI.MAX was a randomised, double-blind, placebo-controlled trial on the effect of antioxidant and mineral supplementation on the incidence of cancer and ischemic cardiovascular disease in the general population (a single daily capsule of a combination of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 μg of selenium, and 20 mg of zinc, or a placebo; median follow-up time was 7.5 years). A total of 157 cases of skin cancer were identified. There was no statistically significant effect of supplementation on skin cancer risk in men (RR: 0.69; 95% CI= 0.43-1.10), an increased risk of skin cancer was observed in supplemented women (RR: 1.68; 95% CI= 1.06-2.65) (Hercberg, 2007).

Malignant melanoma

A large randomised, double-blind, placebo-controlled trial of multivitamin supplementation with median follow-up of 11.2 years enrolled 14 641 male physicians from which 1 312 men had history of skin cancer (PHS II study). No statistically significant effect on malignant melanoma risk was observed (RR: 1.12; 95% CI= 0.85-1.47, 108 cases in the treatment arm and 96 cases in the placebo group). After excluding participants with history of skin cancer, the results did not change substantially (RR of melanoma: 1.12; 95% CI= 0.84-1.49, 100 cases in the treatment arm and 89 cases in the placebo group) (Gaziano, 2012). Mortality for melanoma was lower (but the difference was statistically non-significant) in supplemented participants (RR: 0.91; 95% CI= 0.37-2.25, 9 cases in the treatment arm and 10 cases in the placebo group).

In the SU.VI.MAX trial, a statistically non-significant reduction of melanoma incidence among men (RR: 0.49; 95% CI= 0.12-1.97, 3 cases in the treatment arm and 6 cases in the placebo group) and a statistically significant increase among women (RR: 4.31; 95% CI=1.23-15.13, 13 cases in the treatment arm and 3 cases in the placebo group) were observed (Hercberg, 2007). In a subsequent analysis five years after 7.5 years of treatment (12.5 years total) there was no evidence of a residual or delayed effect of antioxidant supplementation on risk of melanoma in men and women (RR: 1.15; 95% CI=0.31-4.27, 8 cases in the treatment arm and 10 cases in the placebo group; RR: 0.64; 95% CI= 0.18-2.27, 17 cases in the treatment arm and 9 cases in the placebo group, respectively) (Ezzedine, 2010). These results are not directly comparable with those reported in the earlier publication from SU.VI.MAX, described above, due to additional adjustments for sunburn during childhood, phototype, and self-assessed lifetime sun exposure in the 2010 manuscript.

Non-melanoma skin cancer

The SU.VI.MAX trial reported a statistically non-significant reduction in non-melanoma skin cancer incidence among men and a statistically significant increase among supplemented women in the antioxidant and mineral supplementation group (RR: 0.72; 95% CI= 0.44-1.18, 38 cases in the treatment arm and 27 cases in the placebo group; RR: 1.37; 95% CI=0.83-2.28, 30 cases in the treatment arm and 37 cases in the placebo group, respectively (Hercberg, 2007).

In the MRC/BHF Heart Protection double-blind placebo randomized trial there was no effect of 5-year treatment with 600 mg synthetic vitamin E, 250 mg vitamin C, and 20 mg b-carotene daily (Heart protection study collaborative group, 2002).

Basal cell carcinoma

Antioxidant supplementation in the SU.VI.MAX trial had no effect on BCC in men and women (RR: 1.22; 95% CI= 0.64-2.33, 47 cases in the treatment arm placebo groups each; RR: 0.70; 95% CI= 0.48-1.65, 53 cases in the treatment arm and 45 cases in the placebo group, respectively) in analysis five years after the 7.5 years of treatment (12.5 years total) (Ezzedine, 2010).

Squamous cell carcinoma

Antioxidant supplementation in the SU.VI.MAX trial had no effect on SCC (RR: 1.38; 95% CI= 0.49-3.84, 13 cases in the treatment arm and 12 cases in the placebo group in men; RR: 0.95; 95% CI= 0.19-4.67, 6 cases in the treatment arm and 4 cases in the placebo group in women) in analysis five years after the 7.5 years of treatment (12.5 years total) (Ezzedine, 2010).

Cohort studies

Summary

Nine publications from five studies (on melanoma, BCC and SCC) were identified in the 2005 SLR and two publications from one study (on melanoma) were identified in the CUP.

No meta-analysis was conducted due to insufficient number of studies. The study characteristics and results are described and tabulated.

Malignant melanoma

The VITAL cohort study (566 cases) reported a positive statistically non-significant association of multivitamin use and melanoma (RR: 1.16; 95% CI= 0.97-1.39) (Asgari, 2012). Similar results were observed in men (286 cases) and women (165 cases) (RR: 1.05; 95% CI= 0.82-1.34, p-trend=0.67; RR: 1.04; 95% CI= 0.73-1.48, p-trend= 0.85, respectively) (Asgari, 2009).

Multivitamin supplementation was not associated with melanoma in the NHS and NHS II (RR for current users compared to never users: 1.02; 95% CI= 0.82-1.28, 411 cases) (Feskanich, 2003).

A nested case-control study (23 cases) in Maryland, USA reported that users of multivitamin supplements had 2.5 times higher odds of melanoma compared to non-users with a p-value= 0.22 (Cornwell, 1992).

Basal cell carcinoma

The NHS study with 12 years of follow-up of female registered nurses found a statistically non-significant positive association of multivitamin supplementation and BCC, RR: 1.10; 95% CI= 1.00-1.10, 5 392 cases (Fung, 2002b). No association was reported in a previous publication (771 cases, 4 years of follow-up, data not shown in the publication)(Hunter, 1992).

A positive association of high level of multivitamin supplement use with BCC (3 190 cases) was reported in the HPFS study (8 years of follow-up). The multivariate RRs for past multivitamin use and weekly use of < 5, 6–9, and > 9 multivitamin pills were 1.04, 1.03, 1.08, and 1.34 (95% CI: 1.16, 1.55), respectively compared with nonusers.

In a prospective cohort study from Arizona in people with moderate sun-damage and no history of skin cancer, multivitamin supplement use was not related to BCC after 5 years of follow up, compared to daily use (RR: 1.13; 95% CI= 0.78-1.64, 144 cases) (Foote, 2001).

Squamous cell carcinoma

No association between multivitamins intake and SCC risk was identified in a large study using data from the NHS and HPFS cohorts (data not shown in the publication) (Fung, 2003).

In a prospective cohort study from Arizona in people with moderate sun-damage and no history of skin cancer, multivitamin supplement use was not related to SCC after 5 years of follow up, compared to daily use (RR: 1.02; 95% CI= 0.65-1.60) (Foote, 2001).

Table 37 Multivitamin use and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Randomized controlled trial								
Gaziano 2012, USA	PHS II, Randomised Control Trial, Age: ≥50 years, M, Physicians	108 (treatment), 96 (placebo)/ 7 238 (treatment), 7 245 (placebo)	Medical record review	**Supplementation** multivitamin daily (Centrum Silver)	Incidence, MM	Treatment vs. placebo	1.12 (0.85-1.47)	Age, PHS cohort, randomised treatment assignment (beta carotene, vitamin E, and vitamin C), and stratified on baseline cancer
		9 (treatment), 10 (placebo)/ 7 317 (treatment), 7 324 (placebo)	Death certificate		Mortality, MM		0.91 (0.37-2.25)	
Ezzedine 2010, France	SU.VI.MAX, Randomised Control Trial M/W, Age: 51/46 years	10 (treatment), 8 (placebo)/ 2 569 (treatment), 2 572 (placebo), 12.5 years (7.5 y. treatment and 5 y. follow-up)	Histopathology report or other medical record review	**Supplementation** 120 mg vitamin C, 30 mg vitamin E, 6 mg b-carotene, 100 µg selenium and 20 mg zinc in a single daily oral capsule	Incidence, MM, men	Treatment vs. placebo	1.15 (0.31–4.27)	Age, smoking status, dwelling latitude, sunburn during childhood, phototype, self-assessed lifetime sun exposure on the outcomes
		9 (treatment),			Women		0.64 (0.18–2.27)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		17 (placebo)/ 3 912 (treatment), 3 964 (placebo)						
		47 (treatment), 47 (placebo)/			Incidence, BCC, men		1.22 (0.64–2.33)	
		45 (treatment), 53 (placebo)/			Women		0.70 (0.48–1.65)	
		12 (treatment), 13 (placebo)/			Incidence, SCC, men		1.38 (0.49–3.84)	
		6 (treatment), 4 (placebo)/			Women		0.95 (0.19–4.67)	
Hercberg 2007, France	SU.VI.MAX, Randomised Control Trial M/W, Age: 51/46 years	33 (treatment), 43 (placebo)/ 2 569 (treatment), 2 572 (placebo), 7.5 years	Histopathology report or other medical record review	**Supplementation** 120 mg vitamin C, 30 mg vitamin E, 6 mg b-carotene, 100 µg selenium and 20 mg zinc in a single daily oral capsule.	Incidence, SCC, men	Treatment vs. placebo	0.69 (0.43-1.10)	Age, current smoking, dwelling latitude
		51 (treatment), 30 (placebo)/ 3 912 (treatment), 3 964 (placebo)			Women		1.68 (1.06-2.65)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		3 (treatment), 6 (placebo)/			Incidence, MM, men		0.49 (0.12-1.97)	
		13 (treatment), 3 (placebo)/			Women		4.31 (1.23-15.13)	
		30 (treatment), 37 (placebo)/			Incidence, NMSC, men		0.72 (0.44-1.18)	
		38 (treatment), 27 (placebo)/			Women		1.37 (0.83-2.28)	
Heart protection study collaborative group, 2002, UK	MRC/BHF Heart Protection Study, Randomised Control Trial, Age: 40-80 years, M/W Patients with coronary disease, other occlusive arterial disease, or diabetes	271 (treatment), 228 (placebo)/ 10 269 (treatment), 10 267 (placebo), 5 years	Follow-up checks in the study clinics, subjects' general practitioners, UK national cancer and death registries.	**Supplementation** 600 mg synthetic vitamin E, 250 mg vitamin C, and 20 mg b-carotene daily	Incidence, NMSC	Treatment vs. placebo	Event rate ratio read from graph: 0.95 (0.80-1.15)	
Cohorts								
Asgari 2012, USA	VITAL, Prospective	566/ 69 635,	Through linkage with SEER	**Supplement** Self-administered	Incidence, MM	Current vs. never	1.16 (0.97–1.39)	Age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	cohort, Age: 50-76 years M/W	5.84 years		questionnaire				
Asgari 2009, USA	VITAL, Prospective cohort, Age: 50-76 years M/W	451/ 286 (men)/ 165 (women)/ 69 671, 5 years	Through linkage with SEER	**10-y use of multivitamins** Self-administered questionnaire	Incidence, MM, men	Current vs. never	1.05 (0.82-1.34) 0.67	Age at baseline, sex (unless stratified by sex), education, first-degree family history of melanoma, history of NMSC skin cancer, ever had moles removed, freckles between ages 10 and 20 years, 3 or more severe sunburns between ages 10 and 20 years, natural red or blond hair between ages 10 and 20 years, skin reaction to 1 hour in strong sunlight
				Overall use	Women		1.04 (0.73-1.48) 0.85	
					Men and Women		1.04 (0.85-1.27) 0.65	
				Duration	Incidence, MM, men	≥7 vs. 0 years	1.04 (0.80-1.35) 0.57	
					Women		1.08 (0.75-1.56) 0.79	
					Men and women		1.05 (0.85-1.30) 0.55	
				Pill-years	Incidence, MM, men	≥50 vs. 0	1.09 (0.83-1.43) 0.58	
					Women		1.14 (0.78-1.66) 0.58	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Men and women		1.11 (0.89-1.38) 0.44	
				Lifetime use of multivitamins (since age 21 y) Self-administered questionnaire	Incidence, MM, men	≥15 vs. 0 years	1.08 (0.79-1.48) 0.30	
					Women		1.01 (0.68-1.51) 0.73	
					Men and women		1.07 (0.84-1.37) 0.30	
Feskanich, 2003 SKI00696, USA	NHS and NHS-II, Two prospective Cohorts, Age: 25-77 years, W,	414/ 73 432 (NHS); 88 541 (NHS II), >1.6 million person-years	Self-report followed by medical records review	**Supplement** FFQ	Incidence, MM	Current vs. never	1.02 (0.82-1.28)	Age, area of residence, BMI, family history of specific cancer, follow-up cycle, hair colour, height, menopausal status, number of moles, number of sunburns, oral contraceptive use, parity, post-menopausal hormone use, skin reaction
Fung 2003, SKI00818, USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years,	674/ 129 811, 14 years max	Self-report followed by medical records review	**Supplement** FFQ	Incidence, SCC	-		-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M/W, Female nurses and Male Health Professionals							
Fung 2002, SKI01012, USA	NHS, Prospective Cohort, Age: 30-55 years, W, Female nurses	5 392/ 85 836, 951 823 person-years	Self-report	**Supplement** FFQ repeated every 2-4 years	Incidence, BCC	Users vs. non-users	1.10 (1.00-1.10)	Age, ancestry, area of residence, BMI, beer consumption, childhood sun exposure, energy intake, eye colour, hair colour, liquor, missing FFQ, red wine, smoking habits, tendency to burn in childhood, white wine
Foote 2001, SKI07414, USA	Arizona USA 1985-1992, Prospective Cohort, Age: 21-85 years, M/W, Moderately Sun-damaged	144/ 918 57 months	Clinical assessments, pathological diagnoses, active follow-up between visits	**Supplement** Any supplement use, Questionnaire	Incidence, BCC	Never vs. daily	1.13 (0.78-1.64)	Age
					Incidence, SCC		1.02 (0.65-1.60)	
Van Dam 2000, SKI01672, USA	HPFS, Prospective Cohort, Age: 40-75 years,	3 190/ 43 217, 308 071 person-years	Self-report, next of kin, coworkers, postal	**Supplement** FFQ	Incidence, BCC	≥9 tablets/week vs. non users	1.34 (1.16-1.55)	Age, 2 year follow-up periods, energy intake, frequency of physical

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M, Health professionals		authorities, National Death Index					examinations, hair colour, major ancestry, mean solar radiation, smoking habits
Cornwell 1992, SKI03257, USA	Maryland USA 1974-1975, Nested Case Control, M/W	23/ 46	Mass campaign	**Supplement** Questionnaire	Incidence, MM	yes vs. no	2.50 Ptrend:0.22	Not known, partially adjusted
Hunter, 1992 SKI03249 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	771/ 73 366, 4 years max	Self-report	**Supplement** FFQ	Incidence, BCC	-	-	-

5.5.19 Folate, pyridoxine (B_6) and cobalamin (B_{12}) in supplement

Randomised control trials

Summary

No RCTs were identified in the 2005 SLR. Three RCTs (three publications) on combinations of folic acid, B6 and B12 supplements and a pooled analysis of RCT on folic acid or combinations with vitamin B on melanoma risk were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

The three RCTs tested treatments consisting of combinations of folic acid, vitamin B6, and vitamin B12: a daily dose of 2, 25 and 0.5 mg, respectively, in the VITATOPS trial (Hankey, 2012); and 2.5, 50 and 1 mg, respectively, in both the WAFACS (Zhang, 2008) and HOPE 2 trials (Loon, 2006). No statistically significant effects on melanoma were observed compared to placebo administration. The RR were 0.43 (95% CI= 0.09-2.08) in the VITATOPS study after treatment for a median of 3.4 years (Hankey, 2012); RR: 1.00 (95%CI= 0.20-4.96) in the WAFACS study after treatment for up to 7.3years (Zhang, 2008); and RR: 0.42 (95% CI= 0.15–1.19) in the HOPE 2 study after an average of 5 years of intervention.

The three RCTs were combined in a published meta-analysis (Zhang, 2016) that reported a summary of folic acid and vitamins B supplementation on melanoma risk (RR: 0.47; 95% CI= 0.23–0.94; 12 and 26 cases in the treatment and placebo groups respectively).

A pooled analysis of 13 placebo-controlled RCTs of folic acid supplementation (0.5-5 mg/day for an average of 5.2 years) – mostly in combination with vitamins B_6 and/or B_{12} – and cancer incidence, included 64 cases of melanoma identified in the treatment arm and 62 cases in the placebo arm in 11 of the RCT (Vollset, 2013). The RCT in the meta-analysis by Zang, 2016 were also included in the pooled analysis. Folic acid had no effect on melanoma risk (summary RR: 1.04 (95% CI=0.66–1.64)

Table 38 Folate, pyridoxine (B6) and cobalamin (B12) in supplement and MM risk. Results of meta-analyses of randomised control trials published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analysis							
Zhang, 2016	3 randomised control trials	12 /26	Multiple countries over 5 continents – mainly USA, Canada, Australia, India and UK	MM	Treatment vs. placebo	0.47 (0.23–0.94)	0.575
Pooled-analysis							
Vollset, 2013*	13 randomised control trials (11 trials contributed cases)	126	Multiple countries over 5 continents – mainly USA, Canada and Europe	MM	Folate alone or in combination with vitamin B_6 and/or B_{12} vs. placebo	1.04 (0.66–1.64)	0.23 (any first cancer incidence; MM-specific value not given)

Note: All randomised control trials included in the meta-analysis (Zhang, 2016) were identified in the present review.

*Folic acid doses ranged from 0.5-5 mg/day and many trials included vitamins B_6 and/or B_{12} in combination with folic acid.

Table 39 Folate, pyridoxine (B6) and cobalamin (B12) in supplement and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Hankey 2012, 20 countries over 5 continents – mainly Australia, India and UK	VITATOPS, Randomised Control Trial, Age: 62.6 years, M, History of recent stroke or transient ischemic attack	4 (treatment), 11 (placebo)/ 4 089 (treatment), 4 075 (placebo), 3.4 years	Self-report of adverse events, attempted to be verified by hospital records or family physicians	**Supplementation** 2 mg folic acid, 25 mg vitamin B6, 500 µg vitamin B12 daily	Incidence, MM	Treatment vs. placebo	0.43 (0.09-2.08)	Not stated ("any potential imbalance in baseline characteristics and follow-up between the 2 groups")
Zhang 2008, USA	WAFACS, Randomised Control Trial, Age: ≥42 years, W, Health professionals previously randomised to treatment with either vitamin C, vitamin E or beta carotene	3 (treatment), 3 (placebo)/ 2 721 (treatment), 2 721 (placebo), 7.3 years	Self-report or deaths reported by next of kin, postal authorities, National Death Index; permission sought to obtain medical records, further reviewed by an end points committee of physicians blinded to randomisation	**Supplementation** 2.5 mg folic acid, 50 mg vitamin B6, 1000 µg vitamin B12 daily	Incidence, MM	Treatment vs. placebo	1.00 (0.20-4.96)	Age and previous randomised treatment assignment of either vitamin E, vitamin C, and beta carotene

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Lonn 2006, 13 countries over 3 continents – mainly Canada and USA	HOPE 2, Randomised Control Trial, M/W, Age: ≥55 years, history of vascular disease, diabetes, additional risk factors for atherosclerosis	5 (treatment), 12 (placebo)/ 2 758 (treatment), 2 764 (placebo), 5 years	Pathology reports	**Supplementation** 2.5 mg folic acid, 50 mg vitamin B6, 1000 µg vitamin B12 daily	Incidence, MM	Treatment vs. placebo	0.42 (0.15–1.19)	None

5.6.4 Selenium in diet

Cohort studies

Summary

Two studies (two publications on BCC) were identified in the 2005 SLR and one publication on BCC and SCC was identified in the CUP (Table 42).

No meta-analysis was conducted.

Basal cell carcinoma

Dietary selenium was not related to BCC risk in a follow-up study in an Australian cancer prevention trial (NSCS, Heinen, 2007) (RR: 0.95, 95% CI= (0.59-1.50), comparing 99.1 vs. 70.1 µg/day, 321 BCC tumours in 149 participants) after 8 years of follow- up. Opposite associations (statistically non-significant) were observed in the group of participants with no history of skin cancer (RR for highest vs. lowest tertile: 0.49, 95% CI= 0.20-1.20, 658 cases) and with skin cancer history (RR: 1.10, 95% CI= 0.59-1.90, 311 cases). No association was reported in a previous publication of the NSCS (McNaughton, 2005).

Dietary selenium was not related to BCC in the EPIC-Norfolk study (RR for 20 µg/day increment: 1.07, 95% CI= 0.86-1.34) (Davies, 2002).

Squamous cell carcinoma

Dietary selenium was statistically non-significantly positively related to SCC in an Australian study including 221 SC tumours in 116 participants (RR for 99.1 vs. 70.1 µg/day: 1.30, 95% CI=0.77-2.30) (Heinen, 2007). Similar estimates were reported in participants with no skin cancer history (n=646) RR: 1.20, 95% CI= (0.34-4.50) and in participants with skin cancer history (n=294), RR: 1.30, 95% CI= (0.71-2.40), comparing Q3 vs. Q1.

5.6.4 Selenium in blood

Cohort studies

Summary

Five studies (six publications on skin cancer, melanoma, BCC and SCC) were identified in the 2005 SLR and no new studies (one publication on BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Skin cancer

In the Evans County Study, 26 skin cancer cases were identified but no risk estimate was reported (Peleg, 1985).

Malignant melanoma

No association was reported in the Maryland USA study (30 cases) (RR: 0.90, 95% CI= 0.30-2.50 for the highest vs. lowest comparison) (Breslow, 1995) and in a Finnish study (the unadjusted risk estimate was 0.79, statistically non-significant) (Knekt, 1991).

Basal cell carcinoma

In an Australian study, selenium in blood was inversely associated with BCC risk (RR: 0.43, 95% CI= 0.21-0.86) (van der Pols, 2009) in the tumour-based analysis, but not in the person-based analysis (RR: 0.58, 95% CI= (0.32-1.07), comparing 1.4 vs. 0.9 μmol/L (NSCS, van der Pols, 2009). In the Maryland USA study (32 cases), the association was inverse but statistically non-significant, RR: 0.80, 95% CI= (0.10-4.5) (Breslow, 1995). In the FMCHES, a statistically non-significant association was reported in men (R: 0.54) and women (RR: 1.55) (Knekt, 1990b).

Squamous cell carcinoma

In the NSCS study (59 cases), a statistically significant inverse association was reported in the tumour based as well as person-based analyses, RR: 0.36, 95% CI= 0.15-0.82 and RR: 0.49, 95% CI= (0.24-0.99), comparing 1.4 vs. 0.9 μmol/L, respectively (van der Pols, 2009).

Statistically non-significant inverse associations were reported in the SKICAP study (119 cases), RR: 0.67, 95% CI= (0.35-1.29) (Karagas, 1997) and in the Maryland USA study (37 cases), RR: 0.60, 95% CI= (0.20-1.50) (Breslow, 1995).

5.6.4 Selenium in supplements

Randomised controlled trials

Summary

One RCT (three publications on melanoma, BCC) were identified in the 2005 SLR. Two new RCTs (three publications on skin cancer, melanoma, NMSC, BCC, and SCC) were identified in the CUP (Table 42).

The Negative Biopsy Trial (NBT) was a randomized, double-blind clinical placebo controlled trial conducted in United States and New Zealand to investigate the effect on prostate cancer incidence of daily supplementation with 200 μg/day or 400 μg/day of selenium for up to five years (Algotar, 2013).

NPC Trial was performed among residents of low-selenium areas in the Eastern USA. The trial included persons with a history of NMSC. Eligible persons had a history of >= 2 BCCs or 1 SCC with at least 1 carcinoma having occurred within the year preceding randomisation. Participants were randomised to receive 200 mcg selenium supplied in a 0.5-g-high-selenium baker's yeast tablet daily or a placebo.

A small, multicentre, randomised, placebo-controlled, parallel group study in 184 recent organ transplant recipients treated for 3 years with 200 mug/day selenium (91 patients) or a matching placebo (93 patients), tested supplementation effect on warts and various keratoses (main criterion) and skin cancer risk (secondary criterion).

Skin cancer

In the organ transplant patients' study, supplementation had no effect on skin cancer risk (OR: 3.08, p value=0.15) (Dreno, 2007).

Malignant melanoma

In the NBT trial, no effect of selenium supplementation on melanoma risk was observed (p value: 0.87) (Algotar, 2013).

In the NPC trial, in the period 1983-1996, 11 melanoma cancer cases were identified in the selenium group against the 9 in the placebo group (RR: 1.18, 95% CI= (0.49-2.85) (Duffield-Lillico, 2002).

Non-melanoma skin cancer

In a substudy in the NPC trial, after approximately 6 years of intervention, the group receiving 200 μg/day of selenium experienced an increase in NMSC incidence (RR: 1.5, 95% CI = 1.13–2.04, p <.006), whereas there was no evidence of NMSC increase in the group receiving 400 μg/day of selenium (RR: 0.91; 95% CI= 0.69–1.20), in comparison with the placebo group. There was little evidence that baseline selenium status modified the effect of the treatment with 400 μg/day . The increase in NMSC incidence was observed among participants at all levels of selenium status and treated with 200 μg/day. (Reid, 2008).

Basal cell carcinoma

In the NBT trial, there was no effect of selenium supplementation on BCC (p value: 0.82) (Algotar, 2013).

In a substudy in the NPC trial, a statistically non-significant increased risk of BCC was observed in the 200 µg/day treated group (RR: 1.22, 95% CI= 0.88-1.70) but not in the 400 µg/day group (RR: 0.95, 95% CI= 0.69-1.29).

Squamous cell carcinoma

In the NBT trial, there was no effect of selenium supplementation on SCC (p-value: 0.002) (Algotar, 2013).

In the substudy in the NPC trial, an increased risk of SCC was observed in the 200 µg/day treated group (RR: 1.88, 95% CI= 1.28-2.79) but not in the 400 g/day group (RR: 1.05; 95% CI: 0.72–1.53)

Cohorts

Summary

One study was identified in the CUP.

Malignant melanoma

In the VITAL cohort study, inverse but no association was reported (RR: 0.98, 95% CI=0.69-1.41) when comparing intake of ≥50 µg/day vs. none (Asgari, 2009).

Table 40 Selenium from supplements and NMSC risk. Results of meta-analyses of randomised control trials published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Vinceti, 2014	3 randomised control trials	-	USA, New Zealand, France	NMSC	Highest vs. lowest	1.44 (0.95-2.17)	15%

Note: All randomised control trials were identified in the present review.

5.6.4 Selenium in toenail (& fingernail)

Cohorts

Summary

One study on melanoma was identified in the 2005 SLR and none were identified in the CUP (Table 42).

Malignant melanoma

In the Nurses' Health Study (63 cases), positive but statistically non-significant association of nail selenium and melanoma was reported, RR: 1.66, 95% CI= (0.71-3.85), comparing highest vs. lowest quantiles (Garland, 1995).

Table 41 Circulating, toenail selenium or selenium supplement and skin cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Cai, 2016	2 cohort studies and 2 randomised control trials	-	USA, Finland	All types of skin cancer combined	Highest vs. lowest	1.09 (0.98-1.21)	0%

Note: Studies on circulating, toenail selenium or selenium supplement combined.

Table 42 Blood, total, dietary or supplemental selenium and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Algotar, 2013 USA and New Zealand	NBT, Randomised Control Trial, Age: <80 years, M, subjects at high risk of prostate cancer	2 (placebo), 3 (treatment)/ 232 (placebo), 234 (200 µg/day), 233 (400 µg/day) 5 years max	Follow-up every 6 months	**Supplementation** with 200 µg or placebo daily	MM	Treatment vs. placebo	Fisher exact test Pvalue:0.87 (for comparison of three treatments: placebo, 200 µg and 400 µg selenium)	-
		2 (placebo), 2 (treatment)/		400 µg or placebo				

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		15 (placebo), 13 (treatment)/		200 µg or placebo	BCC		Pvalue:0.82(for comparison of three treatments: placebo, 200 µg and 400 µg selenium)	
		15 (placebo), 12 (treatment)/		400 µg or placebo				
		17 (placebo), 10 (treatment)/		200 µg or placebo	SCC		Pvalue:0.002 (for comparison of three treatments: placebo, 200 µg and 400 µg selenium)	
		17 (placebo), 2 (treatment)/		400 µg or placebo				
Asgari, 2009 USA	VITAL, Prospective Cohort Study, Age: 50-76 years M/W	460/ 69 274	Through linkage with SEER	**Supplement** Self-administered questionnaire	Incidence, MM	≥50 µg/day vs. none	0.98 (0.69-1.41) Ptrend:0.98	Age, gender, education, 1st degree family history of melanoma, personal history of NMSC, ever had moles removed, freckles between ages 10-20 years, had ≥3 severe sunburns between ages 10-20 years, natural red/blond

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								hair between ages 10-20 years, reaction to 1-hour in strong sunlight
van der Pols JC, 2009 SKI23427 Australia	NSCS, Nested Case Control, M/W	77 cases/ 562 8 years	Biennial follow-up questionnaires, histological reports	**Serum** selenium was analysed by atomic absorption spectrometry using a graphite furnace and Zeeman background correction	BCC (person-based incidence)	1.4 vs. 0.9 µmol/L	0.58 (0.32-1.07)	Age, sex, alcohol intake, pack years of smoking, time spent outdoors on weekends, history of skin cancer
		59 tumours/ 544			BCC (tumour-based incidence)		0.43 (0.21-0.86)	
		59 cases/ 544			SCC (person-based incidence)		0.49 (0.24-0.99)	
		59 tumours/ 544			SCC (tumour-based incidence)		0.36 (0.15-0.82)	
Reid, 2008 USA	NPC, Randomised Control Trial, M/W	108 (placebo), 98 (treatment)/ 213 (placebo), 210 (400 µg/day) Up to 6 years intervention	Medical records	**Supplementation** with 400 µg Se yeast or placebo daily	Incidence, NMSC	Treatment vs. placebo (Macon)	0.91 (0.69-1.20)	Age, smoking, gender
		83 (placebo), 76 (treatment)/			BCC		0.95 (0.69-1.29)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		53 (placebo), 56 (treatment)/			SCC		1.05 (0.72-1.53)	
		80 (placebo), 99 (treatment)/ 161 (placebo), 154 (200 µg/day)		**Supplementation** with 200 µg Se yeast or placebo daily	Incidence, NMSC	Treatment vs. placebo (Macon)	1.50 (1.13-2.04)	
		69 (placebo), 75 (treatment)/			BCC		1.22 (0.88-1.70)	
		42 (placebo), 65 (treatment)/			SCC		1.88 (1.28-2.79)	
		336 (placebo), 367 (treatment)/ 468 (placebo), 467 (200 µg/day)		**Supplementation** with 200 µg Se yeast or placebo daily	Incidence, NMSC	Treatment vs. placebo (other sites)	1.18 (1.02-1.37)	
		305 (placebo), 332 (treatment)/			BCC		1.12 (0.96-1.31)	
		154 (placebo), 179 (treatment)/			SCC		1.18 (0.95-1.46)	
Dreno, 2007 France	Randomised Control Trial, M/W,	2 (placebo), 6 (treatment)/ 93 (placebo), 91	Follow-up examinations	**Supplementation** with 200 µg selenium or	Incidence Skin cancer	Treatment vs. placebo	3.08 Pvalue:0.15	-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	kidney, liver or heart transplant patients	(treatment), 3-years of supplementation and 2 years of monitoring		placebo daily				
Heinen, 2007 Australia	NSCS, Follow-up of skin cancer trial participants, Age: avg. between 53-65 years, M/W	116 (221 tumours)/ 1 001 8 years	Questionnaires, confirmed through histological reports	**Dietary** 129-item semi-quantitative FFQ	Tumour-based incidence, SCC	99.1 vs. 70.1 µg/day	1.30 (0.77-2.30) Ptrend:0.47	Additionally adjusted for tanning ability of skin
		646 participants			No skin cancer history		1.20 (0.34-4.50)	
		294 participants			With skin cancer history		1.30 (0.71-2.40)	
		149 (321 tumours)			Tumour-based incidence BCC		0.95 (0.59-1.50) Ptrend:0.81	Age, sex, energy intake, skin colour, elastosis of the neck, number of painful sunburns, smoking, treatment allocation, use of dietary supplements, history of skin cancer
		658 participants			No skin cancer history		0.49 (0.20-1.20)	
		311 participants			With skin cancer history		1.10 (0.59-1.90)	
McNaughton, 2005 SKI22177 Australia	NSCS, Nested Case Control, Age: 55 years	90/ 180	Through participants, their doctors and pathology	**Dietary** 129-item semi-quantitative FFQ	Incidence, BCC	Q 4 vs. Q 1	1.13 (0.47-2.74)	Age, sex, supplement use, total energy intake
						Linear trend	1.05 (0.79-1.39)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M/W		laboratories					
				Serum selenium measured by atomic using Zeeman background correction		Q 4 vs. Q 1	0.86 (0.38-1.96)	Age, sex
						Linear trend	0.96 (0.74-1.24)	
		No subjects reported consuming supplement		**Supplement** use		-	-	-
Davies, 2002 SKI00989 UK	EPIC-Norfolk, Nested Case Control, Age: 65 (W), 67.8 (M) years M/W	109/ 1 976	Cancer registry	**Dietary** Self-reported 7-day food diary	Incidence, BCC	Per 20 µg/day	1.07 (0.86-1.34)	BMI, hair colour, dietary components
Duffield-Lillico, 2002 SKI00967 USA	NPC, Randomised Control Trial, Age: 63 years M/W, history of NMSC living in low selenium area	9 (placebo), 11 (treatment)/ 629 (placebo), 621 (treatment), 7.4 years (1983-1996)	Dermatologic examinations	**Supplementation** with 200 µg selenium or placebo daily	Incidence, MM	Treatment vs. placebo	1.18 (0.49-2.85) Ptrend:0.71	Age, sex, smoking habits
Combs, 1997	NPC,	/727	Dermatologic	**Supplementation**	Recurrent	Treatment	1.10	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
SKI02287 USA	Randomised Control Trial, M/W, history of NMSC living in low selenium area	(1983/1990-1993) /408	examinations	with 200 µg selenium or placebo daily	BCC	vs. placebo	Ptrend:0.2	
					SCC		1.14 Ptrend:0.15	
Karagas, 1997 SKI02443 USA	SKICAP, Nested Case Control, Age: 35-84 years, M/W, History > 1 BCC or SCC	119/ 349 5 years	Questionnaire every 4 months and annual dermatological examination	**Plasma** selenium measured using instrumental neutron activation analysis	Incidence, SCC	>0.14 vs. ≤0.12 ppm	0.67 (0.35-1.29) Ptrend:0.25	Age, sex, study centre (matching factors), adjusted for smoking habits
		131/ 392			Any SCC		0.86 (0.47-1.58) Ptrend:0.89	
Clark, 1996 SKI02483 USA	NPC, Randomised Control Trial, Age: 18-80 years, M/W, history of NMSC living in low selenium area	16/ 4.5 years of supplementation and a total of 6.4 years of follow-up (1983-1991)	Dermatologic examinations	**Supplementation** with 200 µg selenium or placebo daily	Incidence, MM	Treatment vs. placebo	0.92 (0.34-2.45) Ptrend:0.87	Age, sex, smoking habits
		350 (placebo), 377 (treatment)/			Incidence, BCC		1.10 (0.95-1.28) Ptrend:0.2	
		190 (placebo), 218 (treatment)/			SCC		1.14 (0.93-1.39) Ptrend:0.15	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Breslow, 1995 SKI02677 USA	Maryland USA 1974-1975, Nested Case Control, Age: 18- years, M/W	30/ 25 620	-	**Plasma** selenium measured using instrumental neutron activation analysis	Incidence, MM	Q 3 vs. Q 1	0.90 (0.30-2.50)	Adjustment for smoking, education, hours since last meal did not substantially change the results
		32/			BCC		0.80 (0.10-4.5)	
		37/			SCC		0.60 (0.20-1.50) Ptrend:0.23	
Garland, 1995 SKI02826 USA	NHS, Nested Case Control, Age: 30-55 years, W, nurses	63/ 62 641 3.4 years	Follow-up questionnaires, death certificates	**Toenail** selenium	Incidence, MM	Q 3 vs. Q 1	1.66 (0.71-3.85) Ptrend:0.21	Smoking habits
Knekt, 1991 SKI03576 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	10/ 28	Finnish cancer registry	**Serum** selenium was measured using electrothermal atomic absorption spectrometric method	Incidence, MM	Per standard deviation increase	0.79 Ptrend:0.68	Unadjusted
Knekt, 1990b SKI22126 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	64/ 39 268 10 years	Finnish cancer registry	**Serum** selenium was measured using graphite furnace atomic absorption spectrometric method	Incidence, BCC, men	≥78 vs. <49 µg/litre	0.54 Ptrend:0.43	Smoking habits
		62/			Women		1.55 Ptrend:0.74	
		54/			Incidence, BCC, men; cases	≥48 vs. ≤49 µg/litre	0.86 (0.35-2.12)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					diagnosed > 2 years follow-up			
		52/			Women; cases diagnosed > 2 years follow-up		1.54 (0.64-3.73)	
Peleg, 1985 SKI23393 USA	Evans County Study, Nested Case Control, Age: 40- years, M/W	26/ 2 530	Through letters, telephone and/or personal visits, confirmed by hospital records	**Serum** selenium was measured using neutron activation analysis	Incidence, skin cancer	-	(mean exposure)	-

5.7.6 Caffeine in diet

Cohort studies

Summary

No studies were identified in the 2005 SLR and four studies (three publications on melanoma, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

In the NHS and NHS II studies, a statistically significant inverse association of caffeine in diet and melanoma risk was reported, RR: 0.74, 95% CI= (0.57-0.96) and RR: 0.66, 95% CI= (0.51-0.87), respectively, comparing ≥393 vs. <60 mg/day (Wu, 2015c). In the HPFS study, the association was inverse but statistically non-significant, RR: 0.94, 95% CI= (0.75-1.20). The pooled summary estimate for men and women was 0.78, 95% CI= (0.64-0.96), comparing ≥393 vs. <60 mg/day (Wu, 2015c).

Basal cell carcinoma

In an Australian cohort study, no dose-response association was observed (RR for 100 mg/day: 0.96, 95% CI= 0.87-1.05) (Miura, 2014). In two North American studies, statistically significant inverse associations were reported in men (HPFS) and women (NHS), RR: 0.87, 95% CI= (0.81-0.94) and RR: 0.82, 95% CI= (0.77-0.86), respectively, comparing Q5 vs. Q1 (Song, 2012).

Squamous cell carcinoma

Associations between caffeine intake and SCC risk were inconsistent. In an Australian cohort study, no association was reported in the highest vs. lowest analysis, RR: 1.05, 95% CI= (0.77-1.42) and in continuous analysis (RR for 100 mg/day: 0.99, 95% CI= 0.87-1.12) (Miura, 2014).

In two North American studies, no association was reported in women (NHS), RR: 1.03, 95% CI= (0.84-1.26) and men, RR: 0.91, 95% CI= (0.71-1.15) in the highest vs. lowest analysis (Song, 2012).

Table 43 Caffeine intake and skin cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Wu, 2015c SKI23425 USA	NHS, Prospective Cohort, Age: 30-55 years, M/W	841/ 74 666 23.6 years	Biennial follow-up questionnaires and medical records	Validated FFQ	Incidence, MM	≥393 vs. <60 mg/day	0.74 (0.57-0.96) Ptrend:0.04	Age, family history of melanoma, personal history of non-skin cancer, natural hair colour, number of moles on legs or arms, sunburn reaction as a child/adolescent, number of blistering, time spent in direct sunlight since high school, cumulative ultraviolet flux since baseline, BMI, smoking status, physical activity, total energy intake, and alcohol intake. Analyses on women further adjusted for rotating night shifts, menopausal status, postmenopausal hormone use
	NHS II Prospective Cohort, Age: 25-42 years, M/W	642/ 89 220 17.3 years					0.66 (0.51-0.87) Ptrend:0.004	
	HPFS, Prospective Cohort, Age: 40-75 years, M/W	771/ 39 424 16.8 years					0.94 (0.75-1.20) Ptrend:0.81	
	Pooled for men and women	2 254/					0.78 (0.64-0.96) Ptrend:0.05	
Miura, 2014 SKI23423 Australia	NSCS, Prospective Cohort, Age: 49.3 years,	323/ 1 325 11 years	Biennial follow-up questionnaires, histological	Validated FFQ	Incidence, BCC	T3 vs. T1	0.87 (0.69-1.08) Ptrend:0.20	Age, sex, tanning ability, treatment allocation, elastosis of neck, freckling back, history of skin cancer
						Per 100 mg	0.96 (0.87-1.05)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M/W	196/	reports		Incidence, SCC	T3 vs. T1	1.05 (0.77-1.42) Ptrend:0.79	Age, sex, treatment allocation, history of skin cancer, tanning ability, freckling of the back, pack-year smoked
						Per 100 mg	0.99 (0.87-1.12)	
Song, 2012 SKI23421 USA	NHS, Prospective Cohort, Age: 30-55 years, W	14 230/ 72 921 24 years	Biennial follow-up questionnaires pathologically unconfirmed	Validated FFQ	Incidence, BCC	Q5 vs. Q1	0.82 (0.77-0.86) Ptrend:<0.0001	Age, BMI, childhood sun reaction, family history of melanoma, hair colour, history of severe sunburn, physical activity, presence of moles, smoking status, UV index at birth, age 15, age 30, history of non-skin cancer, sun exposures at different age intervals
	HPFS, Prospective Cohort, Age: 40-75 years, M	8 556/ 39 976 22 years					0.87 (0.81-0.94) Ptrend:<0.0001	
	NHS, Prospective Cohort, Age: 30-55 years, W	1 043/ 72 921 24 years	Biennial follow-up questionnaires and medical records		Incidence, SCC		1.03 (0.84-1.26) Ptrend:0.81	
	HPFS, Prospective Cohort, Age: 40-75	907/ 39 976 22 years					0.91 (0.71-1.15) Ptrend:0.45	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, M							
	NHS, Prospective Cohort, Age: 30-55 years, W	403/ 72 921 24 years			Incidence, MM		1.31 (0.95-1.79) Ptrend:0.09	
	HPFS, Prospective Cohort, Age: 40-75 years, M	334/ 39 976 22 years					0.91 (0.62-1.32) Ptrend:0.93	

6 Physical activity

6.1 Total physical activity (overall summary measures)

Cohort studies

Summary

One study (one publication on BCC, SCC) was identified in the 2005 SLR and three new studies (two publications on melanoma, BCC, and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

In the NIH-AARP study, a statistically significant positive association with melanoma risk was reported, RR: 1.31, 95% CI= (1.16-1.49), comparing 5+ times/week vs. never or rarely (Loftfield, 2015). Physical activity was defined as activity increasing breathing, heart rate or sweating that lasted 20 minutes or longer. In the NHS and HPFS studies, a statistically non-significant positive association was reported in the overall highest vs. lowest analysis, RR: 1.24, 95% CI= (0.99-1.55) and a statistically significant positive association in the latency analysis (10 years prior to the diagnosis), RR: 1.72, 95% CI= (1.26-2.35) (Pothiawala, 2012).

Basal cell carcinoma

In a prospective cohort study of participants with significant sun damage (≥10 actinic keratoses), physical activity was not related with BCC (RR: 0.96, 95% CI= 0.63-1.48), comparing exercising often vs. never (Foote, 2001). In the NHS and HPFS studies, a statistically significant positive association was reported in the highest vs. lowest analysis, RR: 1.17, 95% CI= (1.12-1.22) (Pothiawala, 2012).

Squamous cell carcinoma

The same study reported a statistically non-significant positive association with SCC risk, RR: 1.40, 95% CI= 0.86-2.29, comparing exercising often vs. never (Foote, 2001).). In the NHS and HPFS studies, a statistically significant positive association was reported in the highest vs. lowest analysis, RR: 1.22, 95% CI= (1.04-1.42) (Pothiawala, 2012).

6.1.1.1 Occupational physical activity

Cohort studies

Summary

One study (one publication on melanoma) was identified in the 2005 SLR and one study (one publication on SCC) was identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

One study identified in the 2005 SLR reported a statistically non-significant positive association, RR: 1.20, 95% CI= (0.70-2.30), comparing heavy manual occupational activity with sedentary (Veierod, 1997).

Squamous cell carcinoma

In an Australian cohort study, a statistically non-significant inverse association of occupational physical activity with SCC was reported in women in the person-based analysis (84 cases), RR: 0.64, 95% CI= (0.33-1.24) and the tumour-based analysis (142 tumours), RR: 0.48, 95% CI= (0.22-1.07), comparing manual vs. sedentary occupational activity (Lahmann, 2011). A statistically non-significant positive association was found in men in the person-based analysis (95 cases), RR: 1.13, 95% CI= (0.76-1.69) and a non-significant inverse association in the tumour-based analysis (208 tumours), RR: 0.90, 95% CI= (0.53-1.53) (Lahmann, 2011).

6.1.1.2 Recreational physical activity

Cohort studies

Summary

Three studies (three publications on melanoma and NMSC) were identified in the 2005 SLR and one study (one publication on SCC) was identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

One study identified in the 2005 SLR reported a statistically non-significant positive association of recreational physical activity with melanoma risk, RR: 1.60, 95% CI= (0.40-7.00), comparing regular hard training vs. sedentary (Veierod, 1997). Another study on college alumni reported no association of physical activity with melanoma. RR estimates were not given in the paper (Whittemore, 1985).

Non-melanoma skin cancer

In the CCPPS study comprising three Danish cohorts, a statistically non-significant positive association was reported for men, comparing highest vs. lowest categories of moderate leisure-time physical activity, RR: 1.36, 95% CI= (0.98-1.89) and a significant positive association was reported with vigorous leisure-time physical activity, RR: 1.72, 95% CI= (1.23-2.40) (Schnohr, 2005). In women, no association was reported for moderate leisure-time physical activity, RR: 0.91, 95% CI= (0.70-1.19) and vigorous leisure-time physical activity, RR: 0.90, 95% CI= (0.65-1.26) when comparing highest vs. lowest levels (Schnohr, 2005).

Squamous cell carcinoma

In an Australian cohort study, a statistically non-significant inverse association was reported in women in person-based analysis (90 cases), RR: 0.85, 95% CI= (0.52-1.38) and in tumour-based analysis (149 tumours), RR: 0.76, 95% CI= (0.42-1.38), comparing highest vs. lowest number of hours of recreational activity (Lahmann, 2011). A statistically non-significant positive association was reported in men in the person-based analysis (98 cases), RR: 1.33, 95% CI= (0.86-2.05) and in tumour-based analysis (219 tumours), RR: 1.71, 95% CI= (0.91-3.21) (Lahmann, 2011). Moderate activity was statistically non-significantly inversely associated with SCC risk in women, RR: 0.66, 95% CI= (0.35-1.27), and not related to SCC

risk in men, RR: 1.05, 95% CI= (0.64-1.70), comparing highest vs. lowest categories (Lahmann, 2011). Vigorous activity was positively but statistically non-significantly associated with SCC risk in women, RR: 1.30, 95% CI= (0.63-2.65), and not associated in men, RR: 1.08, 95% CI= (0.54-2.18), comparing highest vs. lowest categories (Lahmann, 2011).

6.1.1.4 Walking

Cohort studies

Summary

No studies were identified in the 2005 SLR and one study (one publication on SCC) was identified in the CUP.

No meta-analysis was conducted.

Squamous cell carcinoma

In the Australian cohort study, walking was not associated with SCC in women (RR: 1.06, 95% CI= 0.65-1.74, 90 cases) (Lahmann, 2011). A statistically non-significant positive association was found in men in the person-based analysis (98 cases), RR: 1.37, 95% CI= (0.90-2.08) and the tumour-based analysis (219 tumours), RR: 1.59, 95% CI= (0.85-2.98) (Lahmann, 2011).

6.3.3 Heavy work occupation

Summary

One study (one publication on melanoma) was identified in the 2005 SLR and one study (one publication on melanoma, NMSC, BCC) was identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

A Finnish study in elite athletes reported a SIR: 0.68, 95% CI= (0.29-1.33) compared to the general population (Sormunen, 2014). In another Finnish study, the SIR in physical exercise teachers was 2.01, 95% CI= (0.65-4.69) (Pukkala, 1993).

Non-melanoma skin cancer

A Finnish study in elite athletes reported SIR: 1.15, 95% CI= (0.74-1.69) compared to the general populations (Sormunen, 2014). This paper indicated that cancer was “Skin, non-melanoma” and the definition seems to exclude basal cell carcinoma as this type of cancer is further reported in the same paper with a higher number of cases.

Basal cell carcinoma

A Finnish study in elite athletes reported a SIR: 1.18, 95% CI= (0.99-1.39) compared to the general population (Sormunen, 2014).

Table 44 Physical activity and skin cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Loftfield, 2015 SKI23424 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 904/ 447 357 10.5 years	Cancer registry	**Physical activity** Questionnaire	Incidence, MM	5+/week vs. never/rarely	1.31 (1.16-1.49)	Age, sex
Sormunen, 2014 SKI23404 Finland	Finnish male athletes, Prospective Cohort, Age:55 (athletes), 53 (referents) M, Athletes that represented Finland in 1920-1965	8/ 1 324 athletes, 754 referents 21 years	Cancer registry	**Athletes, referents** Records	Incidence, MM	SIR (athletes vs. general population)	0.68 (0.29-1.33)	
		11/				SIR (referents vs. general population)	1.60 (0.80-2.85)	
		25/			NMSC	SIR (athletes vs. general population)	1.15 (0.74-1.69)	
		11/				SIR (referents vs. general population)	1.00 (0.50-1.78)	
		126/			BCC	SIR (athletes vs. general population)	1.18 (0.99-1.39)	
		55/				SIR (referents vs. general population)	0.94 (0.71-1.22)	
Pothiawala, 2012 SKI23449 USA	NHS and HPFS, Prospective Cohort, M/W, Age: 30-75	-	Medical records and self-reported diagnoses confirmed by physicians	**Total physical activity**, interview, self-reported	Incidence, MM of skin	Highest vs. lowest	1.24 (0.99-1.55) Ptrend:0.06	Age, sunburn reaction, family history of melanoma, number of severe
					BCC		1.17 (1.12-1.22) Ptrend:<0.0001	
					SCC		1.22 (1.04-1.42)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
							Ptrend:0.01	sunburns, number of moles, hair colour, sun exposure at different age intervals, UV index at residence at different ages, and history of cardiovascular diseases, type 2 diabetes, and cancer
					Incidence, MM of skin, 10 years prior to the diagnosis		1.72 (1.26-2.35) Ptrend:0.0007	
Lahmann, 2011 Australia	NSCS, Prospective Cohort, Age:25-75 years, M/W	95/1 171 16 years	Verified histologically	**Occupational activity** Questionnaire	Person-based incidence, SCC, men	Manual vs. sedentary	1.13 (0.76-1.69)	Age, treatment allocation, elastosis of the neck, freckling of the back and skin cancer history
		84/			Women		0.64 (0.33-1.24)	
		208 tumours/			Tumour-based incidence men		0.90 (0.53-1.53)	
		142 tumours/			Women		0.48 (0.22-1.07)	
		98/		**Recreational activity**	Person-based incidence, SCC, men	>4 (M), >3 (W) vs. ≤1.5 (M), ≤1 (W) hours/week	1.33 (0.86-2.05) Ptrend:0.14	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		90/			Women		0.85 (0.52-1.38) Ptrend:0.65	
		219 tumours/			Tumour-based incidence men		1.71 (0.91-3.21) Ptrend:0.08	
		149 tumours/			Women		0.76 (0.42-1.38) Ptrend:0.41	
		98/		**Moderate activity**	Person-based incidence, SCC, men	≥1.7 (M), ≥1.5 (W) vs. <1.7 (M), <1.5 (W) hours/week	1.05 (0.64-1.70) Ptrend:0.87	
		90/			Women		0.66 (0.35-1.27) Ptrend:0.14	
		219/			Tumour-based incidence men		1.22 (0.59-2.51) Ptrend:0.60	
		149/			Women		0.60 (0.27-1.34) Ptrend:0.19	
		98/		**Vigorous activity**	Person-based incidence, SCC, men	≤12 (M), ≤8 (W) hours/week vs. none	1.08 (0.54-2.18)	
		90/			Women		1.30 (0.63-2.65)	
		219/			Tumour-based		0.73 (0.27-1.96)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					incidence men			
		149/			Women		0.90 (0.29-2.85)	
		98/		**Walking**	Person-based incidence, SCC, men	≥3.5 (M), ≥2.5 (W) vs. <1.2 (M), <1 (W) hours/week	1.37 (0.90-2.08) Ptrend:0.14	
		90/			Women		1.06 (0.65-1.74) Ptrend:0.997	
		219/			Tumour-based incidence men		1.59 (0.85-2.98) Ptrend:0.15	
		149/			Women		1.12 (0.63-2.01) Ptrend:0.92	
Schnohr, 2005 SKI22211 Denmark	CCPPS (Copenhagen City Heart Study; the Copenhagen County Centre of Preventive Medicine and the	410/ 15 043 14 years	Cancer registry	**Moderate leisure-time physical activity** Self-administered questionnaire	Incidence, NMSC, men	High vs. low	1.36 (0.98-1.89)	Age, birth cohort, cohort membership and occupational physical activity,
		357/ 13 216			Women		0.91 (0.70-1.19)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Copenhagen Male Study), Prospective Cohort, Age:49.3 (W), 52 (M) years, M/W	410/		**Vigorous leisure-time physical activity**	Men		1.72 (1.23-2.40)	smoking, education, alcohol intake
		357/			Women		0.90 (0.65-1.26)	
Foote, 2001 SKI07414 USA	Arizona, USA 1985-1992, Case Cohort Age:21-85 years, M/W, ≥10 AKs on the forearms	144/ 918 5 years	Dermatologist examination	**Physical exercise** Questionnaire	Incidence BCC	Often vs. never	0.96 (0.63-1.48)	Age
		105/			SCC		1.40 (0.86-2.29)	
Veierod, 1997 SKI17728 Norway	Norway 1977-1983, Prospective Cohort, Age: 16-56 years, M/W	108/ 50 757 12.4 years	Cancer registry	**Occupational physical activity** Questionnaire	Incidence, MM	Heavy manual vs. sedentary	1.20 (0.70-2.30) Ptrend:0.68	Age, gender, area of residence
		108/		**Recreational physical activity**		Regular hard training vs. sedentary	1.60 (0.40-7.00) Ptrend:0.68	
Pukkala, 1993 SKI03124	Finland 1967-1991, Prospective Cohort,	5/382	Cancer registry	**Physically active work**	Incidence, MM	SIR (PE teachers vs. general population)	2.01 (0.65-4.69)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Finland	Age:, W, PE and languages teachers	10		Interview	PE teachers Languages teachers	SIR (languages teachers vs. general population)	0.84 (0.40-1.54)	
Whittemore, 1985 SKI22091 USA	HPALS, Case Cohort, M/W, college alumni	/51 477	Alumni offices and questionnaires	**Physical activity** Questionnaire	Incidence, MM		No association	-

8 Anthropometry

8.1.1 BMI

Overall summary

Thirty eight publications from 35 studies that examined body mass index (BMI) were identified. Seventeen publications were new, identified during the CUP. This included a pooled study of seven cohorts (the Vorarlberg Health Monitoring and Prevention Programme, the Oslo Study I, the Norwegian Counties Study, the Cohort of Norway and the Age 40 programme, the Malmö Preventive Project and the Västerbotten Intervention Project) (Nagel, 2012).

Dose-response meta-analyses were conducted on BMI and melanoma, non-melanoma skin cancer (NMSC), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Table 45 BMI and skin cancer risk. Number of studies in the CUP SLR.

	Number
Studies identified	Total: 35 (38 publications) 29 (27 publications) melanoma risk 13 (6 publications) NMSC risk 9 (9 publications) BCC 14 (8 publications) SCC risk
Studies included in forest plot of highest compared with lowest exposure	20 (13 publications) melanoma risk 10 (3 publications) NMSC risk 6 (5 publications) BCC 13 (6 publications) SCC risk
Studies included in linear dose-response meta-analysis	21 (14 publications) melanoma risk 11 (4 publications) NMSC risk 7 (6 publications) BCC 13 (6 publications) SCC risk
Studies included in non-linear dose-response meta-analysis	13 (7 publications) melanoma risk NMSC risk – not enough studies 6 (5 publications) BCC 12 (5 publications) SCC risk

Skin cancer

Summary

Main results:

Twenty one out of 29 (27 publications) studies identified could be included in the dose-response meta-analysis on melanoma, 11 studies out of 13 (6 publications) on NMSC, 7 studies out of 9 (9 publications) on BCC, and 13 studies out of 14 (8 publications) on SCC.

Dose-response meta-analysis on all skin cancer was not conducted as only one study(the Harvard Alumni Health Study cohort) was identified. No association beween BMI in middle-age and skin cancer mortality was reported in this study (Gray, 2012).

Malignant melanoma

BMI was not associated with melanoma risk, RR: 1.02, 95% CI= (0.98-1.05). High and statistically significant heterogeneity was observed. Egger's test showed no statistical evidence of publication or small study bias. However, a Korean study (Oh, 2005) reporting a positive association was an outlier in the funnel plot. This was a large study with a low number of melanoma incident cases in men (51 cases) in which weight and height were measured at baseline.

Similar results were observed in stratified analyses, except for a positive marginal association observed in men, RR: 1.09, 95% CI= (0.99-1.19), I^2=60%, 0.01 that was driven by the Korean study (Oh, 2005). No association was observed in never smokers, summary RR for 5 kg/m^2: 1.01, 95 % CI= (0.93-1.09), I^2: 63%, p-value heterogeneity test: 0.07, 3 studies.

Eight studies were excluded from the dose-response meta-analysis. Two studies reported statistically significant increased risk of melanoma in men when comparing obese vs. non-obese war veterans (Samanic, 2004) and highest vs. lowest BMI quintile (Thune, 1993). In the same study, BMI was inversely marginally associated with melanoma risk in women (Thune, 1993). In the WHI study, the reported risk estimate was close to 1 per increment of 1 score (Heo, 2015). Three studies were on cohorts of obese people in Sweden and Denmark and the standardized incidence ratios of melanoma were estimated using as reference population those not hospitalized for obesity (in Sweden) or the general population (in Denmark). None of the studies reported statistically significant difference in melanoma risk in obese and non-obese people (Moller, 1994; Hemminki, 2011; Wolk, 2001). Two excluded studies did not provide risk estimates (Vessey, 2000; Whittemore, 1985).

Sensitivity analysis

In influence analysis, the summary RR did not change materially when each study was omitted in turn.

Nonlinear dose-response meta-analysis:

There was statistical evidence of non-linearity ($p<0.001$) showing a risk increase with increasing BMI up to approximately 29 kg/m^2 and decrease in risk thereafter. Similar nonlinear dose-response asociation was reported in a large UK study (Bhaskaran, 2014). No other study explored the shape of the association using nonlinear models.

Non-melanoma skin cancer

BMI was statistically significantly inversely associated with NMSC risk, RR: 0.87, 95% CI= (0.77-0.98). High and significant heterogeneity (I^2: 91.6%) was observed. Most studies reported inverse associations although not always statistically significant. Egger's test was not conducted due to low number of publications.

Two studies reporting standardized incidence ratios for NMSC risk were excluded from the dose-response meta-analysis. None of the two studies reported statistically significant difference of NMSC risk in obese compared to nonobese people (Moller, 1994; Wolk, 2001).

Basal cell carcinoma

BMI was statistically significantly inversely associated with BCC , RR: 0.87, 95% CI= (0.82-0.91). There was moderate heterogeneity that did not reach statistical significance (p=0.06). The four larger cohort studies published in 2012 and 2015 were the only studies that reported statistically significant inverse associations (only in women in one of the studies). These studies were adjusted for several measures of UV exposure and skin reaction to sun exposure. No association was observed in two studies published in 2003 or before: one was a twin-matched nested case-control study in Finland (Milan, 2003) and in a follow-up of a small trial of vitamin A for skin cancer prevention in men with severe sun damage in Texas, USA (Foote, 2001).

Two studies were excluded from the dose-response meta-analysis. One study provided no risk estimate (McNaughton, 2005) and the other study reported statistically significant inverse association in a model not adjusted for potential confounding (Davies, 2002). In addition, the Me-Can study (Nagel, 2012) was not included as relative risk estimates were not reported due to very small numbers (55 cases); none of the associations with BCC investigated in this study reached statistical significance.

There was no statistical significant evidence of publication or small study bias.

In stratified analyses, similar summary association was found in men, RR: 0.90, 95% CI= (0.87-0.92) and women, RR: 0.84, 95% CI= (0.79-0.89).

Only in the Danish study (Praestegarrd, 2015) the inverse association was observed in women but not in men, in analyses adjusted for age, sun sensitivity, degree of freckling, number of nevi and waist circumference.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear association for BCC (p=0.86).

Squamous cell carcinoma

BMI was not associated with SCC risk, RR: 0.95, 95% CI= (0.83-1.08). High and statistically significant heterogeneity was observed that appears to be driven by a small trial of vitamin A for skin cancer prevention in men with severe sun damage in Texas, USA (Foote, 2001) in which no association with BCC was reported (Foote, 2001). Foote, 2001 was the only study on SCC that reported positive association and was an outlier in the funnel plot High number of actinic keratoses was an inclusion criteria in the trial, and these can be an early form of SCC whereas BCCs are not thought to arise from actinic keratosis. The ratio of BCC to SCC in the study population was lower than in the general population (Foote, 2001).When this study was excluded in sensitivity analysis, the summary RR was 0.89, 95% CI= (0.81-0.97).

One study that reported standardized incidence ratio when comparing hospitalized obesity patients with non-hospitalized obese poeple was excluded from the dose-response meta-analysis. No difference in risk among the groups was observed (Hemminki, 2012).

Egger's test showed no evidence of publication or small study bias.

In stratified analyses, statistically significant associations were observed in women (RR: 0.81, 95 CI% = (0.72-0.90) and in more adjusted studies RR: 0.87, 95 CI% = (0.76-0.99).

Sensitivity analyses:

In influence analysis, the association ranged from 0.89, 95% CI=(0.81-0.97) when Foote, 2001 (9.3% weight) was omitted to 0.99, 95% CI=(0.85-1.16) when (Pothiawala, 2012) (22.4% weight) was omitted.

Nonlinear dose-response meta-analysis:

There was no evidence of non-linear association (p=0.07).

Study quality:

Six studies used self-reported weight and height (Asgari, 2012; Pothiawala, 2012; Andreotti, 2010; Reeves, 2007; Freedman, 2003a). These studies were all included in the dose-response meta-analyses on melanoma, and only Pothiawala, 2012 was included in the meta-analyses on BCC and SCC. Weight and height was measured by standardised procedures in all remaining studies.

The level of adjustment for skin type and sunlight exposure varied between the studies included in the dose-response meta-analyses. In the analyses on melanoma, in seven out of 14 included publications some measure of skin sensitivity to sunlight and sunlight exposure (Tang, 2013; Pothiawala, 2012; Freedman, 2003a), sun sensitivity, degree of freckling and number of nevi (Lahmann, 2016, Praestegaard, 2015, Kvaskoff, 2014), and wearing sunscreen (Andreotti, 2010) were included in the adjustment, and in two studies, only age and sex adjusted models were shown (Loftfield, 2015; Asgari, 2012).

In the analyses on BCC, three out of six studies –those reporting inverse association - were adjusted for several indicators of UV exposure and skin sensitivity to sun exposure (Praestegaard, 2015; Gerstenblith, 2012; Pothiawala, 2012) and one study was only age adjusted (Foote, 2001). In the analyses on SCC, three out of six publications were adjusted for several indicators of UV exposure and/or skin sensitivity (Lahmann, 2016; Praestegaard,

2015, Pothiawala, 2012) and two studies were only age-adjusted (Odenbro, 2005, Foote, 2001). One study was a follow-up of vitamin A trial "moderately sun-damaged" participants having 10 or more actinic keratosis (Foote, 2001) and one study followed-up randomized controlled trial participants (Lahmann, 2016, Nambour Skin Cancer Prevention Trial). The Finish Adult Twin Cohort Study included matched twin pairs assuming they had similar sun exposure (Milan, 2003).

Two studies on NMSC (Tang, 2013, WHI; Tang, 2010, MrOS) and one study on BCC (Olsen, 2006, NSCS) included incident and prevalent cases. In the WHI study, similar risk estimate remained when participants with a history of skin cancer were excluded. In the NSCS, results did not differ substantially when 46% participants with previous history of BCC were excluded.

Table 46 BMI and skin cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP.

	2005 SLR	**CUP**
Increment unit used	5 kg/m^2	5 kg/m^2
Malignant melanoma		
Studies (n)	1	21
Cases	51	19 187
RR (95%CI)	2.10 (1.26-3.50)	1.02 (0.98-1.05)
Heterogeneity (I^2, p-value)	-	61.1%, <0.01
P value Egger test	-	0.35
Non-melanoma skin cancer		
Studies (n)	-	4
Cases	-	3347
RR (95%CI)	-	0.87 (0.77-0.98)
Heterogeneity (I^2, p-value)	-	92%, <0.001
P value Egger test	-	-
Basal cell carcinoma		
Studies (n)	3*	7
Cases	343	33 030
RR (95%CI)	0.78 (0.54-1.13)	0.87 (0.82-0.91)
Heterogeneity (I^2, p-value)	63%, 0.04	53%, 0.06
P value Egger test	-	0.64
Squamous cell carcinoma		

Studies (n)	2*		13
Cases	856		4 136
RR (95%CI)	1.24 (0.73-2.12)		0.95 (0.83-1.08)
Heterogeneity (I^2, p-value)	91%, <0.01		81%, <0.01
P value Egger test	-		0.15
Malignant Melanoma: stratified and sensitivity analysis			
Sex	**Men**	**Women**	
Studies (n)	15	16	
Cases	>2 789**	>4 435**	
RR (95%CI)	1.09 (0.99-1.19)	0.99 (0.95-1.04)	
Heterogeneity (I^2, p-value)	60%, 0.01	39%, 0.10	
P value Egger test	0.28	0.26	
Geographic area	**Asia**	**Australia**	**Europe**
Studies (n)	1	1	12
RR (95%CI)	1.95 (1.17-3.25)	1.00 (0.62-1.54)	1.02 (0.95-1.09)
Heterogeneity (I^2, p-value)	-	-	75%, <0.01
Geographic area	**North-America**		
Studies (n)	7		
RR (95%CI)	1.01 (0.98-1.05)		
Heterogeneity (I^2, p-value)	29%, 0.22		
Weight and height assessment	**Self-reported**	**Measured**	
Studies (n)	8	13	
RR (95%CI)	0.99 (0.95-1.03)	1.07 (0.99-1.15)	
Heterogeneity (I^2, p-value)	34%, 0.17	75%, <0.01	
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	5	12	4
RR (95%CI)	0.99 (0.93-1.06)	1.01 (0.98-1.03)	1.04 (0.88-1.22)

Heterogeneity (I^2, p-value)	69%, 0.01	0%, 0.85	82%, <0.01
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	6	4	11
RR (95%CI)	1.06 (0.99-1.13)	0.93 (0.81-1.07)	1.02 (0.98-1.06)
Heterogeneity (I^2, p-value)	19%, 0.29	64%, 0.06	76%, <0.01
Publication year	**≤2010**	**>2010**	
Studies (n)	5	16	
RR (95%CI)	1.08 (0.96-1.22)	1.00 (0.98-1.02)	
Heterogeneity (I^2, p-value)	79%, <0.01	16%, 0.30	
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**	
Studies (n)	8	13	
RR (95%CI)	1.03 (0.99-1.08)	1.01 (0.97-1.06)	
Heterogeneity (I^2, p-value)	0%, 0.59	78%, <0.01	
NMSC: stratified and sensitivity analysis			
Sex	Men	Women	
Studies (n)	2	2	
Cases	963	10 310	
RR (95%CI)	0.76 (0.40-1.47)	0.93 (0.89-0.96)	
Heterogeneity (I^2, p-value)	63%, 0.10	5%, 0.30	
Geographic area	**Europe**	**North-America**	
Studies (n)	9	2	
RR (95%CI)	0.85 (0.74-0.98)	0.76 (0.41-1.41)	
Heterogeneity (I^2, p-value)	86%, <0.01	61%, 0.11	
BCC: stratified and sensitivity analysis			

Sex	Men	Women	
Studies (n)	5	5	
Cases	9 777	23 109	
RR (95%CI)	0.90 (0.87-0.92)	0.84 (0.79-0.89)	
Heterogeneity (I^2, p-value)	0%, 0.79	55%, 0.06	
Geographic area	**Australia**	**Europe**	**North-America**
Studies (n)	1	2	4
RR (95%CI)	0.96 (0.85-1.09)	0.89 (0.73-1.10)	0.85 (0.82-0.89)
Heterogeneity (I^2, p-value)	-	77%, 0.04	40%, 0.19
Publication year	**≤2010**	**>2010**	
Studies (n)	2	5	
RR (95%CI)	0.99 (0.85-1.16)	0.85 (0.81-0.90)	
Heterogeneity (I^2, p-value)	0%, 0.77	59%, 0.07	
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**	
Studies (n)	6	1	
RR (95%CI)	0.86 (0.82-0.91)	0.96 (0.72-1.28)	
Heterogeneity (I^2, p-value)	60%, 0.04	-	
SCC: stratified and sensitivity analysis			
Sex	Men	Women	
Studies (n)	11	10	
Cases	2 158	1 872	
RR (95%CI)	0.94 (0.88-1.01)	0.81 (0.72-0.90)	
Heterogeneity (I^2, p-value)	14%, 0.32	33%, 0.22	
Geographic area	**Australia**	**Europe**	**North-America**
Studies (n)	1	9	3

RR (95%CI)	1.00 (0.83-1.19)	0.91 (0.82-1.00)	1.16 (0.56-2.38)
Heterogeneity (I^2, p-value)	-	36%, 0.21	95%, <0.01
Publication year	**≤2010**	**>2010**	
Studies (n)	2	11	
RR (95%CI)	1.26 (0.73-2.18)	0.85 (0.79-0.92)	
Heterogeneity (I^2, p-value)	90%, <0.01	31%, 0.23	
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**	
Studies (n)	4	9	
RR (95%CI)	0.87 (0.76-0.99)	1.06 (0.83-1.34)	
Heterogeneity (I^2, p-value)	52%, 0.13	87%, <0.01	

* Partially adjusted studies that included some, but not all, of the following adjustment variables: age, ethnic group/skin type, or restriction of a particular ethnic group/skin type, some measure of sunlight/UV exposure, smoking (results for SCC only); Fully adjusted summary risk estimates were derived combining results for men and women using fixed effect model for BCC 1.01 (0.71-1.45) (Milan, 2003) and melanoma 0.98 (0.79-1.23) (Freedman, 2003a).

**The exact number is unclear as Bhaskaran, 2014 study did not report the number of cases by sex (total number: 8505 cases).

Table 47 BMI and malignant melanoma risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Sergentanis, 2013	7 cohort, 8 case-control studies (men)	4460 cases in case-control studies; 7 895 cases in cohort studies (men and women combined)	Australia, USA, Canada, Italy, Greece, Denmark, UK, Sweden, Norway, Austria, Korea	Malignant melanoma	Men ≥25 kg/m^2 vs. <25 kg/m^2 Cohort studies	1.30 (1.20-1.40)	24%, 0.20
					Case-control studies	1.37 (1.17-1.60)	0%, 0.52
					All studies	1.31 (1.22-1.41)	7%, 0.36
	6 cohort, 10 case-control studies (women)				Women ≥25 kg/m^2 vs. <25 kg/m Cohort studies	1.13 (0.94-1.35)	31%, 0.11
					Case-control studies	0.93 (0.84-1.03)	31%, 0.14
					All studies	0.97 (0.89-1.06)	29%, 0.07
Renehan, 2008	6 cohort studies	3 492	North America, Europe and Australia, Asia-Pacific	Malignant melanoma	Per 5 kg/m^2 Men	1.17 (1.05-1.30)	44%, <0.01
	5 cohort studies	4 786			Women	0.96 (0.92-1.01)	0%, 0.05

Table 48 BMI and skin cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Benn, 2016 Denmark	CGPS and CCHS, Prospective cohort, M/W	4.7 years 3 347/ 108 817 4.7 years	Danish cancer registry, Danish death registry	Weight and height measured at baseline	Incidence, NMSC	≥30 vs. <18 kg/m²	0.65 (0.58-0.72)	Age, sex, C-reactive protein concentrations, smoking in pack-years, physical activity, alcohol consumption, education, birth year, and for women menopausal status	
		3420/				Per 10 kg/m²	0.63 (0.58-0.70)		RR rescaled for an increment used
Lahmann, 2016	NSCS, Follow-up of a trial on skin cancer, Age: 25-75, M/W	28/ 1 171 14.4 years	Cancer registry (melanoma), BCC and SCC were verified histologically	Weight and height measured at baseline	Incidence, MM	Per 1 kg/m²	1.00 (0.91-1.09)	Age, treatment allocation, BCC/SCC history, elastosis of the neck, freckling of the back, smoking status	RR rescaled for an increment used
		11/			Men		0.90 (0.74-1.08)		
		17/			Women		1.03 (0.94-1.13)		
		334/			Incidence, BCC	Q4 vs. Q1	0.93 (0.74-1.18)		Nothing estimated
		160/506			Men	30.6 vs. 22.3 kg/m²	1.06 (0.76-1.48)		
		174/ 665			Women	31 vs. 21.3 kg/m²	0.89 (0.64-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		188/			Incidence, SCC	Q4 vs. Q1	0.97 (0.69-1.35)		
		98/ 506			Men	30.6 vs. 22.3 kg/m^2	1.23 (0.77-1.95)		
		90/ 665			Women	31 vs. 21.3 kg/m^2	0.78 (0.47-1.27)		
Loftfield, 2015 USA	NIH-AARP, Prospective cohort, M/W, Age: 62.6	2 904/ 447 357 10.5 years	Cancer registry	Weight and height self-reported at baseline	Incidence, MM	Per 1 kg/m^2	1.00 (1.00-1.01)	Age, sex	RR rescaled for an increment used
Praestegaard, 2015 Denmark	DCH, Prospective cohort, M/W	188/ 26 685	MM cases identified by linkage to the Danish Cancer Registry, whereas all NMSC cases were identified through linkage to NMSC database	Weight and height obtained by trained healthcare professionals	Incidence, MM Men	>28 vs. ≤24 kg/m^2	1.2 (0.65-2.22)	Age, sun sensitivity, degree of freckling and number of nevi, waist circumference	RRs for men and women combined using fixed effects model, RR rescaled for an increment used, number of non-cases per category
						Per 2 kg/m^2	1.15 (0.98-1.36)		
		169/ 29 243 14.4 years			Women	>27 vs. ≤22 kg/m^2	0.56 (0.29-1.09)		
						Per 2 kg/m^2	0.95 (0.83-1.1)		
		1 671/ 26 685			BCC, men	>28 vs. ≤24 kg/m^2	0.85 (0.69-1.05)		
						Per 2 kg/m^2	0.96 (0.9-1.01)		
		1 794/			Women	>27 vs. ≤22	0.67 (0.54-0.82)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		29 243				kg/m²			
						Per 2 kg/m²	0.9 (0.86-0.94)		
		203/ 26 685			SCC, men	>28 vs. ≤24 kg/m²	0.87 (0.49-1.58)		
						Per 2 kg/m²	1.06 (0.9-1.24)		
		138/ 29 243			SCC, women	>27 vs. ≤22 kg/m²	0.46 (0.22-0.97)		
						Per 2 kg/m²	0.8 (0.68-0.94)		
Bhaskaran, 2014 UK	CPRD, Prospective Cohort, M/W, Age: 16-	8 505/ 5 240 000 7.5 years	CPRD clinical records were searched for codes showing malignant disease	Measured by standardized procedures	Incidence, MM	Per 5 kg/m²	0.99 (0.96-1.02)	Age, diabetes status, smoking, alcohol use, socioeconomic status, calendar year, and stratified by sex	99% CIs converted to 95% CIs, RRs for men combined using fixed effects model
		4 477/			Never smokers	Per 5 kg/m²	0.96 (0.92-1.00)		
		/			Men,<24 kg/m²	Per 5 kg/m²	1.48 (1.17-1.87)		
		/			Men, ≥24 kg/m²	Per 5 kg/m²	0.99 (0.93-1.06)		
		/			Women	Per 5 kg/m²	0.96 (0.92-1.00)		
Kvaskoff, 2014 France	E3N, Prospective Cohort,	580 /92 050 19 years	Pathology reports and confirmed by physicians	Self-reported height and weight was	Incidence, MM	>23.9 vs. <21.4 kg/m²	0.85 (0.70-1.04) Ptrend:0.13	Age, hair colour, skin complexion,	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		maximum		collected at baseline and in the 1994, 2000, 2002 and 2005 questionnaires				number of naevi, number of freckles, skin sensitivity to sun exposure, physical activity, and mean UV radiation dose in countries of birth and of residence at baseline	
Tang, 2013 USA	WHI-OS, Prospective Cohort W, Age:50-79	386/ 61 657	Self-reported cases of melanoma and NMSC were ascertained annually by questionnaire and melanoma cases were physician-adjudicated, using medical records	Measured at baseline	Incidence, MM	Obese vs. Normal	1.10 (0.95-1.28)	Age, education, smoking, skin type, sun exposure, previous history of skin cancer, hormone therapy use, and sunscreen use	Mid-points of BMI categories
	Nested case-control design	9 915/ 61 657			Incidence, NMSC	Obese vs. Normal	0.86 (0.80-0.91)		
Asgari, 2012 USA	VITAL, Prospective Cohort	553/ 69 635 5.84 years	SEER cancer registry, ascertained histopathologically	Self-reported	Incidence, MM	≥30 vs. <25 kg/m^2	0.65 (0.41-0.83) Ptrend: <0.01	Age, sex	Mid-points of BMI categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W, Age: 50-76 (62)								
Gerstenblith, 2012 USA	USRT, Prospective Cohort, M/W, Age:	1 768/ 46 582	Among the 2,258 subjects reporting a BCC, medical records were obtained for 666 (29%) and validated for 638 (96%). Because of the high proportion of self-reported BCCs confirmed by medical records, potentially eligible cases for whom medical records could not be obtained were included, for a total of 2,291 BCC cases	Self-reported height and weight	Incidence, BCC, Men	≥35 vs. <25 kg/m^2	0.65 (0.39-1.08) Ptrend: 0.003	Age, hair, eye, and skin colour, geographic measure of sun exposure (TOMS, hours outdoors in summer, number of lifetime blistering sunburns, acute and chronic reactions to sunlight, tobacco and alcohol use, physical activity, cumulative occupational ionizing radiation dose from head/neck, education and household income level	The number of person years per category, mid-point of BMI categories, RR for men and women combined using fixed effects model
		480/ 11 631			Women		0.57 (0.44-0.74) Ptrend: <0.0001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Gray, 2012 USA	HAHS, Prospective Cohort, M, Age: 45.1	63/ 21 582	Death certificates	Self-reported height and weight at the age of 45.1, on average	Mortality, skin cancer, men	Per 2.55 kg/m^2	1.14 (0.90-1.44)	Age	Dose-response meta-analysis on skin cancer was not conducted
						≥25.8 vs. <22.8 kg/m^2	1.47 (0.68-3.17)		
Nagel 2012, Austria, Norway, Sweden,	Me-Can (7 cohorts: (the Vorarlberg Health Monitoring and Prevention Programme), Norway (the Oslo Study I, the Norwegian Counties Study, the Cohort of Norway and the Age 40 programme) and Sweden (the Malmö Preventive Project and the Västerbotten Intervention	1015/ 289 866	Ascertained through linkages with nation-wide, high-quality registers in Austria, Norway and Sweden	Measured height and weight	Incidence, MM, men	≥30.8 vs. <21.5 kg/m^2	1.28 (1.01-1.62) Ptrend: 0.402	Stratified by centre and year of birth, adjusted for age at recruitment, smoking status, BMI, blood pressure, total cholesterol, and triglyceride and corrected for measurement error by regression calibration	Person-years and non-cases per quantile, RRs in men and women combined using fixed effects model
		713/ 288 834			Women	≥31.7 vs. <20.0 kg/m^2	1.13 (0.85-1.49) Ptrend: 0.851		
		230/ 578 700			Mortality, MM	Q5 vs. Q1	1.61 (1.0-2.61) Ptrend: 0.290		
		785/ 289 866			Incidence, NMSC Men	≥30.8 vs. <21.5 kg/m^2	1.0 (0.77-1.31) Ptrend: 0.672	Stratified by centre and year of birth, adjusted for age at recruitment, smoking status,	
		395/ 288 834			Women	≥31.7 vs. <20.0 kg/m^2	0.69 (0.48-1.01) Ptrend:0.234		
		587/			Incidence,	≥30.8 vs. <21.5	0.78 (0.57-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Project), M/W	289 866			SCC, men	kg/m²	Ptrend: 0.133	BMI and corrected for measurement error by regression calibration	
		286/ 288 834			Women	≥31.7 vs. <20.0 kg/m²	0.71 (0.46-1.10) Ptrend: 0.397		
Pothiawala, 2012 USA	NHS and HPFS, Prospective Cohort, M/W, Age: 30-75	966/ 143 129	Medical records and self-reported diagnoses confirmed by physicians	Self-reported height and weight	Incidence, MM, NHS + HPFS	≥30 vs. 18-24.9 kg/m²	1.05(0.83, 1.34) Ptrend: 0.46	Age, sunburn reaction, family history of melanoma, number of severe sunburns, number of moles, hair colour, sun exposure at different age intervals, UV index at residence at different ages, physical activity (quintiles), and history of cardiovascular diseases, type 2 diabetes and cancer	Person-years and non-cases per BMI category, mid-points of BMI categories.
		697/ 102 748			HPFS	≥30 vs. 18-24.9 kg/m²	0.85 (0.53, 1.36) Ptrend: 0.50		
		269/ 40 381			NHS	≥30 vs. 18-24.9 kg/m²	1.20 (0.91, 1.59) Ptrend: 0.097		
		26 506/ 143 129			BCC, NHS + HPFS	≥35 vs. 18-24.9 kg/m²	0.61 (0.54, 0.68) Ptrend: <0001		
		7 317/ 40381			HPFS	≥35 vs. 18-24.9 kg/m²	0.76 (0.60, 0.97) Ptrend: <0001		
		19 189/ 102 748			NHS	≥35 vs. 18-24.9 kg/m²	0.58 (0.51, 0.65) Ptrend: <0001		
		1 878/ 143 129			SCC, NHS + HPFS	≥35 vs. 18-24.9 kg/m²	0.56 (0.36, 0.88) Ptrend: <0001		
		1015/ 40 381			HPFS	≥35 vs. 18-24.9 kg/m²	0.37 (0.12, 1.15) Ptrend: 0.088		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		1 358/ 102 748			NHS	≥35 vs. 18-24.9 kg/m²	0.68 (0.42, 1.11) Ptrend: <0001		
Andreotti, 2010 SKI22187 USA	AHS, Prospective Cohort, M/W, Pesticide applicators and their spouses	125/	Population-based state cancer registries	Self-reported height and weight in questionnaire, missing values were supplemented by the 5-year follow-up phone interview and from the driver's licenses	Incidence, MM, men	Per 1 kg/m²	1.01 (0.95-1.06)	Age, diabetes, wear sunscreen and stratified by sex	RR rescaled for an increment used
						30-34.9 vs. 18.5-24.9 kg/m²	0.97 (0.53-1.76)		
		79/			Women	Per 1 kg/m²	1.03 (0.99-1.08)		
						≥35 vs. 18.5-24.9 kg/m²	1.89 (0.84-4.26)		
Tang, 2010 USA	MrOS, Nested Case-control, M, Age: 65-	178/ 1 441	Ascertained through subject self-report and not histological confirmation	Measured weight and height	Incident and prevalent cases, NMSC	Per 1 kg/m²	0.86 (0.73-1.02)	Adjusted for quintiles of 25(OH)D, age, BMI, season of blood draw, clinic site, outdoor walking activity, and cigarette smoking	RR rescaled for an increment used
Reeves, 2007	MWS,		Registries	Self-reported	Mortality, MM	≥30 vs. <22.5	1.06 (0.73-1.52)	Age,	FAR continuous

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
SKI22194 UK	Prospective Cohort, Age: 50-64 years, W			height and weight		kg/m²		geographical region, socioeconomic status, age at first birth, parity, smoking status, alcohol intake, physical activity	risk estimates left as they are, only RRs for categories converted to conventional risk estimates, RR rescaled for an increment used; person-years and non-cases per category for nonlinear analysis
						Per 10 units	1.02 (0.67-1.56)		
		1 635/			Incidence, MM	Per 10 units	0.94 (0.82-1.07)		
						≥30 vs. <22.5 kg/m²	0.94 (0.83-1.07)		
		891/			Never smokers	Per 10 units	1.02 (0.85-1.22)		
		98/			Premenopause	Per 10 units	1.62 (0.97-2.70)		
		566/			Postmenopause	Per 10 units	0.92 (0.74-1.15)		
Samanic, 2006 SKI22195 Sweden	SCWC, Prospective Cohort, Age: 18-67 years, M	1 083/ 362 552 19 years	Linkage with the national Swedish cancer register	Height and weight were measured at baseline and at each follow-up examination at 2-5 year intervals	Incidence, MM	≥30 vs. 18.5-24.9 kg/m²	1.35 (1.06-1.73) Ptrend:0.001	Age, calendar year, smoking status	Mid-points of BMI categories, person-years per category
		440/			Never smokers	≥30 vs. 18.5-24.9 kg/m²	1.31 (0.90-1.92) Ptrend:0.11		
Odenbro, 2005 SKI00013 Sweden	Sweden 1971-1992, Prospective	753/ 337 311 19.4 years	Health screening program	Measured height and weight	Incidence, SCC	>30 vs. ≤18.5 kg/m²	0.98 (0.73-1.32)	Age	Mid-points of BMI categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Cohort, Age: 14-82 years, M, Construction Industry Workers								
Oh, 2005 SKI22228 Korea	KNHIC, Prospective Cohort, Age: 20- years, M, Asian	51/ 781 283	Health screening program	Measured height and weight	Incidence, MM	27.0-29.9 vs. 23.0-24.9 kg/m^2	2.82 (1.15-6.70) Ptrend:0.007	Age, alcohol consumption, area of residence, family history of specific cancer, physical activity, smoking habits	Mid-points of BMI categories
Freedman, 2003a SKI00519 USA	USRT, Prospective Cohort, Age: 39 years, M/W, radiologic technologists	48/ 68 588 (men and women)	Self-reports confirmed by pathology reports and medical records	Self-reported height and weight	Incidence, MM, men	≥27.5 vs. ≤23.3 kg/m^2	1.40 (0.50-4.10) Ptrend:0.85	Age, sex, adult sunlight exposure, alcohol consumption, area of residence, decade since began to work as radiological technician, educational	Person-years per BMI quantile, mid-points of BMI quantiles
		159/			Women	≥24.8 vs. ≤20.4 kg/m^2	0.90 (0.60-1.40) Ptrend:0.95		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								level, hair colour, personal history of NMSC, skin pigmentation, smoking habits	
Milan, 2003 SKI00640 Finland	Finnish Adult Twin Cohort Study, Case Cohort, M/W	149/ 13 888 (twin pairs, men, women) 15.2 years	Histologically confirmed	Self-reported height and weight	Incidence, BCC, men	Per 1 kg/m^2	0.98 (0.88-1.10)	Age, ethnicity, sunlight (most twin pairs were exposed to a similar environment until the age of 16)	RR rescaled for an increment used, RRs for men and women combined using fixed effects model
		184/			Women		1.02 (0.93-1.12)		
Foote, 2001 SKI07414 USA	Arizona USA 1985-1992, Prospective Cohort, Age: 21-85 years, M/W, Moderately Sun-damaged	144/ 918 57 months	Pathology reports, dermatopathologist reviewed	Self-reported height and weight	Incidence, BCC	≥28.5 vs. ≤23.3 kg/m^2	1.01 (0.62-1.66)	Age	Mid-points of BMI categories
		106/			SCC	≥28.5 vs. ≤23.3 kg/m^2	2.64 (1.45-4.83)		

Table 49 BMI and skin cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Heo, 2015 SKI23437 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 169/ 144 701 12 years	Self report verified by medical record and pathology report	Measured	Incidence, MM	Per 1 score	0.99 (0.92-1.06)	Age, alcohol, educational level, ethnicity, height, hormone use, randomisation, smoking	Superseded by Tang, 2013, missing data for meta-analysis
Jensen, 2012 Denmark	DHC, Prospective cohort, M/W	/ 57 054 11.4 years	Danish Cancer Registry or the Danish Registry of Pathology	Weight and height measured in clinics	Incidence, BCC	Per 1 kg/m^2	0.96 (0.94-0.97)	Unadjusted	Superseded by Praestegaard, 2015
		/			Incidence, SCC		0.97 (0.93–1.01)		
Hemminki, 2011 Sweden	MigMed2, Prospective Cohort, M/W	54/ 30 020 17.7 years	Nationwide Swedish Cancer Registry	Hospital records	Incidence, MM	SIR: Familial all 1 + All + 1 All follow-up	0.88 (0.66–1.15) 0.86 (0.64–1.13) 0.83 (0.57–1.16)		Excluded, SIR only
		35/ 12.2 years			Incidence, SCC	SIR: Familial all 1 + All + 1 All follow-up	0.93 (0.64–1.29) 0.92 (0.63–1.28) 0.84 (0.43–1.48)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Dennis, 2008 USA	AHS, Prospective Cohort, M/W, Pesticide applicators and their spouses	168/ 44 086	Population-based state cancer registries	Self-reported height and weight in questionnaire	Incidence, MM	≥27 vs. <25 kg/m^2	0.85 (0.61-1.20) Ptrend:0.40	Age, sex, tendency to burn	Superseded by Andreotti, 2010
Odenbro, 2007 Sweden	SCWC, Prospective Cohort, Age: 18-67 years, M	1 309/ 339 802 22.6 years	Linkage with the national Swedish cancer register	Height and weight were measured at baseline and at each follow-up examination at 2-5 year intervals	Incidence, MM	≥25 vs. <18.5-<25 kg/m^2	1.34 (1.19-1.52)	Age, birth cohort, sunlight exposure, tobacco product usage	Superseded by Samanic, 2006, only highest vs. lowest comparison
Lukanova, 2006 SKI22191 Sweden	NSHDC, Prospective Cohort, Age: 29-61 years, M/W	44/ 68 786 (men and women) 8.2 years	Medical records	Measured by nurse, some participants had repeated weight and height measurements taken on average 10 years apart	Incidence, MM, men	≥27.6 vs. 18.5-23.4 kg/m^2	2.04 (0.81-5.80) Ptrend:0.35	Age, calendar year, smoking habits	Superseded by Pooled study Nagel, 2012
		48/			Women	≥27 vs. 18.5-22.1 kg/m^2	2.56 (1.04-7.18) Ptrend:0.16		
Olsen, 2006 Australia	NSCS, Follow-up of a trial on skin	66/ 1 109	All lesions clinically diagnosed as BCC	Measured weight and height at	Incidence and prevalent cases (54% had no	≥30 vs. 25 kg/m^2	1.00 (0.60-1.70)	Adjusted for age, and history of	Superseded by Lahmann, 2016

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	cancer, Age: 25-75, M/W		were biopsied for histologic confirmation	baseline	previous history of BCC), BCC, men			BCC and eye colour	
		75/ 1 109			Women	≥30 vs. <25 kg/m²	1.20 (0.70-2.10)		
McNaughton, 2005 SKI22177 Australia	NSCS, Nested Case Control, M/W	250		A physical examination was conducted in 1992 and height and weight were measured using standardised protocols	Incidence, BCC	(mean exposure)		Matched by Age, sex	Excluded, no risk estimate
Rapp, 2005 SKI22197 Austria	VHM&PP, Prospective Cohort, Age: 18-94 years, M/W	122/ 145 931 (men and women) 9.93 years	Cancer registry/ death certificates	Collected by medical staff at physical examination	Incidence, MM, men	≥30 vs. 18.5-24.9 kg/m²	0.59 (0.27-1.31) Ptrend:0.32	Age, occupation, smoking status	Superseded by pooled study Nagel, 2012
		130/			Women		0.86 (0.47-1.57) Ptrend:0.72	Age, occupation, smoking status	
Samanic, 2004 SKI00468 USA	US Veterans Affairs, Prospective Cohort, Age: 18-100	4 001/ 4 500 700 12 years	Discharge records	Hospital records	Incidence, MM, white men	Obese vs. non-obese	1.29 (1.14-1.46)	Age, contemporary date	Excluded, obese vs. non-obese
		96/	Discharge records		Incidence, MM,		2.39 (1.20-4.75)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, M, War veterans				black men				
Davies, 2002 SKI00989 UK	EPIC-Norfolk, Nested Case Control, M/W	57/ 136 controls	Not stated		Incidence, BCC, men	Per 1 kg/m^2	0.927 (0.869-0.989)	-	Excluded, unadjusted results
Wolk, 2001 SKI22093 Sweden	Sweden 1965-1993, Prospective Cohort, Age: 46 years, M/W, obese patients	39/ 28 129 10.3 years	Hospital discharge registrations	Obesity diagnosis from hospital discharge files (defined as: for men BMI>30, for women BMI>28.6)	Incidence, MM	Obese vs. general Swedish population	0.80 (0.60-1.10)	-	Excluded, SIR only
		45/			Incidence, NMSC		1.10 (0.80-1.50)		
Vessey, 2000 SKI17457 UK	OFPACS, Prospective Cohort, Age: 25-39 years, W, users of contraceptives	48/ 17 032	Family planning clinic	Questionnaire	Incidence, MM	-	-	-	Excluded, no quantified result
Veierod, 1997 SKI17728 Norway	Norway 1977-1983, Prospective Cohort, Age: 16-56 years,	106/ 50 757 12.4 years	Health screening programme	Recorded at screening	Incidence, MM	≥2.69 vs. ≤2.25 g/cm^2	0.90 (0.50-1.50) Ptrend:0.62	Age, area of residence	Superseded by Nagel, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W								
Moller, 1994 SKI22085 Denmark	Denmark 1977-1987, Prospective Cohort, Age: 0-90 years, M/W, obese patients	32// 37 957 4.8 years	Hospital discharge registrations	Physical appearance of hospital patients	Incidence, MM	Obese vs. Danish population	1.00 (0.70-1.40)	-	Excluded, SIR only
		190			Incidence, NMSC		0.90 (0.70-1.00)		
Thune, 1993 SKI15897 Norway	Norway 1963-1975, Prospective Cohort, Age: 30-84 years, M/W	2 144/ 1 327 089 (men and women)		National Mass-Radiography Service measured the height and weight of all those who participated in a tuberculosis screening program between 1963 and 1975.	Incidence, MM, men	Q 5 vs. Q 1	1.26 (1.10-1.45)	Age, area of residence, birth cohort, height	Excluded, no BMI levels per quintiles, used in the high vs. low analysis
		2 814/	Health screening programme		Women	Q 5 vs. Q 1	0.88 (0.78-1.00)		
Whittemore, 1985 SKI22091 USA	HPALS, Case Cohort, M/W, college alumni	51 477	Alumni offices and questionnaires	College physical examination	Incidence, MM	-	-	-	Excluded, no risk estimate

Figure 39 RR estimates of melanoma by levels of BMI

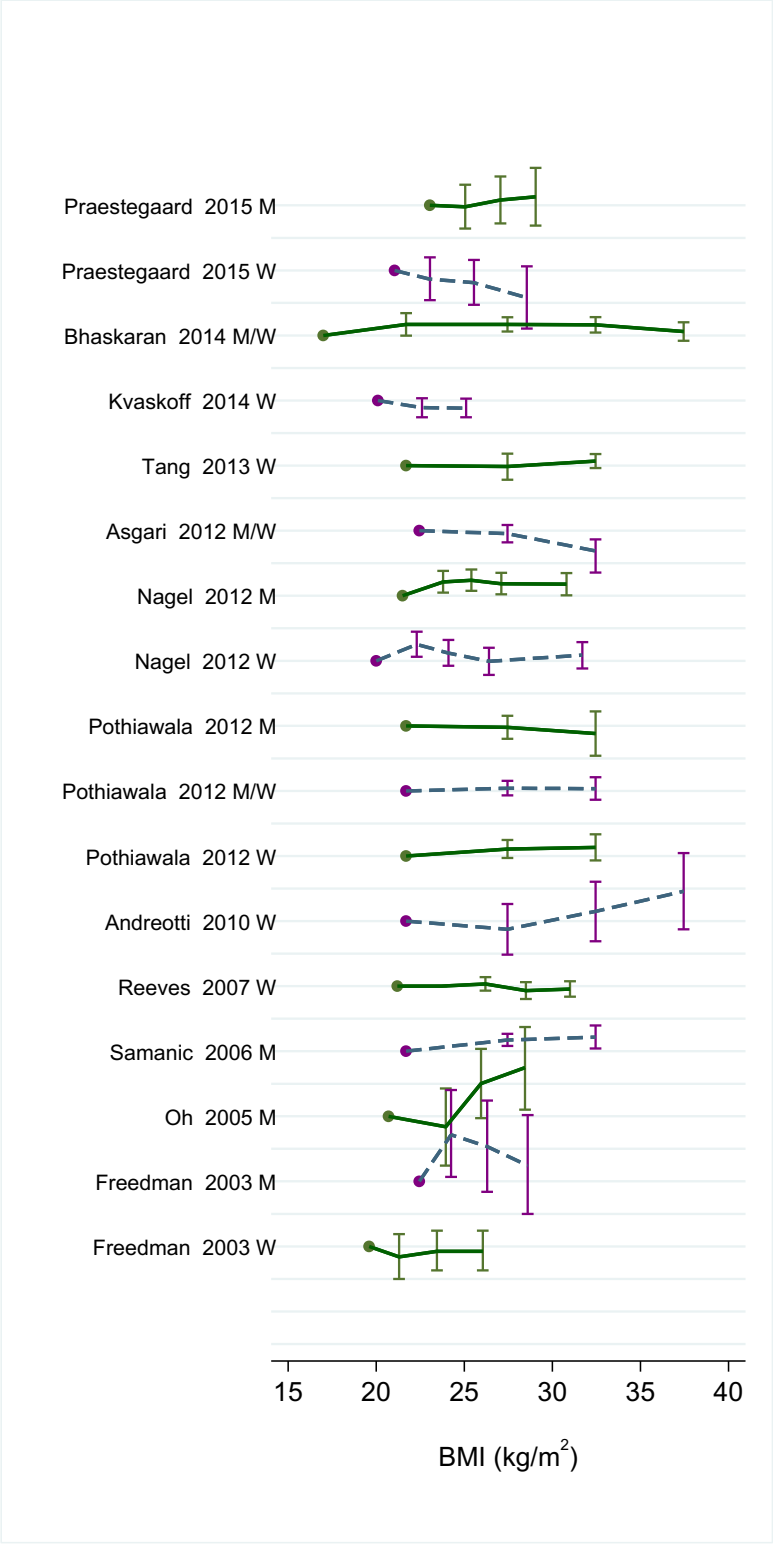


Figure 40 RR (95% CI) of melanoma for the highest compared with the lowest level of BMI

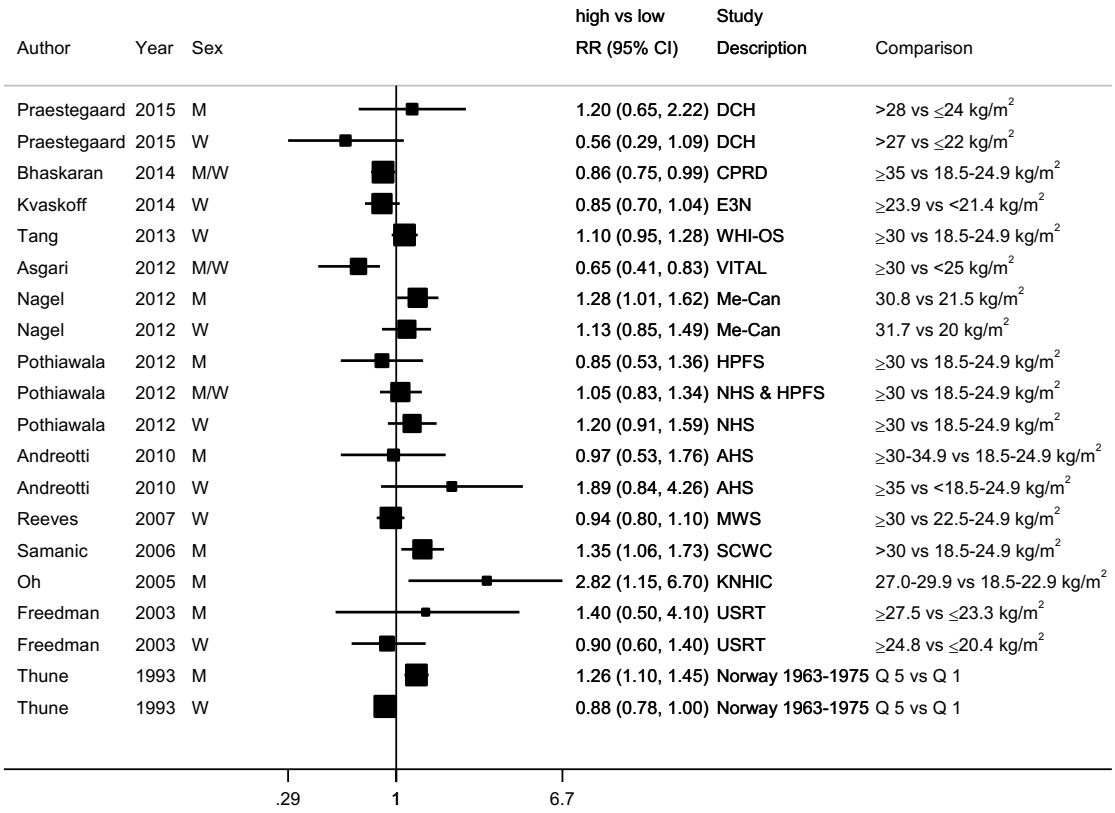


Figure 41 Relative risk of melanoma for 5 kg/m2 increase of BMI

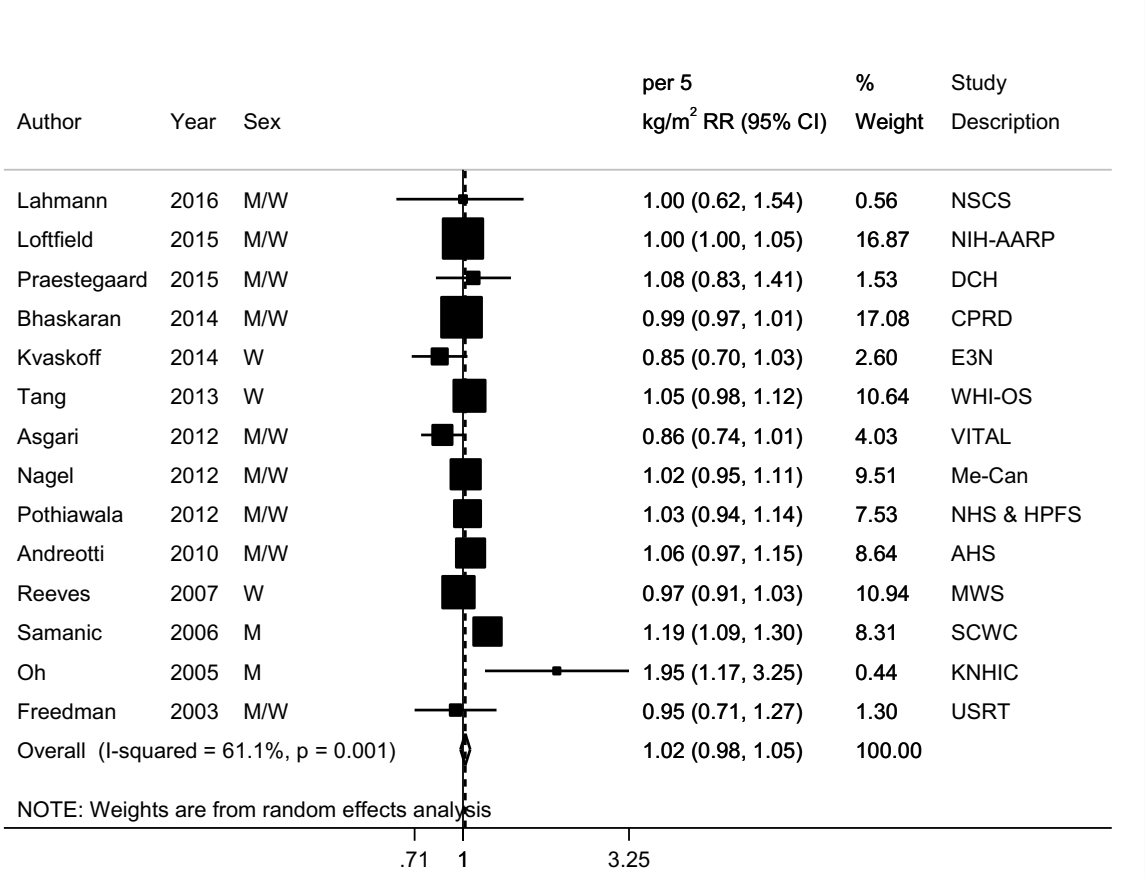


Figure 42 Funnel plot of studies included in the dose response meta-analysis of BMI and melanoma

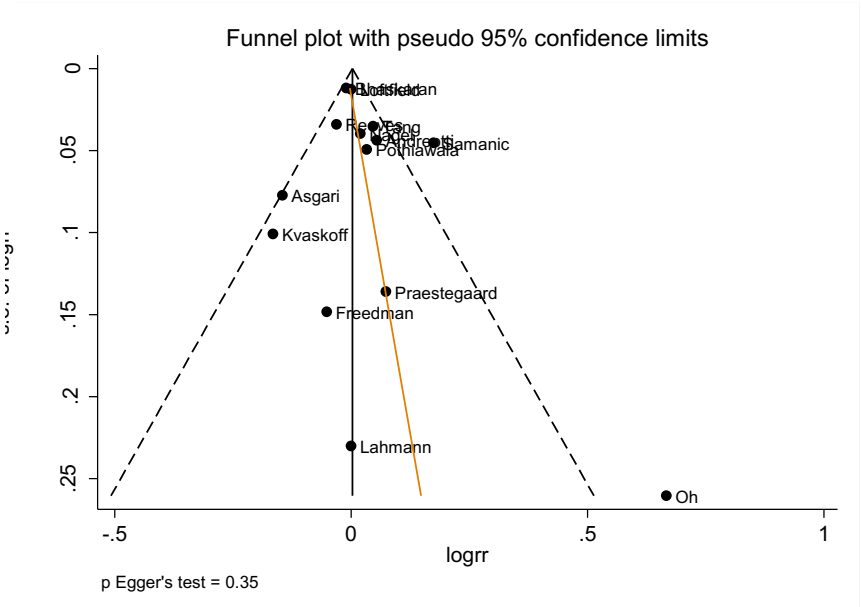


Figure 43 Relative risk of melanoma for 5 kg/m2 increase of BMI, by sex

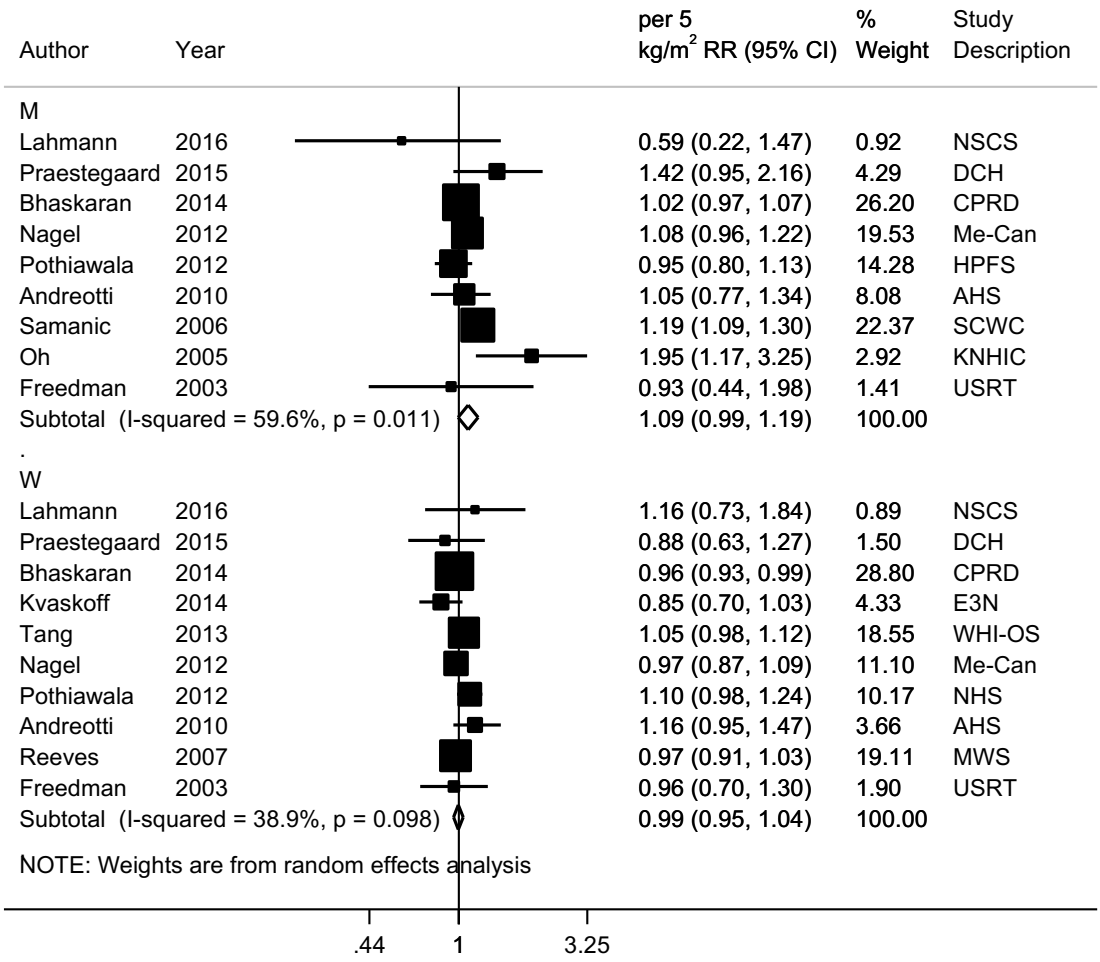


Figure 44 Relative risk of melanoma for 5 kg/m2 increase of BMI, by geographic location

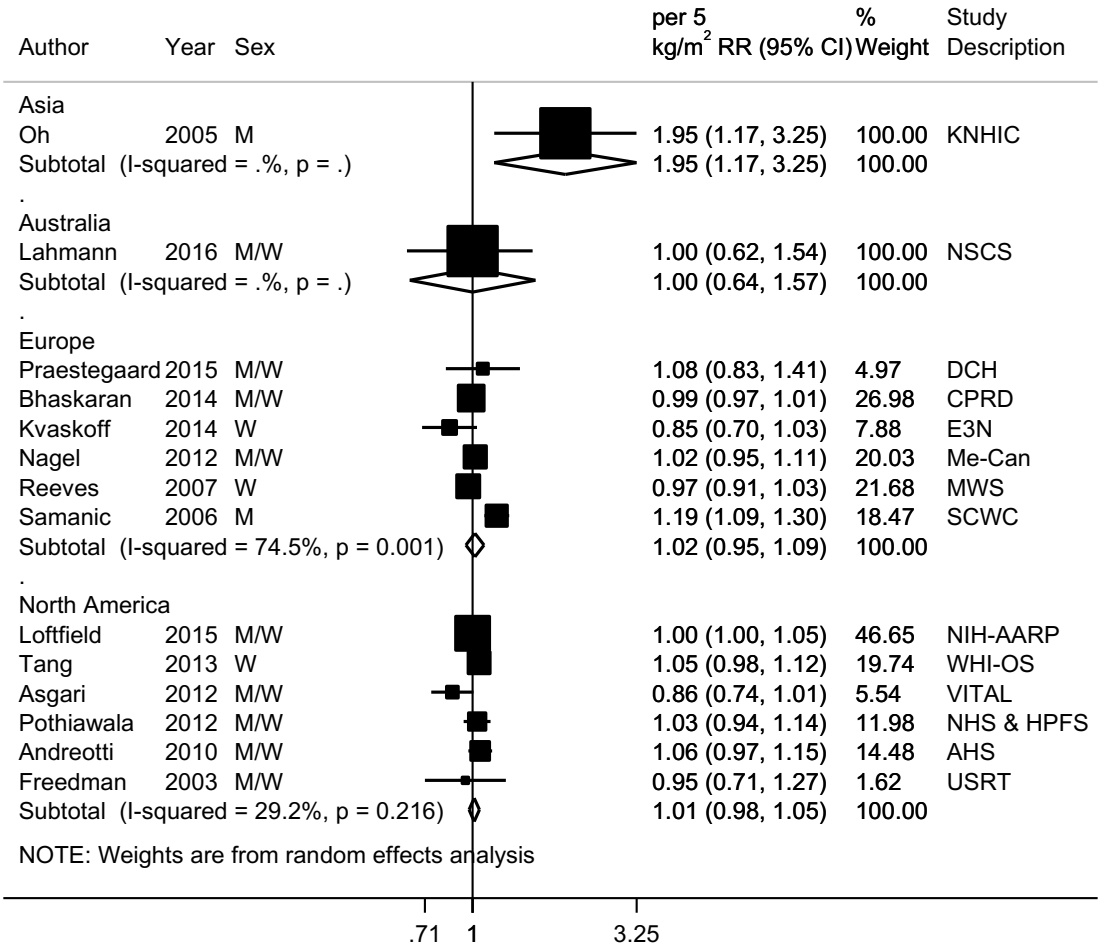


Figure 45 Relative risk of melanoma for 5 kg/m2 increase of BMI, by assessment method

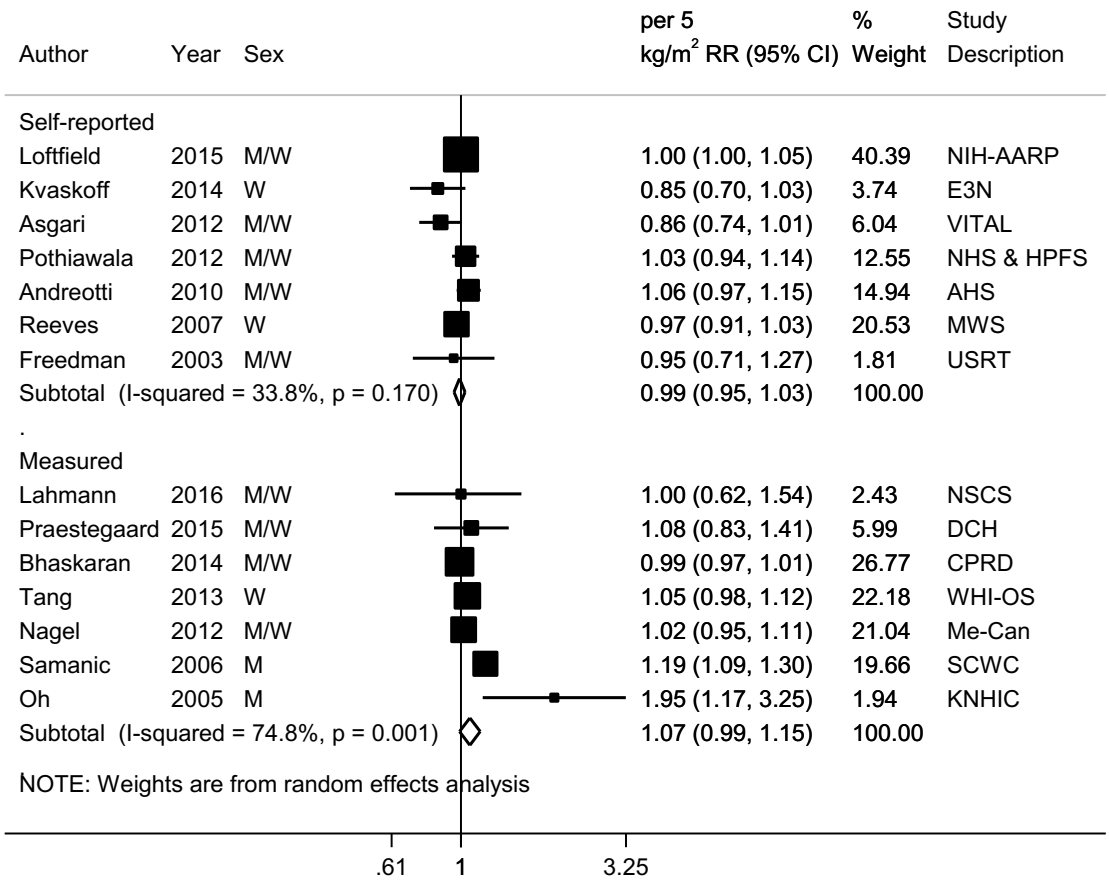
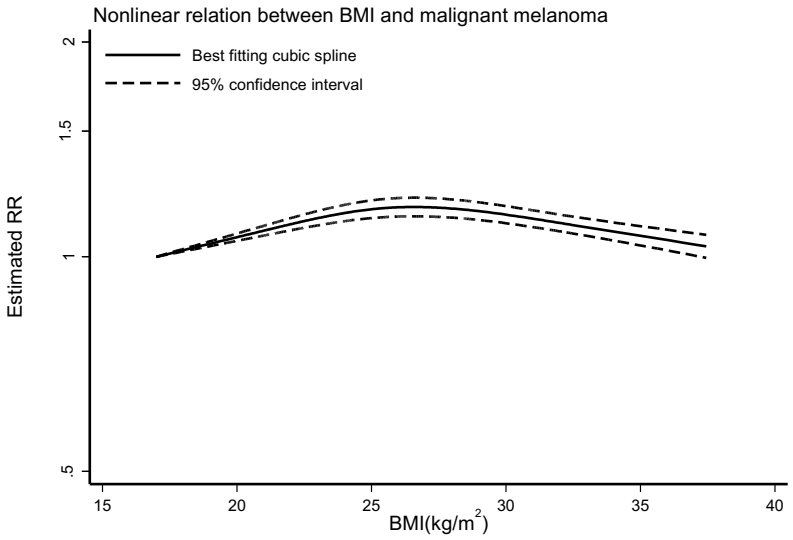


Figure 46 Nonlinear dose-response meta-analysis of BMI and melanoma



P nonlinear <0.001

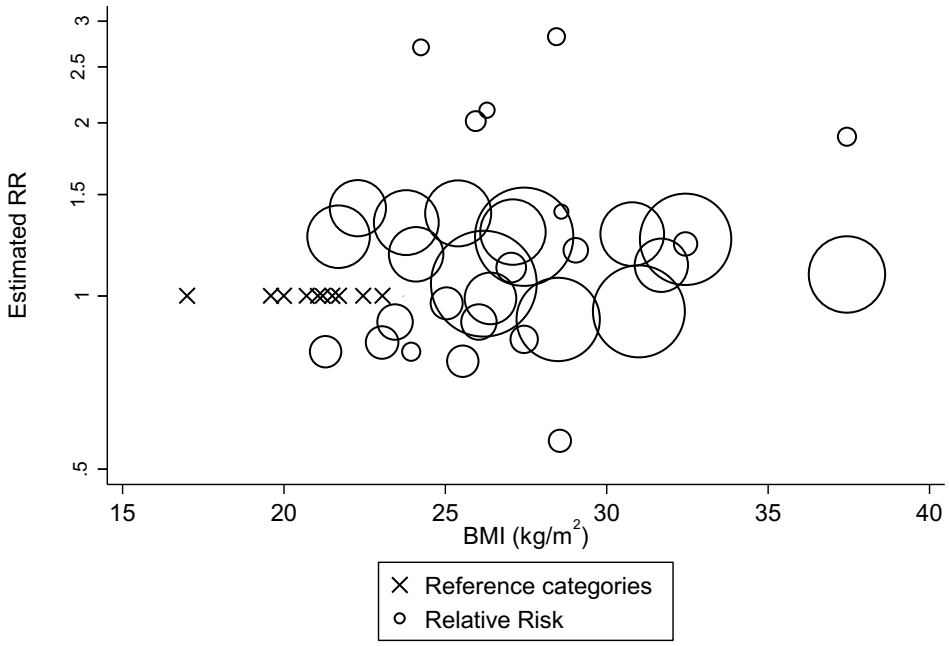


Table 50 Relative risk of melanoma and BMI estimated using non-linear models

BMI (kg/m^2)	RR (95%CI)
17	1.00
20	1.07 (1.05-1.08)
22.5	1.12 (1.10-1.15)
24	1.15 (1.12-1.18)
26	1.17 (1.14-1.21)
27.5	1.17 (1.14-1.21)
28.5	1.16 (1.13-1.20)
30.8	1.13 (1.10-1.17)
32.5	1.11 (1.08-1.14)
37.5	1.03 (1.00-1.07)

Figure 47 RR estimates of NMSC by levels of BMI

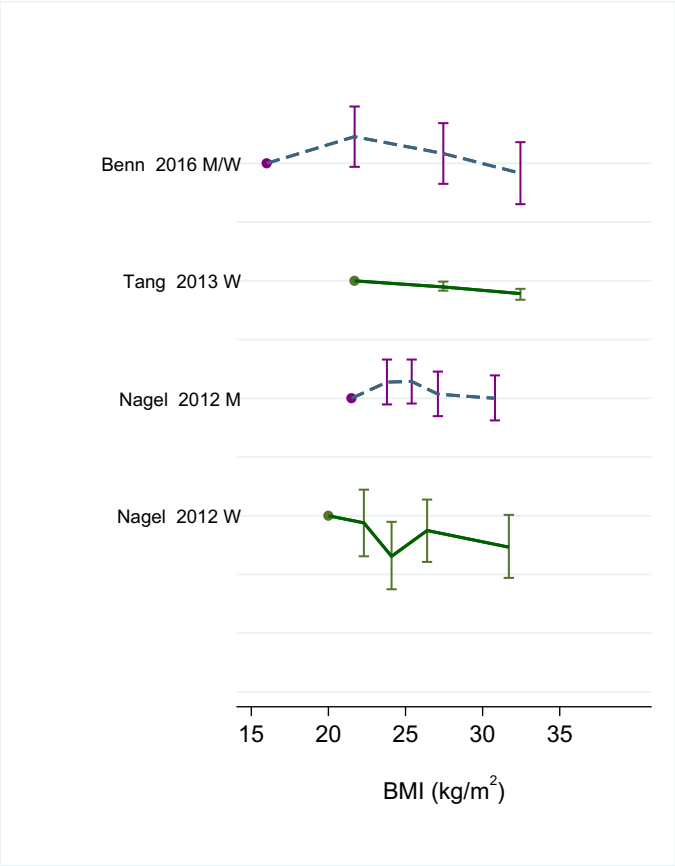


Figure 48 RR (95% CI) of NMSC for the highest compared with the lowest level of BMI

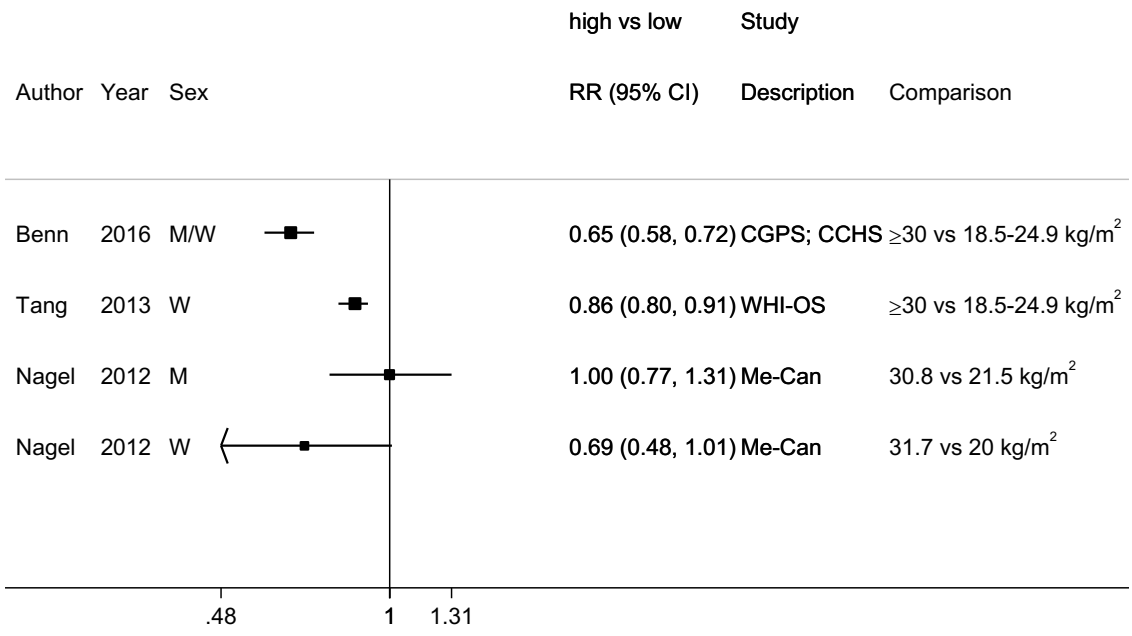


Figure 49 Relative risk of NMSC for 5 kg/m2 increase of BMI

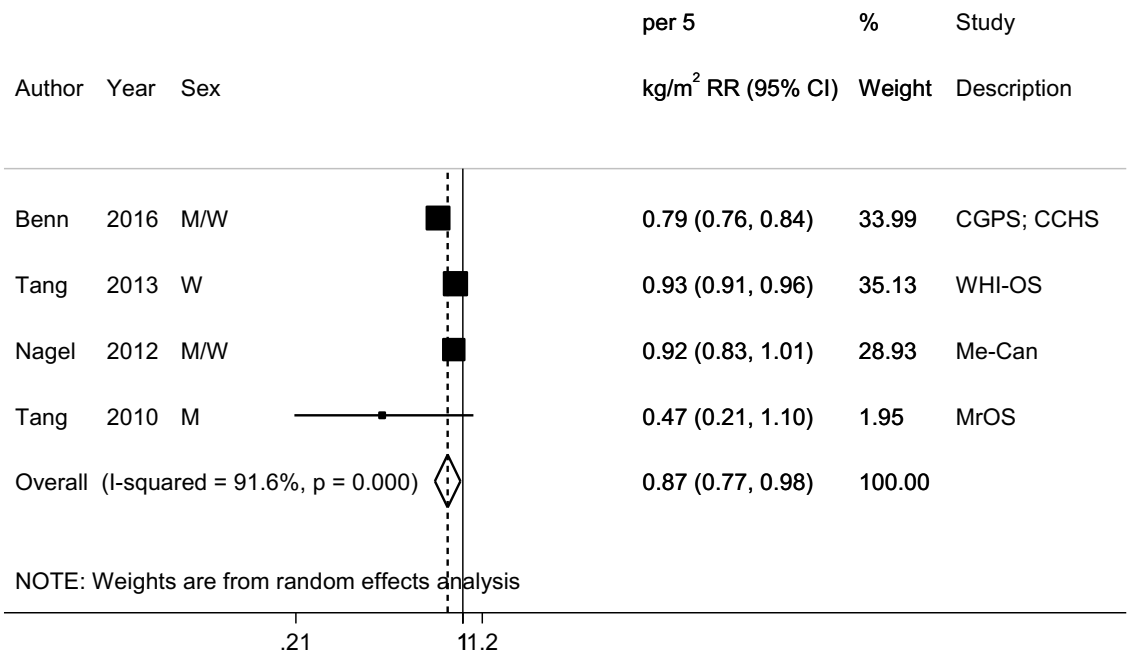


Figure 50 Relative risk of NMSC for 5 kg/m2 increase of BMI, by sex

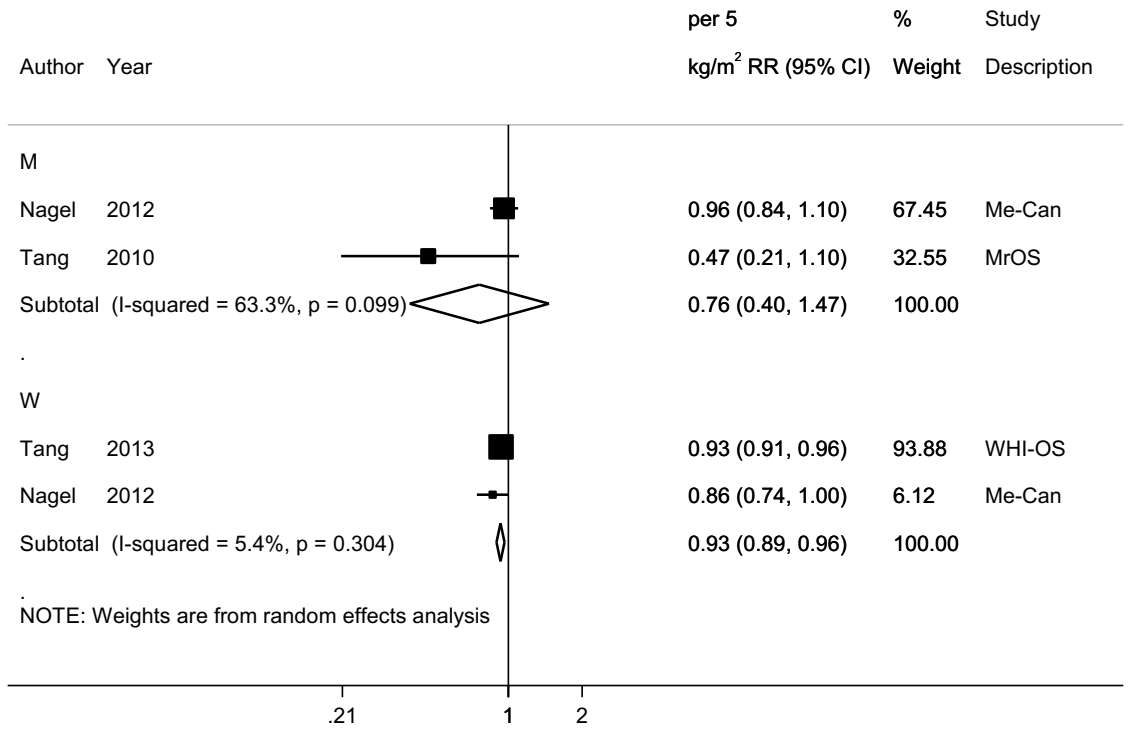


Figure 51 Relative risk of NMSC for 5 kg/m2 increase of BMI, by geographic location

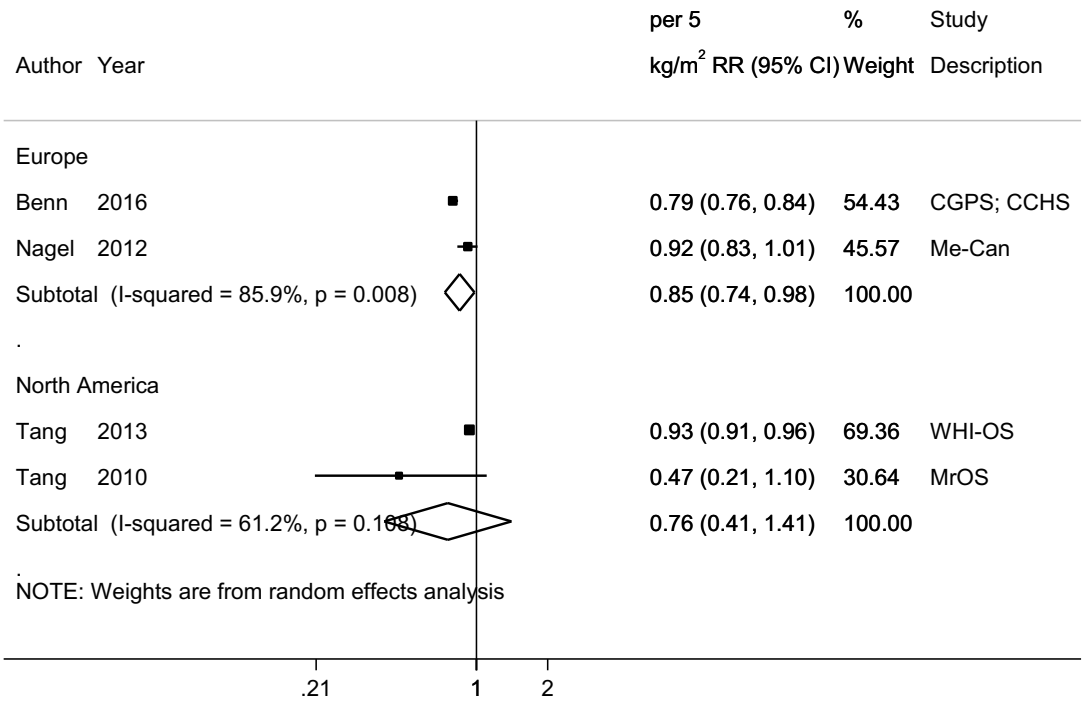


Figure 52 RR estimates of BCC by levels of BMI

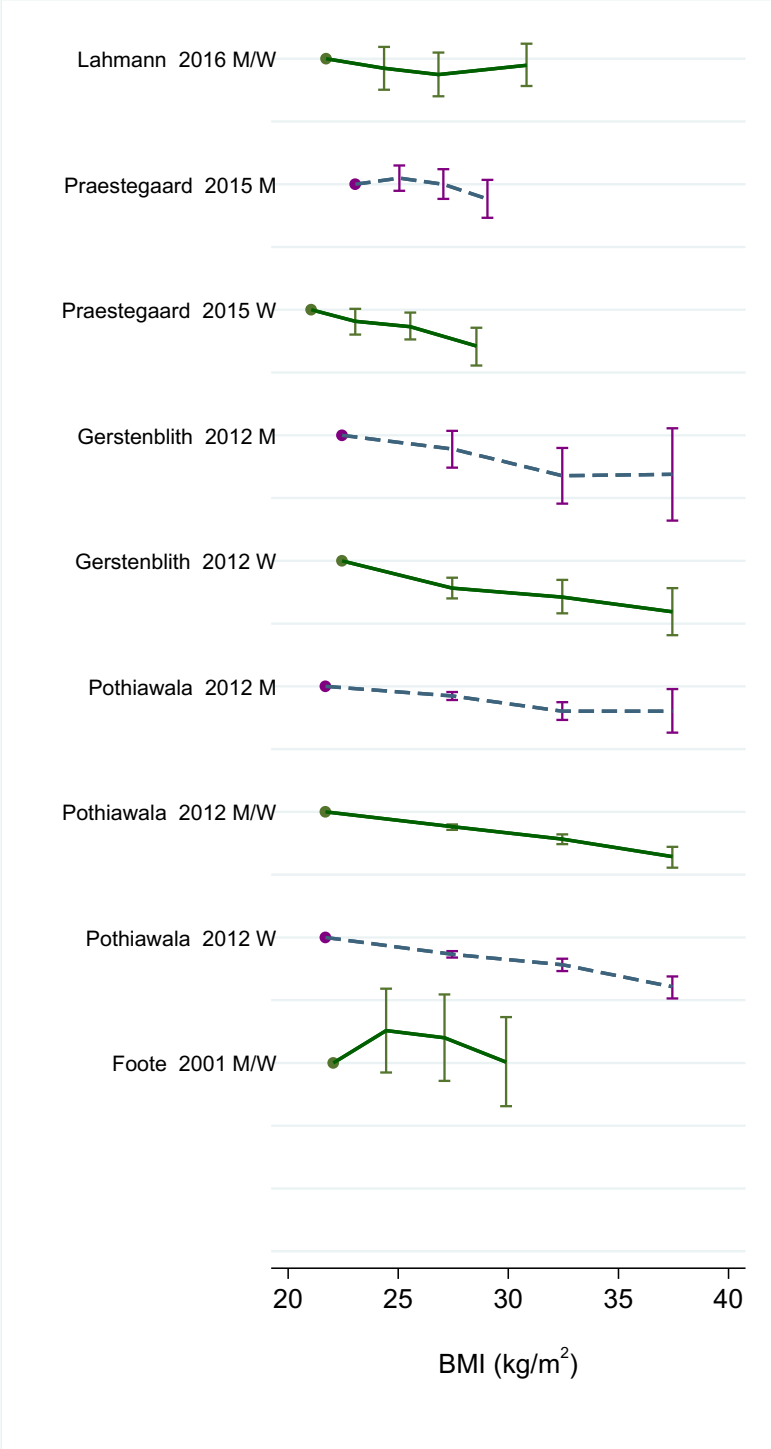


Figure 53 RR (95% CI) of BCC for the highest compared with the lowest level of BMI

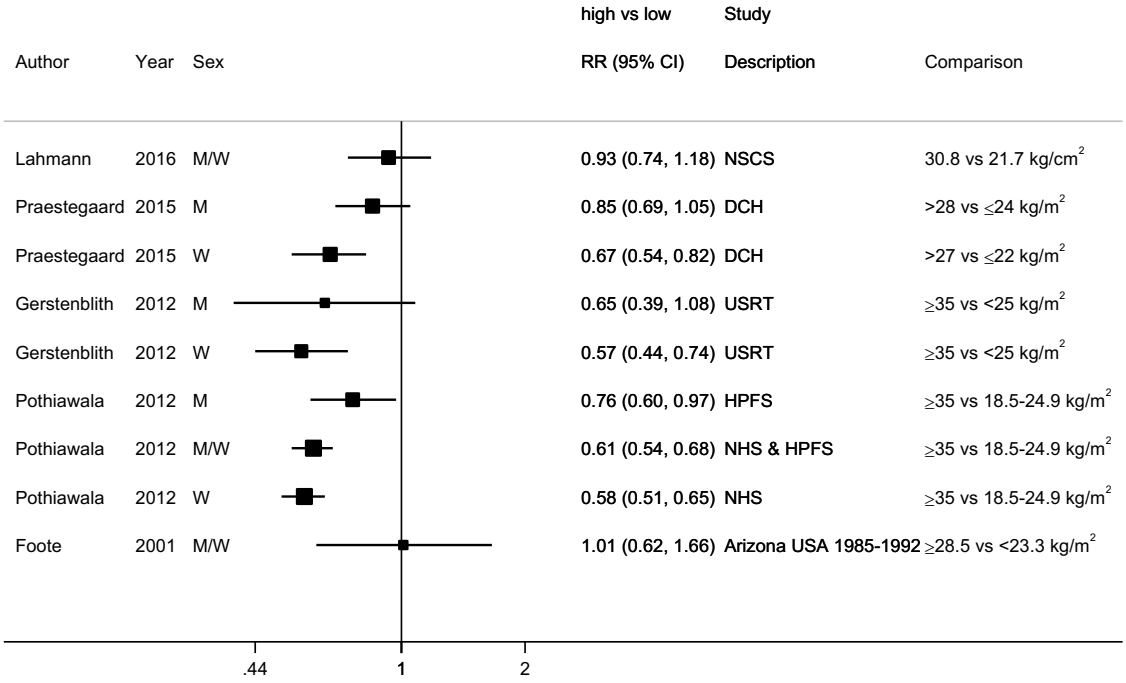


Figure 54 Relative risk of BCC for 5 kg/m2 increase of BMI

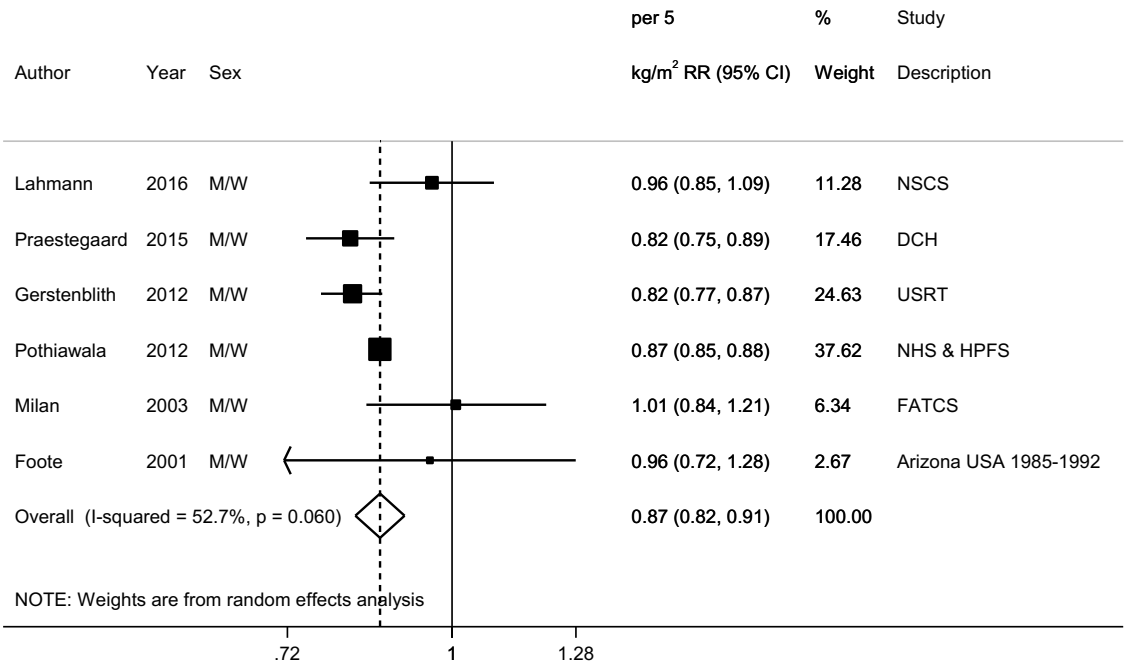


Figure 55 Funnel plot of studies included in the dose response meta-analysis of BMI and BCC

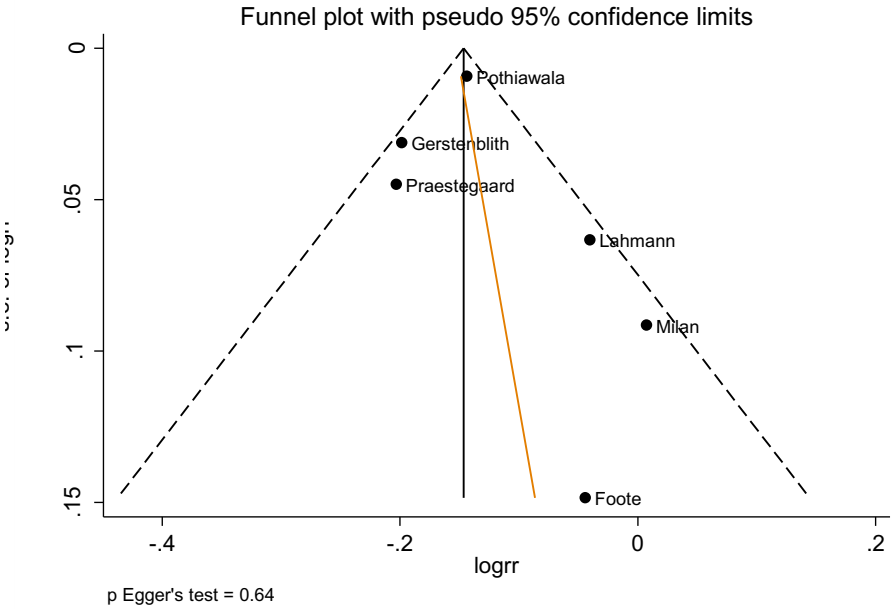


Figure 56 Relative risk of BCC for 5 kg/m2 increase of BMI, by sex

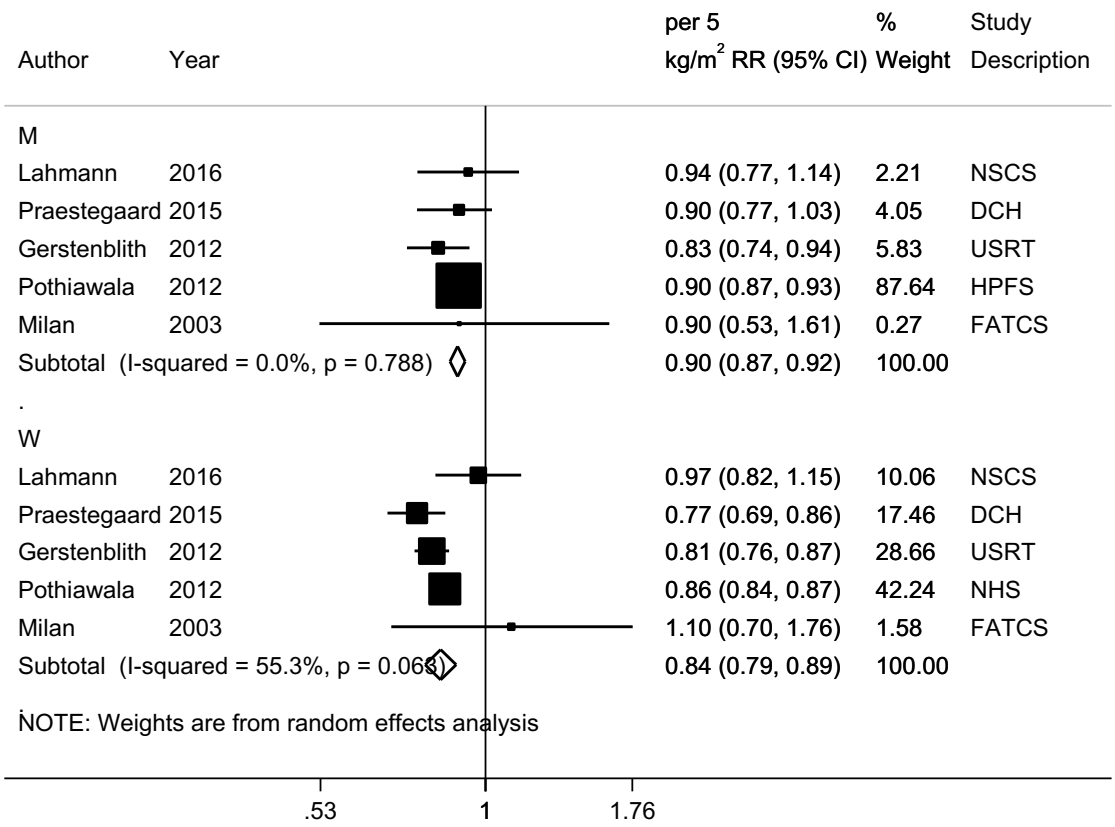


Figure 57 Relative risk of BCC for 5 kg/m2 increase of BMI, by geographic location

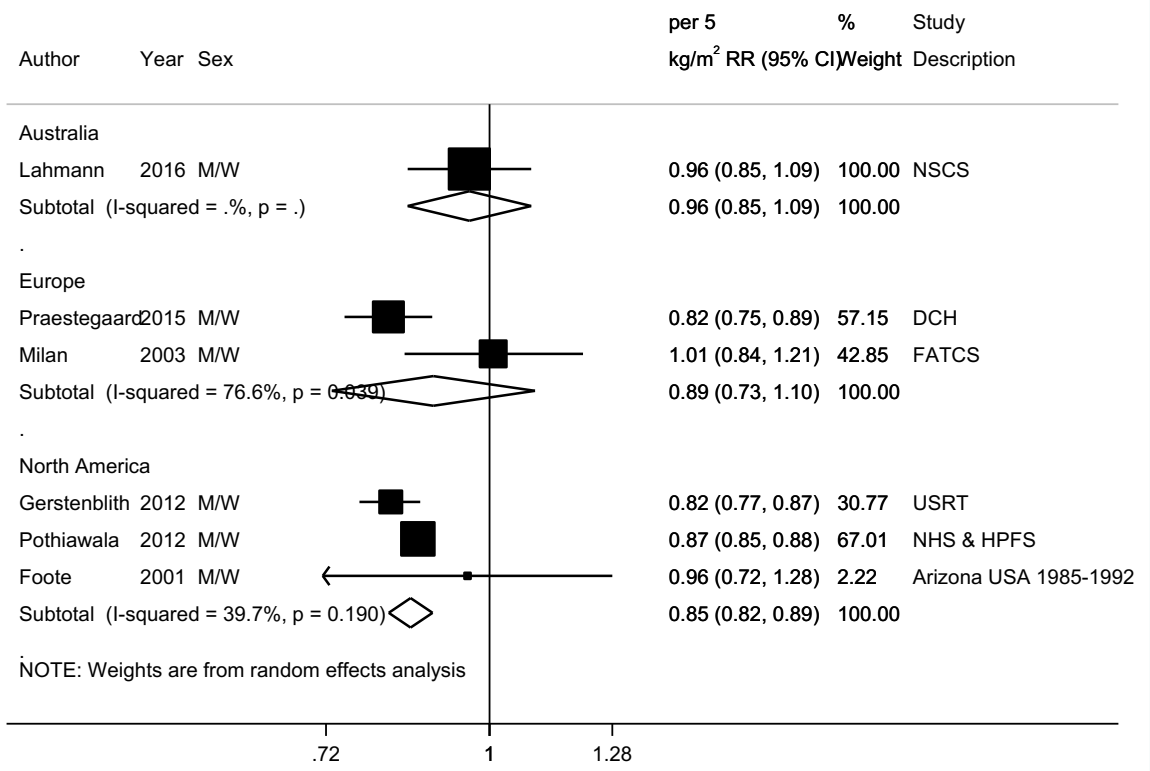
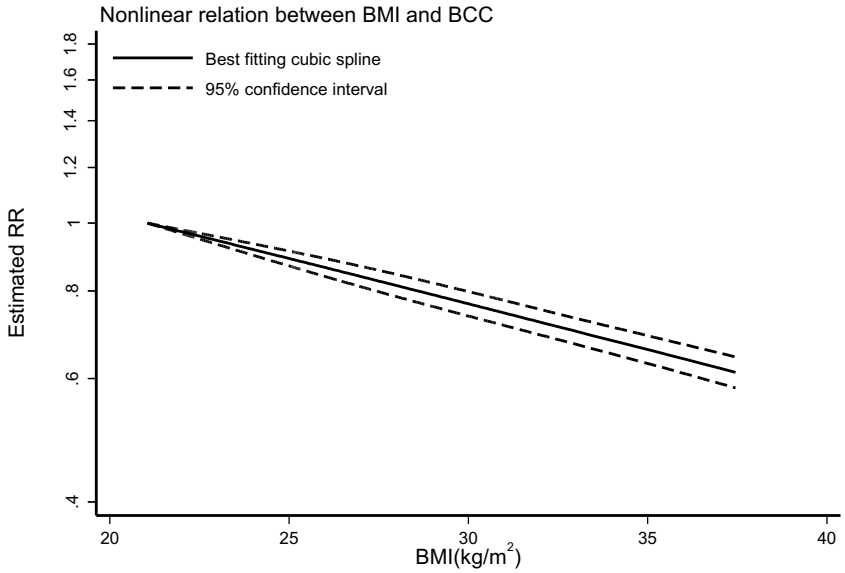


Figure 58 Nonlinear dose-response meta-analysis of BMI and BCC



P nonlinear = 0.86

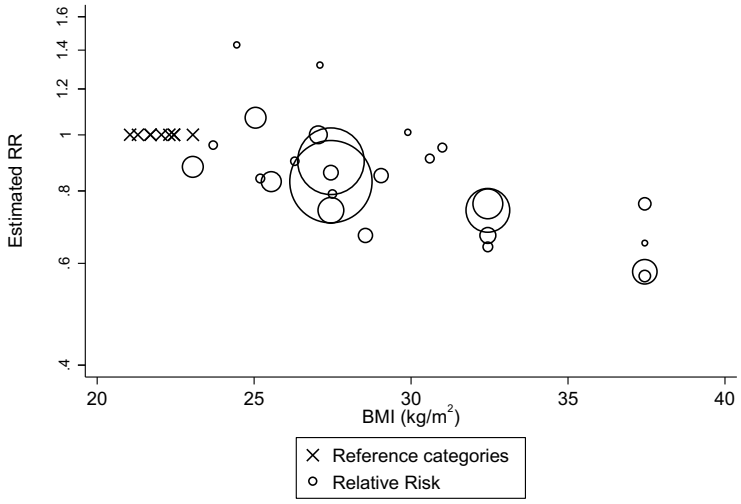


Table 51 Relative risk of BCC and BMI estimated using non-linear models

BMI (kg/m^2)	RR (95%CI)
21	1.00
22.5	0.96 (0.95-0.97)
24.5	0.90 (0.89-0.92)
27.0	0.84 (0.81-0.87)
29.0	0.79 (0.76-0.82)
32.5	0.71 (0.68-0.74)
37.5	0.61 (0.58-0.64)

Figure 59 RR estimates of SCC by levels of BMI

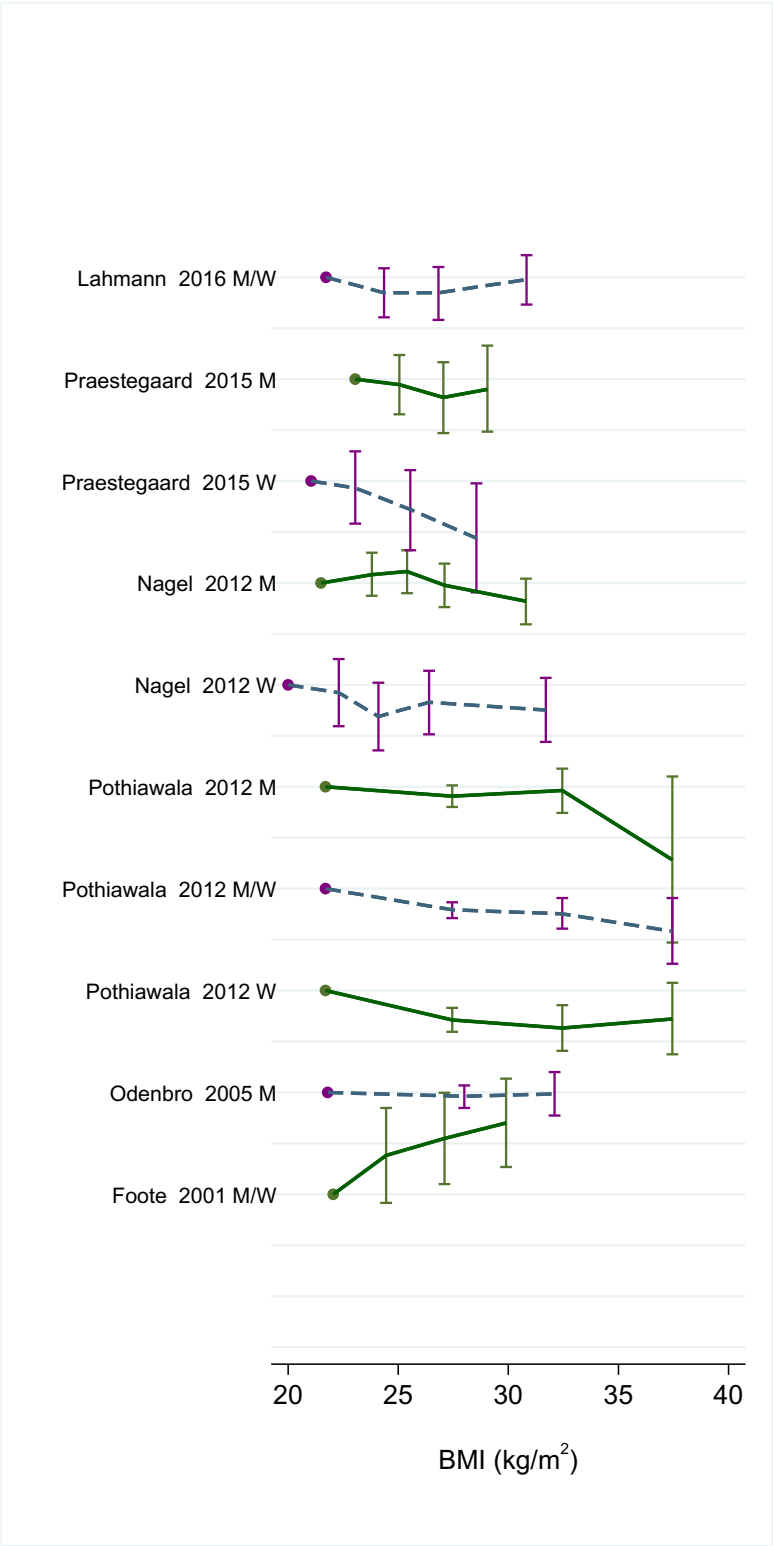


Figure 60 RR (95% CI) of SCC for the highest compared with the lowest level of BMI

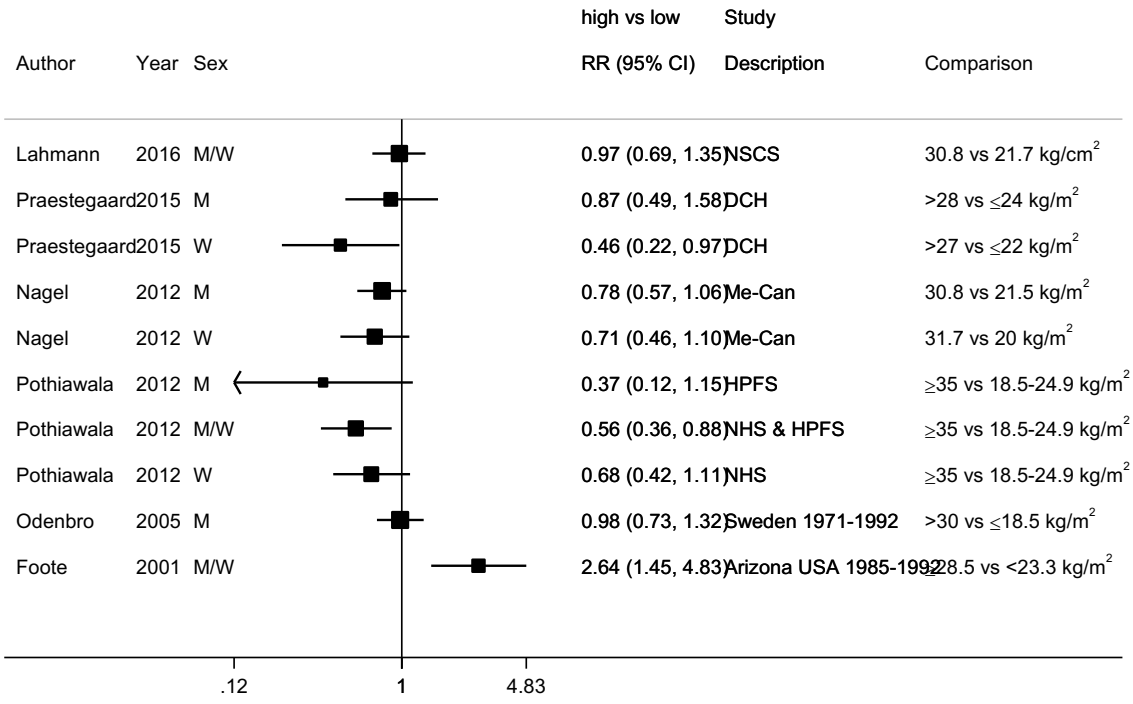


Figure 61 Relative risk of SCC for 5 kg/m2 increase of BMI

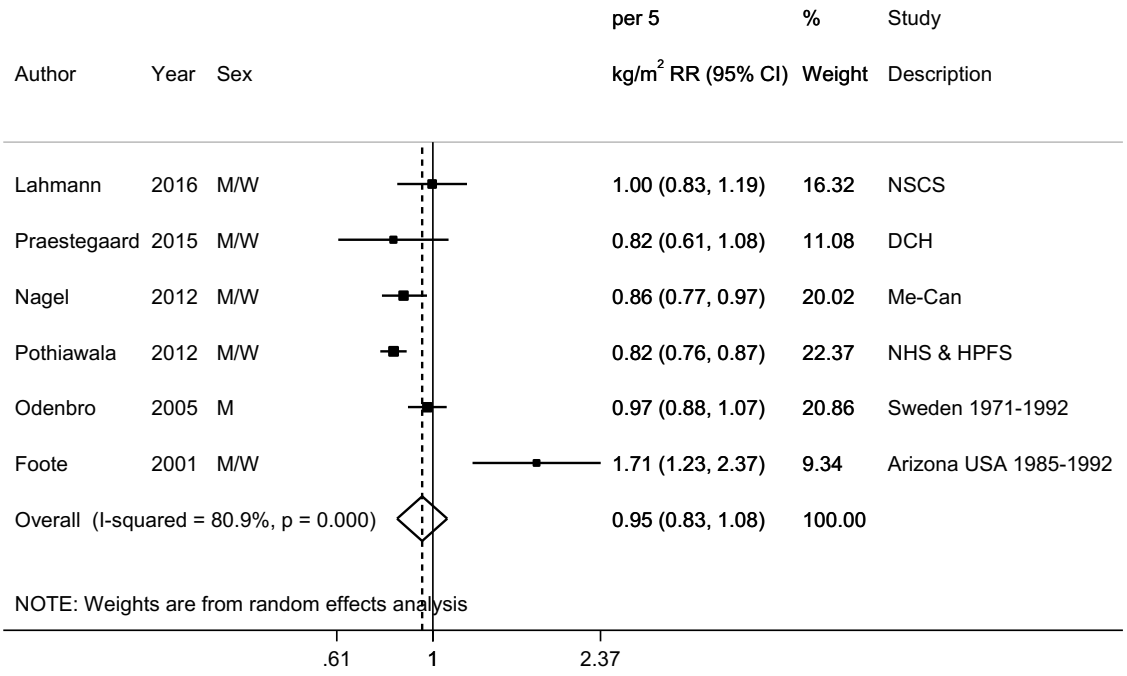


Figure 62 Funnel plot of studies included in the dose response meta-analysis of BMI and SCC

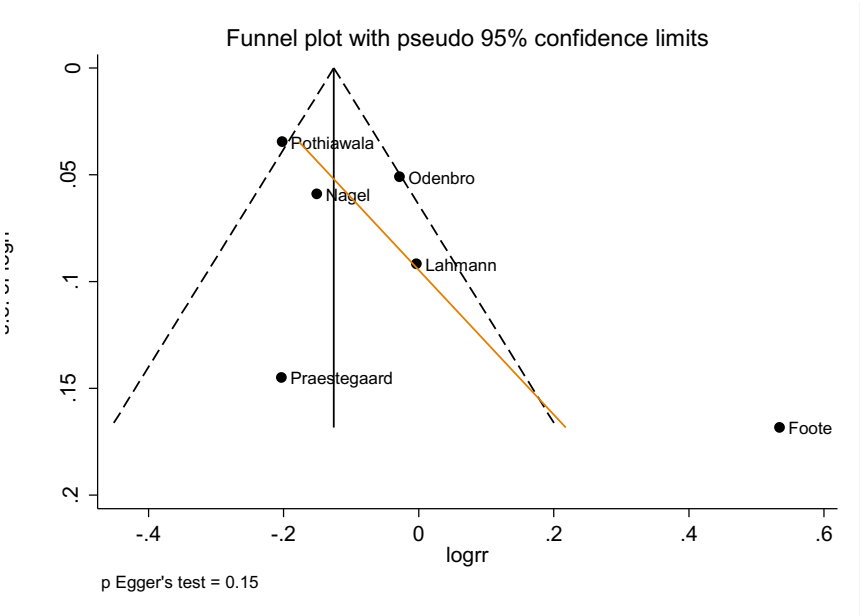


Figure 63 Relative risk of SCC for 5 kg/m2 increase of BMI, by sex

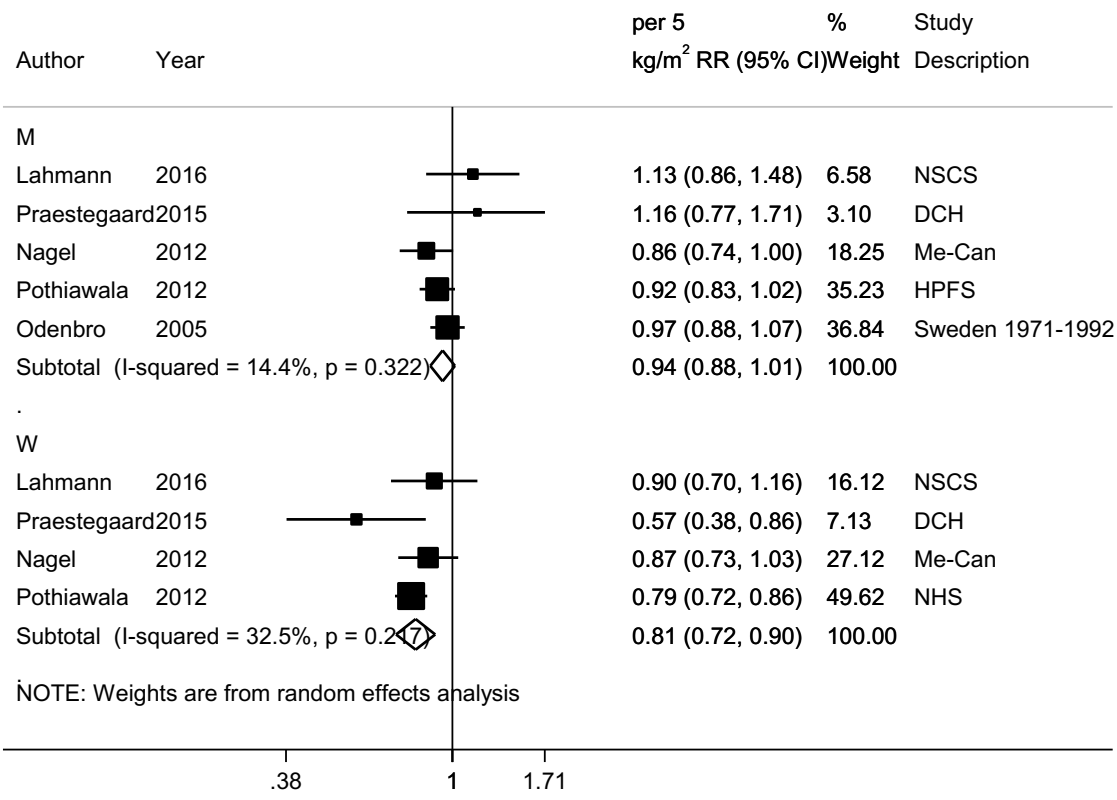


Figure 64 Relative risk of SCC for 5 kg/m2 increase of BMI, by geographic location

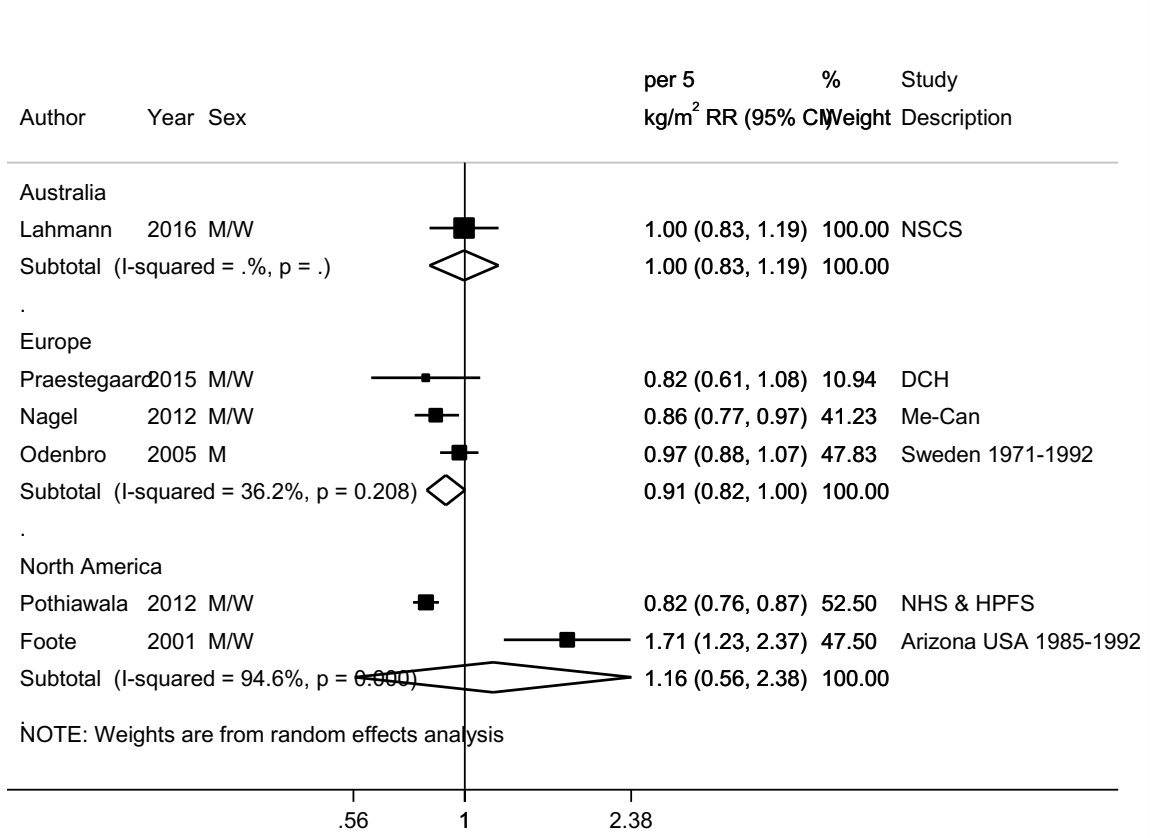
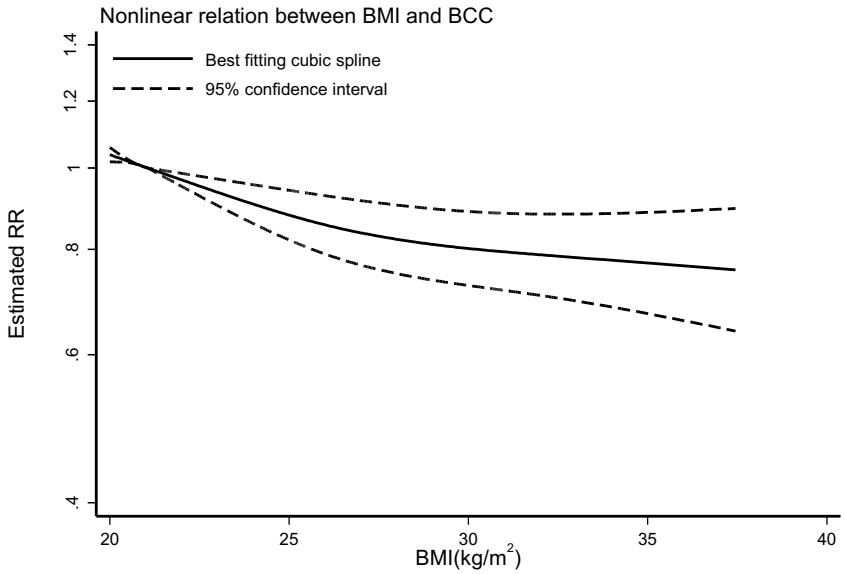


Figure 65 Nonlinear dose-response meta-analysis of BMI and SCC



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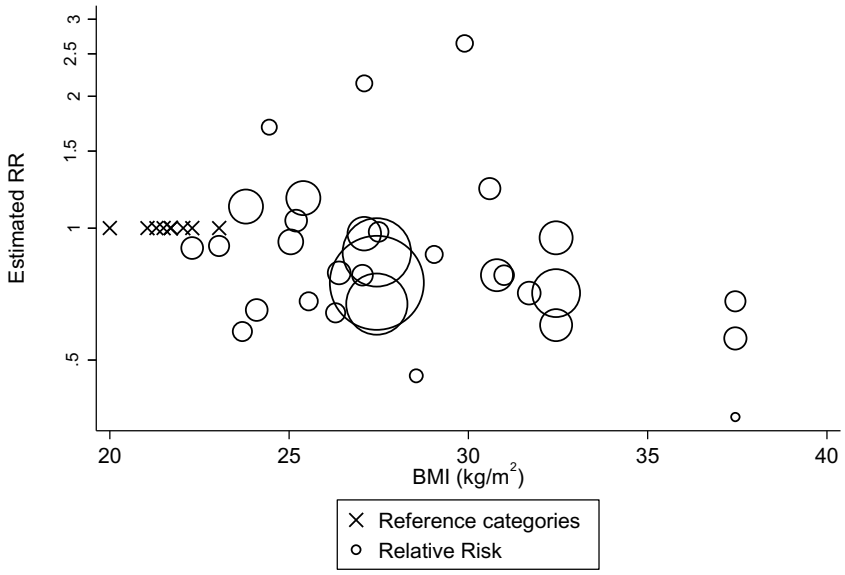


Table 52 Relative risk of SCC and BMI estimated using non-linear models

BMI (kg/m^2)	RR (95%CI)
20	1.04 (1.02-1.06)
21	1.00
22	0.97 (0.95-0.98)
24.1	0.90 (0.85-0.95)
27	0.84 (0.77-0.91)
31.7	0.79 (0.71-0.88)
32.5	0.79 (0.70-0.88)
37.5	0.76 (0.64-0.89)

8.1.1 BMI in early adulthood

Cohort studies

Summary

No studies were identified in the 2005 SLR and two studies (two publications on skin cancer and melanoma) were identified in the CUP. One study on body shape at menarche and early adulthood was identified.

No meta-analysis was conducted.

Skin cancer

In the Harvard Alumni Health Study cohort, BMI at around 18 years was positively but statistically non-significantly associated with skin cancer mortality after 56.5 years of follow-up, on average, RR: 1.29, 95% CI= (0.96-1.75), per 2.56 kg/m^2 increase in BMI (Gray, 2012).

Malignant melanoma

In the Agricultural Health Study cohort, self-reported BMI at the age of 20 was statistically significantly positively associated with melanoma incidence later in life, RR: 2.55, 95% CI= (1.52-4.30), comparing BMI of 25+ vs. <20 kg/m^2 (Dennis, 2008).

In the E3N cohort study, an inverse association was observed between a large body shape at menarche and melanoma risk (RR: 0.78, 95% CI= (0.62-0.98) compared with lean; Ptrend = 0.11), while body shapes at other ages were not associated with risk (Kvaskoff, 2014).

Table 53 BMI in early adulthood and skin cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Gray, 2012 USA	HAHS, Prospective Cohort, M, Age: 18.4	66/ 15 781 56.5 years	Death certificates	Measured height and weight during routine medical examination	Mortality, skin cancer, men	Per 2.56 kg/m^2	1.29 (0.96-1.75)	Adjusted for age, cigarette smoking status and physical activity at college entry & BMI in 1962/66
						>23 vs. <20 kg/m^2	1.60 (0.65-3.94) Ptrend:0.25	
Dennis, 2008 USA	AHS, Prospective Cohort, M/W, Age: 20 Pesticide applicators and their spouses	168/ 43 567	Cancer and death registries	Self-reported height and weight	Incidence, MM	25+ vs. <20 kg/m^2	2.55 (1.52-4.30) Ptrend:<0.001	Age at enrolment, gender, and tendency to burn

8.1.3 Weight

Cohort studies

Summary

Five studies (five publications on melanoma, NMSC and BCC) were identified in the 2005 SLR and five new studies (5 publications on melanoma and BCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

In the E3N prospective cohort (580 cases), inverse but no association was reported in women, RR: 0.96, 95% CI= (0.78-1.17), comparing ≥63 vs. <56 kg (Kvaskoff, 2014). Statistically non-significant positive association was reported in the AHS (168 cases), RR: 1.34, 95% CI= (0.81-1.20), comparing 75-150 vs. 201-499 pounds (Dennis, 2008). Positive but statistically non-significant associations were reported in the radiologic technologists' cohort in men and women, RR: 2.20, 95% CI= (0.80-6.10) and RR: 1.20, 95% CI= (0.70-2.00), respectively (Freedman, 2003a). In the WHI study, weight was not related to melanoma risk, RR: 0.99, 95% CI= (0.93-1.06), per increment of 1 score (Heo, 2015). Another two prospective cohort studies reported no estimates of association (Vessey, 2000; Whittemore, 1985).

Non-melanoma skin cancer

Two studies on NMSC reported no estimates of association (Schaumberg, 2004; Vessey, 2000).

Basal cell carcinoma

In the radiologic technologists' cohort, statistically significant inverse association of weight with BCC was reported in men and women, RR: 0.62, 95% CI= (0.44-0.87) and RR: 0.57, 95% CI= (0.48-0.68), respectively (Gerstenblith, 2012). In the Australian and the Finnish cohorts, no association was found in men, RR: 1.00, 95% CI= (0.60-1.50) and RR: 1.00, 95% CI= (0.71-1.41), respectively (Olsen, 2006; Milan, 2003). The same studies reported statistically non-significant association in women, RR: 1.40, 95% CI= (0.90-2.40) and RR: 1.09, 95% CI= (0.79-1.51), respectively (Olsen, 2006; Milan, 2003).

Table 54 Weight and skin cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Heo, 2015 SKI23437 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 169/ 144 701 12 years	Self-report verified by medical record and pathology report	Measured	Incidence, MM	Per 1 score	0.99 (0.93-1.06)	Age, alcohol, educational level, ethnicity, height, hormone use, randomisation, smoking
Kvaskoff, 2014 SKI23428 France	E3N, Prospective Cohort, W	580/ 91 972	Follow up questionnaires (self-report), medical record and pathology reports	Self-reported weight was available in each questionnaire	Incidence, MM	≥63 vs. <56 cm	0.96 (0.78-1.17)	Age, hair colour, number of freckles, number of naevi, physical activity, skin complexion, mean UV radiation dose in countries of birth and of residence, skin sensitivity to sun exposure
Gerstenblith, 2012 SKI23432 USA	USRT, Prospective Cohort, M/W, radiologic technologists	485/ 11 631 8.75 years	Self-report verified by medical record and pathology report	Self-reported weight from the baseline questionnaire.	Incidence, BCC, men	≥215 vs. ≤164 lbs	0.62 (0.44-0.87) Ptrend:0.01	Age, alcohol intake, educational level, eye colour, hair colour, household income, number of sunburns, physical activity, radiation dose, skin colour, tobacco use, acute and chronic reactions to sunlight, geographical measure of sun exposure (TOMS), hours outdoors in summer
		1 781/ 46 582			Women	≥170 vs. ≤124 lbs	0.57 (0.48-0.68) Ptrend:<0.0001	
Dennis, 2008 USA	AHS, Prospective	168/ 44 086	Population-based state	Self-reported weight in	Incidence, MM	201-499 vs. 75-150 lbs	1.34 (0.81-2.20) Ptrend:0.20	Age, sex, tendency to burn

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Cohort, M/W, Pesticide applicators and their spouses		cancer registries	questionnaire				
Olsen, 2006 SKI23434 Australia	NSCS, Prospective Cohort, Age: 25-75 years, M/W	80/ 650 4.5 years	Dermatologists & pathology labs	Measured at baseline and re-measured at the end of the field trial	Incidence, BCC, women	Q 4 vs. Q 1	1.40 (0.90-2.40) Ptrend:0.22	Age, history of BCC
		76/ 486			Men		1.00 (0.60-1.50) Ptrend:0.29	
		80/701			Prevalence BCC, women		1.10 (0.70-1.90) Ptrend:0.14	Age
		87/532			Men		0.90 (0.50-1.00) Ptrend:0.45	
Schaumberg, 2004 SKI00367 USA	PHS, Case Cohort, Age: 40-84 years, M	22 071	Not stated		Incidence, NMSC	Lean vs. not lean	Ptrend:<0.001	-
Freedman, 2003a SKI00519	USRT, Prospective Cohort,	159/ 68 588 (men and women)	Ongoing or prior study	Questionnaire	Incidence, MM, women	≥68.1 vs. ≤54.4 kg	1.20 (0.70-2.00) Ptrend:0.7	Age, sex, adult sunlight exposure, alcohol consumption, area of residence, decade since began to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	Age: 39 years, M/W, radiologic technologists				Men	≥88.6 vs. ≤72.6 kg	2.20 (0.80-6.10) Ptrend:0.14	work as radiological technician, educational level, hair colour, height, personal history of NMSC, skin pigmentation, smoking habits
Milan, 2003 SKI00640 Finland	Finnish Adult Twin Cohort Study, Case Cohort, M/W	184/ 13 888 15.2 years	Histologically confirmed	Self-reported height and weight	Incidence, BCC, women	Per 1 kg	1.09 (0.79-1.51)	Age, ethnicity, sunlight (most twin pairs were exposed to a similar environment until the age of 16)
		149/			Men		1.00 (0.71-1.41)	
Vessey, 2000 SKI17457 UK	OFPACS, Prospective Cohort, Age: 25-39 years, W, users of contraceptives	48/ 17 032	Family planning clinic	Questionnaire	Incidence, MM	-	-	-
		83/ 17 032			NMSC			
Whittemore, 1985 SKI22091 USA	HPALS, Case Cohort, M/W, college alumni	51 477	Alumni offices and questionnaires	College physical examination	Incidence, MM	-	-	-

8.1.6 Change in weight

Cohort studies

Summary

No studies were identified in the 2005 SLR and two studies (two publications on melanoma and BCC) were identified in the CUP.

No meta-analysis was conducted. The few studies identified did not support an association of weight change and melanoma or BCC.

Malignant melanoma

In the VHM&PP prospective cohort, inverse but statistically non-significant association was reported in women (RR for weight change >0.3 compared to -0.1-<0.1 kg/m^2/year: 0.45, 95% CI= 0.20-1.02) and positive but statistically non-significant association was reported in men, (RR for weight change >0.3 compared to -0.1-<0.1 kg/m^2/year: 1.25, 95% CI=0.56-2.81) (Rapp, 2008).

Basal cell carcinoma

In an Australian cohort, no association with short term weight change was reported in men (RR for weight change 4-10 kg compared to -3.9 -4 kg: 1.10, 95% CI= 0.60-1.90) and women (RR for weight change ≥10 kg compared to -3.9 -4 kg: 1.70, 95% CI= 0.50-5.60) (Olsen, 2006).

8.2.1 Waist circumference

Cohort studies

Summary

No studies were identified in the 2005 SLR and four studies (four publications on melanoma, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

In the Danish Cohort Study, no association of melanoma risk with waist circumference was reported in men and women (RR for an increment of 5 cm: 1.06, 95% CI= 0.94-1.19, and 0.91, 95% CI=0.82-1.02), respectively)(Praestegaard, 2015). No association was observed in the E3N, a French women cohort with self-reported anthropometric measurements (RR: 1.04, 95% CI= 0.80-1.35, comparing ≥81 vs. <73 cm) (Kvaskoff, 2014).

Basal cell carcinoma

In the Danish Cohort Study, weight circumference was inversely related BCC (RR for an increment of 5 cm: 0.94, 95% CI= 0.90-0.98 in men and 0.96, 95% CI= 0.93-0.99 in women). Adjustment included sun sensitivity, degree of freckling, number of nevi and hip circumference (Praestegaard, 2015). No association was found when comparing highest with lowest waist circumference levels in an Australian cohort, RR: 1.00, 95% CI= 0.60-1.50 in men 1.00, 95% CI= 0.80-1.40 in women) (Olsen, 2006).

Squamous cell carcinoma

In the Danish Cohort Study, no association was reported in men, RR: 0.99, 95% CI= 0.88-1.11 and women, RR: 1.02, 95% CI= (0.91-1.15), for an increment of 5 cm (Praestegaard, 2015).

8.2.2 Hip circumference

Cohort studies

Summary

No studies were identified in the 2005 SLR and two studies (two publications on melanoma, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted. The few studies identified don't support an association of hip circumference and risk of melanoma or BCC. One study is suggestive of an inverse association with SCC.

Malignant melanoma

In the Danish Cohort Study, no association was reported in men, RR: 1.04, 95% CI= 0.87-1.24) and women, RR: 1.10, 95% CI= (0.96-1.25), for an increment of 5 cm (Praestegaard, 2015), and in the E3N, a French women cohort, RR: 0.95, 95% CI= (0.73-1.22), when comparing ≥100 vs. <94 cm (Kvaskoff, 2014).

Basal cell carcinoma

In the Danish Cohort Study, no association was reported in men, RR: 0.98, 95% CI= (0.92-1.04) and women, RR: 0.96, 95% CI= (0.92-1.00), for an increment of 5 cm (Praestegaard, 2015).

Squamous cell carcinoma

In the Danish Cohort Study, no association was reported in men, RR: 0.93, 95% CI= (0.78-1.11) and women, RR: 0.86, 95% CI= (0.74-1.01), for an increment of 5 cm (Praestegaard, 2015). In the highest vs. lowest analysis, statistically significant inverse association was reported in women, RR: 0.51, 95% CI= (0.27-0.96), comparing >105 cm vs. ≤95 cm.

8.2.3 Waist to hip ratio

Cohort studies

Summary

No studies were identified in the 2005 SLR and four studies (four publications on melanoma, BCC and SCC) were identified in the CUP.

No meta-analysis was conducted.

Malignant melanoma

No association was reported in the Danish Cohort Study, in men, RR: 1.07, 95% CI= (0.95-1.21) and women, RR: 0.92, 95% CI= (0.82-1.02), for an increment of 0.05 unit

(Praestegaard, 2015), and in the E3N, a French women cohort, RR: 1.15, 95% CI= (0.88-1.48), comparing ≥0.82 vs. <0.77 units (Kvaskoff, 2014).

Basal cell carcinoma

In the Danish Cohort Study, statistically significant inverse association was reported in men, RR: 0.93, 95% CI= (0.89-0.97) and in women, RR: 0.94, 95% CI= (0.91-0.98), for an increment of 0.05 units (Praestegaard, 2015). In the Australian cohort, waist-to-hip ratio was not associated with BCC in men, RR: 0.90, 95% CI= (0.50-1.50) and women, RR: 1.10, 95% CI= (0.70-1.70) in the high vs. low comparison of two categories (Olsen, 2006).

Squamous cell carcinoma

In the Danish Cohort Study, no association was reported in men, RR: 0.97, 95% CI= (0.86-1.09) and women, RR: 1.01, 95% CI= (0.90-1.13), for an increment of 0.05 units (Praestegaard, 2015).

Table 55 Change in weight, waist circumference, hip circumference, waist to hip ratio and skin cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Heo, 2015 SKI23437 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 169/ 144 701 12 years	Self-report verified by medical record and pathology report	Measured **Waist circumference**	Incidence, MM	Per 1 score	0.97 (0.91-1.04)	Age, alcohol, educational level, ethnicity, height, hormone use, randomisation, smoking
				Waist to hip ratio			0.97 (0.91-1.03)	
Praestegaard, 2015 Denmark	DCH, Prospective cohort, M/W	169/ 29 243 14.4 years	MM cases identified by linkage to the Danish Cancer Registry, whereas all NMSC cases were identified through linkage to NMSC database	Measured by trained healthcare professionals **Waist circumference**	Incidence, MM, women	Q4 vs. Q1	0.73 (0.41-1.31)	Age, sun sensitivity, degree of freckling and number of nevi, waist circumference and hip circumference are mutually adjusted
						Per 5 cm	0.91 (0.82-1.02)	
				Hip circumference		Q4 vs. Q1	1.34 (0.76-2.36)	
						Per 5 cm	1.10 (0.96-1.25)	
				Waist to hip ratio		Q4 vs. Q1	0.76 (0.49-1.19)	
						Per 0.05 unit	0.92 (0.82-1.02)	
		188/ 26 685		**Waist circumference**	Men	Q4 vs. Q1	1.05 (0.60-1.83)	
						Per 5 cm	1.06 (0.94-1.19)	
				Hip		Q4 vs. Q1	1.24 (0.71-2.18)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
				circumference		Per 5 cm	1.04 (0.87-1.24)	
				Waist to hip ratio		Q4 vs. Q1	1.06 (0.71-1.61)	
						Per 0.05 unit	1.07 (0.95-1.21)	
		1 794/ 29 243		**Waist circumference**	BCC, women	Q4 vs. Q1	0.85 (0.72-1.01)	
						Per 5 cm	0.96 (0.93-0.99)	
				Hip circumference		Q4 vs. Q1	0.86 (0.72-1.02)	
						Per 5 cm	0.96 (0.92-1.00)	
				Waist to hip ratio		Q4 vs. Q1	0.88 (0.77-1.01)	
						Per 0.05 unit	0.94 (0.91-0.98)	
		1 671/ 26 685		**Waist circumference**	Men	Q4 vs. Q1	0.83 (0.68-1.01)	
						Per 5 cm	0.94 (0.90-0.98)	
				Hip circumference		Q4 vs. Q1	0.94 (0.77-1.14)	
						Per 5 cm	0.98 (0.92-1.04)	
				Waist to hip ratio		Q4 vs. Q1	0.78 (0.68-0.91)	
						Per 0.05 unit	0.93 (0.89-0.97)	
		138/ 29 243		**Waist circumference**	SCC, women	Q4 vs. Q1	0.83 (0.45-1.55)	
						Per 5 cm	1.02 (0.91-1.15)	
				Hip circumference		Q4 vs. Q1	0.51 (0.27-0.96)	
						Per 5 cm	0.86 (0.74-1.01)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
				Waist to hip ratio		Q4 vs. Q1	1.06 (0.66-1.69)	
						Per 0.05 unit	1.01 (0.90-1.13)	
		203/ 26 685		**Waist circumference**	Men	Q4 vs. Q1	0.72 (0.42-1.26)	
						Per 5 cm	0.99 (0.88-1.11)	
				Hip circumference		Q4 vs. Q1	0.75 (0.43-1.31)	
						Per 5 cm	0.93 (0.78-1.11)	
				Waist to hip ratio		Q4 vs. Q1	0.79 (0.52-1.20)	
						Per 0.05 unit	0.97 (0.86-1.09)	
Kvaskoff, 2014 SKI23428 France	E3N, Prospective Cohort, W	351/ 91 972 18 years maximum	Follow up questionnaires (self-report) confirmed by medical records and pathology reports	Self-reported **Waist circumference**	Incidence, MM	≥81 vs. <73 cm	1.04 (0.80-1.35)	Age, hair colour, number of freckles, number of naevi, physical activity, skin complexion, mean UV radiation dose in countries of birth and of residence, skin sensitivity to sun exposure
		350/		**Hip circumference**		≥100 vs. <94 cm	0.95 (0.73-1.22)	
		349/		**Waist to hip ratio**		≥0.82 vs. <0.77 ratio	1.15 (0.88-1.48)	
Rapp, 2008 SKI22184 Austria	VHM&PP, Prospective cohort, Age: 42.3 years, M/W	64/ 36 938 8 years	Cancer registry	Measured at every screening examination **Weight change**	Incidence, MM women	>0.3 vs. -0.1-<0.1 kg/m²/year	0.45 (0.20-1.02) Ptrend:0.07	Age, smoking status, blood glucose, occupational group and BMI at baseline
		53/ 28 711			Men		1.25 (0.56-2.81) Ptrend:0.72	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Olsen, 2006 SKI23434 Australia	NSCS, Prospective Cohort, Age: 25-75 years, M/W	73/ 572 4.5 years	Dermatologists & pathology labs	Measured at baseline **Weight change**	Incidence, BCC, women	4-10 vs. -4-3.9 kg	1.30 (0.80-2.30) Ptrend:0.62	Age, history of BCC, weight at baseline, hair and eye colour
		73/ 432			Men	+10 vs. -4-3.9 kg	1.70 (0.50-5.60) Ptrend:0.63	
		79/ 643		**Waist circumference**	Women	80-87.9 vs. <80 cm	1.00 (0.80-1.40)	Age, history of BCC, hair colour
		76/ 481			Men	102+ vs. <94 cm	1.00 (0.60-1.50)	
		79/ 642		**Waist to hip ratio**	Women	>0.85 vs. ≤ 0.85	1.10 (0.70-1.70)	Age, history of BCC
		76/ 481			Men	>1 vs. ≤ 1	0.90 (0.50-1.50)	

8.3.1 Height (and proxy measures)

Overall summary

Twenty-one publications examining the association of height and risk of any type of skin cancer were identified. Eighteen publications included data of 13 cohort studies on cancer incidence and 1 cohort on cancer mortality, and three publications were pooled analyses; one with 7 cohorts in cancer incidence (Me-Can project on melanoma; cohorts: Oslo, NCS, CONOR, 40-years--, VHM&PP, VIP, MPP; Wiren, 2014), and two on mortality including 44 cohorts (Asian Pacific cohorts, Batty, 2010), and 121 cohort (ERFC, 2012) respectively. Six of the studies were identified in the 2005 SLR.

Dose-response meta-analysis was conducted to examine the association between height and risk of melanoma. The studies on mortality for malignant melanoma and height were not summarised in a dose-response meta-analysis due to overlap of study populations.

Table 56 Height and skin cancer risk. Number of studies in the CUP SLR.

	Number
Studies identified (excluding studies on mortality)	20 (19 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (3 publications) melanoma risk NMSC, BCC, SCC – not enough studies
Studies included in linear dose-response meta-analysis	15 (9 publications) melanoma risk NMSC, BCC, SCC – not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

*Incidence only

Skin cancer

Summary

Main results:

Fifteen studies out of 18 identified studies (14 publications) on melanoma incidence could be included in the dose-response meta-analysis on melanoma, including a pooled analysis of seven cohort studies. There were not enough studies to conduct dose-response meta-analysis on other types of skin cancer.

Two studies reported on any skin cancer. Height was not associated with skin cancer incidence in men and women in one study (Sung, 2009) but it was significantly positively associated with skin cancer mortality in another study in men (Batty, 2006).

Malignant melanoma

Height was statistically significantly positively associated with melanoma, RR: 1.12, 95% CI=(1.09-1.16). The data on cancer incidence from the Me-Can study (Wiren, 2014) were included in the analysis. Three studies were excluded from the dose-response meta-analysis on incidence. One study reported a statistically significant positive association in men and women (Thune, 1993) and the other two studies did not report estimates of association (Vessey, 2000; Whittemore, 1985).

Mortality from melanoma was investigated in three pooled analyses (Me-Can, Wiren, 2014; APCSC, 44 studies, Batty, 2010; ERFC, 2012). In the Me-Can, there was no association in men (246 cases), RR: 1.10, 95% CI=0.99-1.21, and women (102 cases), RR: 1.09, 95% CI=0.92-1.29 (Wiren, 2014). In the APCSC, the association was statistically significant and positive in men (63 cases), RR: 1.44, 95% CI=1.15-1.79, and there was no association in women (25 cases), RR: 1.04, 95% CI=0.71-1.52 (Batty, 2010). The ERFC (679 cases) reported a statistically significant positive association, RR: 1.26, 95% CI=(1.12-1.42), for an increment of 6.5 cm (ERFC, 2012).

There was statistically significant evidence of heterogeneity in the dose-response meta-analysis. Egger's test showed no statistical significant evidence of publication or small study bias. However, the funnel plot show asymmetry that was driven by a stronger than expected positive asociation in a small Norwegian study (28 cases, Lahmann, 2016).

The high heterogeneity was not explained in stratified analyses by sex, geographical region, level of adjustment, number of cases, and duration of follow-up. No heterogeneity was found in European studies and studies adjusted for age, sex and some indicator of skin colour and/or sun exposure.

Sensitivity analyses:

In influence analysis excluding one study at a time, the association ranged from 1.11 (95% CI=1.08-1.14) when Kabat, 2013a (CNBSS; 8 % weight) was omitted to 1.13 (95% CI=1.10-1.17) when Kabat, 2014 (22 % weight) was omitted.

Nonlinear dose-response meta-analyses were not conducted due to low number of studies.

Non-melanoma skin cancer

No individual cohort studies investigating the association of height and risk of NMSC were identified. A pooled analysis of seven cohort studies reported a statistically significant positive association of height with NMSC in men (699 cases), RR: 1.10, 95% CI=(1.03-1.16) and women (424 cases), RR: 1.12, 95% CI=(1.04-1.22), for an increment of 5cm in measured height (Wiren, 2014).

Sensitivity and nonlinear dose-response meta-analyses were not conducted due to low number of studies.

Basal cell carcinoma

Two studies reported on BCC incidence (Gerstenblith, 2012; Lahmann, 2016). One study reported a statistically significant positive association in women (1 786 cases), RR: 1.64, 95% CI=(1.40-1.93), and a statistically non-significant positive association in men (481 cases), RR: 1.34, 95% CI=(0.94-1.89), comparing highest vs. lowest quintile of self-reported height (Gerstenblith, 2012).

In a follow-up study of participants in a trial on skin cancer prevention, a statistically significant positive association was reported, RR: 1.28, 95% CI=(1.01-1.62, 334 cases), comparing highest vs. lowest quartile of measured height (Lahmann, 2016). In stratified analysis, a statistically non-significant positive association was reported in men (160 cases), RR: 1.21, 95% CI=(0.86-1.70) and women (174 cases), RR: 1.35, 95% CI=(0.96-1.90).

Sensitivity and nonlinear dose-response meta-analyses were not conducted due to low number of studies.

Squamous cell carcinoma

One study investigating the association between height and risk of SCC was identified (Lahmann, 2016). No association was reported, RR: 1.11, 95% CI=(0.78-1.58), comparing highest vs. lowest quartile of measured height. In stratified analysis, statistically non-significant positive association was reported in men (98 cases), RR: 1.53, 95% CI=(0.93-2.51), and non-significant inverse association was reported in women, RR: 0.80, 95% CI=(0.47-1.37), (90 cases).

Sensitivity and nonlinear dose-response meta-analyses were not conducted due to low number of studies.

Study quality:

Four studies used self-reported height (Kabat, 2014; Kvaskoff, 2014; Kabat, 2013a CNBSS; Walter, 2013) and all remaining studies used measured height.

Three studies adjusted for some indicator of skin colour and/or sun exposure in addition to other confounders (Lahmann, 2016; Kabat, 2014; Kvaskoff, 2014). Lahmann, 2016 adjusted for elastosis of the neck and freckling of the back, Kabat, 2014 adjusted for UV exposure and Kvaskoff, 2014 adjusted for skin and hair colour, skin sensitivity to sun exposure, number of freckles, number of naevi and mean UV radiation dose in countries of birth and residence.

One study was adjusted minimally for age, sex, and race (Walter, 2013). The pooled study of seven cohorts adjusted for date of birth, age, and stratified for sub-cohort within the model (Wiren, 2014).

Three studies included participants from randomized controlled trials (Lahmann, 2016 NSCS; Kabat, 2013b WHI; Kabat, 2013a CNBSS). The study that originated from a breast cancer screening randomised controlled trial (Kabat, 2013a CNBSS) and a follow-up study of trial participants on skin cancer (Lahmann, 2016 NSCS) reported positive associations.

Table 57 Height and melanoma risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP.

	2005 SLR*	CUP
Increment unit used	5 cm	
Malignant melanoma		
Studies (n)	-	15
Cases	-	13 020
RR (95%CI)	-	1.12 (1.09-1.16)
Heterogeneity (I^2, p-value)	-	64%, <0.01
P value Egger test	-	0.31
Malignant Melanoma: stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	10	14
Cases	4 711	7 960
RR (95%CI)	1.10 (1.05-1.15)	1.12 (1.08-1.17)
Heterogeneity (I^2, p-value)	45%, 0.14	58%, 0.02
Geographic area	**Australia**	**Europe**
Studies (n)	1	9
RR (95%CI)	1.28 (0.97-1.71)	1.15 (1.12-1.18)
Heterogeneity (I^2, p-value)	-	0%, 0.83
Geographic area	**North America**	
Studies (n)	5	
RR (95%CI)	1.10 (1.06-1.14)	
Heterogeneity (I^2, p-value)	53%, 0.08	
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**
Studies (n)	4	11
RR (95%CI)	1.08 (1.06-1.10)	1.13 (1.09-1.18)
Heterogeneity (I^2, p-value)	0%, 0.64	60%, 0.04
Duration of follow-up	**<10 years**	**≥10 years**
Studies (n)	2	13

RR (95%CI)	1.14 (1.10-1.18)	1.12 (1.07-1.16)
Heterogeneity (I^2, p-value)	0%, 0.34	66%, <0.01
Number of cases	**<1000 cases**	**≥1000 cases**
Studies (n)	5	10
RR (95%CI)	1.15 (1.08-1.23)	1.11 (1.07-1.15)
Heterogeneity (I^2, p-value)	31%, 0.23	80%, <0.01

*Dose-response meta-analysis was not conducted in the 2005 SLR.

Table 58 Height and malignant melanoma cancer mortality. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses	-	-	-	-	-	-	-
Pooled-analyses							
Me-Can Wiren, 2014	7 prospective cohorts	246	Austria, Norway, Sweden	Mortality, melanoma, men	Per 5 cm	1.10 (0.99-1.21)	-
		102		Women		1.09 (0.92-1.29)	-
ERFC, 2012	121 prospective cohorts	679	Worldwide	Mortality, melanoma	Per 6.5 cm	1.26 (1.12-1.42)	43%
APCSC Batty, 2010	44 prospective cohorts	63	Asia Pacific	Mortality, melanoma, men	Per 6 cm	1.44 (1.15-1.79)	-
		25		Women		1.04 (0.71-1.52)	-

Table 59 Height and skin cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Lahmann, 2016 SKI23471 Australia	NSCS, Follow-up of a trial on skin cancer, Age: 25-75, M/W	28/ 1 171 14.4 years	Cancer registry (melanoma), BCC and SCC were verified histologically	Height measured at baseline	Incidence, MM	Per 5 cm	1.28 (0.97-1.71)	Age, treatment allocation, BCC/SCC history, elastosis of the neck, freckling of the back, smoking status	RR rescaled to 5 cm increment
		11/			Men		1.55 (0.97-2.47)		
		17/			Women		1.12 (0.76-1.64)		
		334/			Incidence, BCC	Q4 vs. Q1	1.28 (1.01-1.62) Ptrend:0.015		Mid-points of exposure categories
		160/506			Men	≥179.9 vs. <170.9 cm	1.21 (0.86-1.70)		
		174/ 665			Women	≥166.5 vs. <158 cm	1.35 (0.96-1.90)		
		188/			Incidence, SCC	Q4 vs. Q1	1.11 (0.78-1.58)		
		98/ 506			Men	≥179.9 vs. <170.9 cm	1.53 (0.93-2.51)		
		90/ 665			Women	≥166.5 vs. <158 cm	0.80 (0.47-1.37)		
Kabat, 2014 SKI23403 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W,	3 556/ 288 683 10.5 years	Cancer registry and national death index	Self-reported height	Incidence, MM, men	Per 10 cm	1.18 (1.13-1.23)	Age, BMI, educational level, race, smoking, UV exposure [ground level dose in residence place]	RRs rescaled to 5 cm increment RRs for men and women combined
		1 224/			Women		1.14 (1.05-1.24)	Additionally adjusted for	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Retired	192 514 10.5 years						age at menarche	using fixed effects model
Kvaskoff, 2014 SKI23428 France	E3N, Prospective Cohort, W	588/ 91 972 18 years maximum	Follow up questionnaires (self-report) confirmed by medical records and pathology reports	Self-reported height	Incidence, MM	≥164 vs. ≤159 cm	1.18 (0.97-1.44)	Age, hair colour, number of freckles, number of naevi, physical activity, skin complexion, mean UV radiation dose in countries of birth and of residence, skin sensitivity to sun exposure	Mid-points of exposure categories
Wiren, 2014 Austria, Norway, Sweden	Me-Can, Pooled analysis of seven prospective cohorts (Oslo, NCS, CONOR, 40-y, VIP, MPP, VHM&PP)	1 096/ 288 772 12.7 years	Cancer registries	Measured height	Incidence, MM, men	Per 5 cm	1.13 (1.08-1.19)	Date of birth, age and stratified for sub-cohort within the model	RRs for men and women combined using fixed effects model
		893/ 297 156 12.7 years			Women		1.17 (1.11-1.24)		
		699			Incidence, NMSC, men		1.10 (1.03-1.16)		
		424			Women		1.12 (1.04-1.22)		
		246			Mortality, MM, men		1.10 (0.99-1.21)		Dose-response meta-analysis on mortality was not conducted
		102			Women		1.09 (0.92-1.29)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Kabat, 2013a SKI22182 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	327/ 88 256 16.2 years	Record linkages to cancer database and the national mortality database	Measured height	Incidence, MM	Per 10 cm	1.51 (1.27-1.80)	Age at baseline, menopausal status, years of education, BMI	RR rescaled to 5 cm increment
Kabat, 2013b SKI23430 USA	WHI, Prospective Cohort, Age: 50-79 years, W	1 169/ 144 701 12 years	Self-report verified by medical records and pathology reports	Measured height	Incidence, MM	Per 10 cm	1.15 (1.04-1.26)	Age, alcohol, BMI, educational level, ethnicity, hormone replacement therapy, pack-years, randomisation, smoking status	RR rescaled to 5 cm increment
Walter, 2013 SKI23431 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	349/ 65 038 7.3 years	Cancer registry	Self-reported height	Incidence, MM	Per 5 inches	1.28 (1.05-1.55)	Age, sex, race	RR rescaled to 5 cm increment
Green, 2011 SKI23433 UK	MWS, Prospective Cohort, Age: 56.1 years, W	3 583/ 1 297 124 9.4 years	Cancer registry	Measured height	Incidence, MM	Per 10 cm	1.32 (1.22-1.42)	Age, age at first child, age at menarche, alcohol intake, BMI, parity, region, smoking status, socio-economic status, strenuous exercise	RRs rescaled for an increment used
		1 943/			Never		1.34 (1.20-1.49)	Age, region,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers			socioeconomic status, alcohol intake, BMI, strenuous exercise, age at menarche, parity, age at first birth	
		478/			Current smokers		1.31 (1.06-1.61)		
Sung, 2009 SKI22178 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, M/W, middle-class adults	334/ 449 214 8.72 years	Linkage with cancer registry, national health insurance and death report	Measured height	Incidence, skin cancer, men	Per 5 cm	1.10 (0.99-1.22)	Age, BMI, cigarette smoking, alcohol consumption, regular exercise, area of residence, monthly salary level, occupation	
						≥171.1 vs. ≤164.5	1.41 (1.05-1.91)		
		202/ 339 575 8.72 years			Incidence, skin cancer, women	Per 5 cm	1.12 (0.97-1.29)	Age, BMI, cigarette smoking, alcohol consumption, regular exercise, age at menarche, duration of breastfeeding, age at first childbirth, menopausal status, oestrogen replacement, use of OC	
						≥158.1 vs. ≤151	1.42 (0.96-2.12)		
Freedman, 2003a SKI00519 USA	USRT, Prospective Cohort, Age: 39 years,	207/ 68 588 698 028 person-years	Self-report verified by medical record and pathology	Self-reported height	Incidence, MM,	-	-	Age, sex, adult sunlight exposure, alcohol consumption, area of residence, decade since	Persons-at risk and mid-points per exposure category;

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W, radiologic technologists		report					began to work as radiological technician, educational level, hair colour, personal history of NMSC, skin pigmentation, smoking habits, weight	RRs for men and women combined using fixed effects model
		159/ 54 045			Women	≥169 vs. ≤160 cm	1.30 (0.80-2.10) Ptrend:0.13		
		48/ 14 543			Men	≥184 vs. ≤173 cm	0.80 (0.30-1.90) Ptrend:0.79		

Table 60 Height and skin cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Yang, 2014 SKI23429 UK	MWS, Prospective Cohort, Age: 50-64 years, W	1 795/ 453 023 9.2 years	Cancer registry	Measured height	Incidence, MM	≥170 vs. ≤154 cm	RR (99% CI) 1.18 (1.04-1.33)	Age, year of birth, region of residence, socioeconomic status, having been breast fed as an infant, maternal smoking during pregnancy, maternal height, paternal height, age at menarche, parity, age had first baby, use of MHT, BMI, strenuous exercise, alcohol consumption, birth weight, smoking	Superseded by Green, 2011
The Emerging Risk Factor Collaboration, 2012	121 prospective studies, M/W	679/ 1 085 949		Measured for 81% and self-reported for 19%	Mortality, MM	Per 6.5 cm	1.26 (1.12-1.42)	Age, sex, smoking and year of birth	Dose-response meta-analysis on mortality not conducted. Overlapping other studies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Gerstenblith, 2012 SKI23432 USA	USRT, Prospective Cohort, M/W, radiologic technologists	1 786/ 46 582 8.75 years 481/ 11 631 8.75 years	Self-report verified by medical record and pathology report	Self-reported height	Incidence, BCC, Women men	≥67 vs. ≤62 inch ≥73 vs. ≤67 inch	1.64 (1.40-1.93) Ptrend:<0.0001 1.34 (0.94-1.89) Ptrend:0.05	Age, alcohol intake, educational level, eye colour, hair colour, household income, number of sunburns, physical activity, radiation dose, skin colour, tobacco use, acute and chronic reactions to sunlight, geographical measure of sun exposure (toms), hours outdoors in summer, weight	Dose-response meta-analysis for BCC was not conducted
Batty, 2010 Asia Pacific	APCSC, Pooled analysis of 44 Prospective Cohorts, Age: 48 years, M/W	63/ 506 648 (men and women) 25/	-	Measured height	Mortality, MM, men women	Per 6 cm	1.44 (1.15-1.79) 1.04 (0.71-1.52)	Age, study, year of birth	Dose-response meta-analysis on mortality was not conducted
Olsen, 2006 SKI23434 Australia	NSCS, Prospective Cohort, Age: 25-75 years, M/W	75/ 911 4.5 years 66/ 710 4.5 years	Dermatologists & pathology labs	Measured height	Incidence, BCC, women Men	Q 4 vs. Q 1	1.30 (0.80-2.30) Ptrend:0.62 0.90 (0.60-1.40) Ptrend:0.16	Age, history of BCC	Superseded by Lahmann, 2016

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Batty, 2006 SKI22199 UK	Whitehall study, Prospective Cohort, Age: 40-64 years, M	42/ 17 353 35 years	National cancer registers	Measured height	Mortality, skin cancer men	Per 5 cm ≥181 vs. ≤170.9 cm	1.35 (1.06-1.70) 7.27 (1.64-32.30) Ptrend:0.02	BMI, cholesterol, diabetes, disease at baseline, glucose intolerance, marital status, physical activity, smoking habits, systolic blood pressure, triceps skinfold thickness	Dose-response meta-analysis was not conducted
Milan, 2003 SKI00640 Finland	Finnish Adult Twin Cohort Study, Case Cohort, M/W	184/ 13 888 15.2 years 149/	Finnish Cancer Registry database	Questionnaire	Incidence, BCC, women Men	Per 1 SD	1.11 (0.49-2.48) 1.21 (0.66-2.21)	Age, ethnicity, sunlight	Excluded, exposure increment in not given
Vessey, 2000 SKI17457 UK	OFPACS, Prospective Cohort, Age: 25-39 years, W, users of contraceptives	17 032	Family planning clinic		Incidence, MM Incidence, NMSC	-	-	-	Excluded, no risk estimate
Veierod, 1997 SKI17728 Norway	NCS, Prospective Cohort, Age: 16-56 years, M/W	106/ 50 757 12.4 years	Cancer Registry of Norway	Measured height	Incidence, MM	≥177 vs. ≤163 cm	3.10 (1.40-6.70) Ptrend:<0.01	Age, sex, area of residence	Superseded by Pooled study Wiren, 2014

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Thune, 1993 SKI15897 Norway	NSPT, Prospective Cohort, Age: 30-84 years, M/W	2 814/ 697 647	Cancer Registry of Norway	Measured height	Incidence, MM, women	Q 5 vs. Q 1	1.59 (1.41-1.79)	Age, area of residence, BMI, birth cohort	Excluded, height in each quantile is not given, used in the highest vs. lowest comparison
		2 144/ 629 442			Men		1.60 (1.39-1.84)		
Whittemore, 1985 SKI22091 USA	HPALS, Case Cohort, M/W, college alumni	104/ 51 977	Alumni offices and questionnaires	Measured height	Incidence, MM	-	-	-	Excluded, no risk estimate

Figure 66 RR estimates of melanoma by levels of height

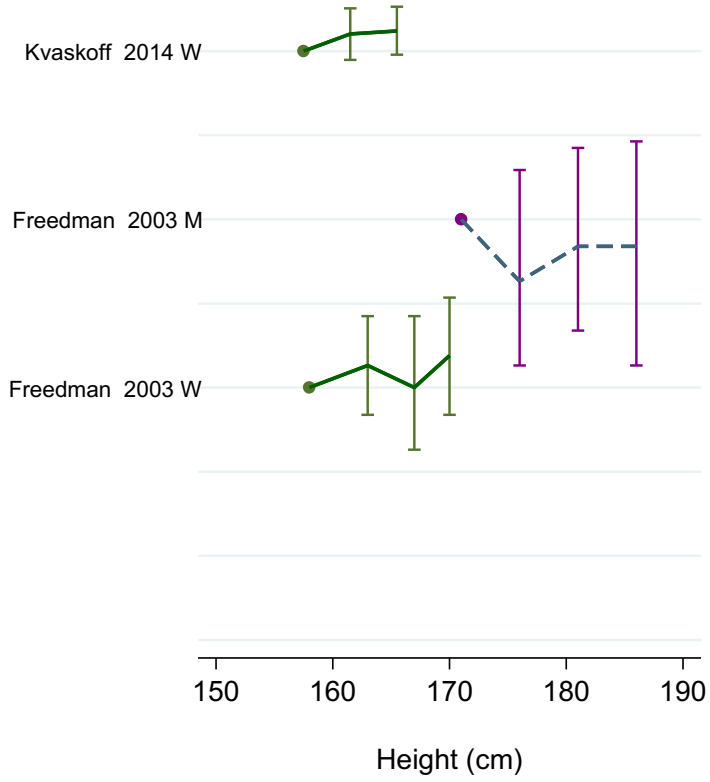


Figure 67 RR (95% CI) of melanoma for the highest compared with the lowest level of height

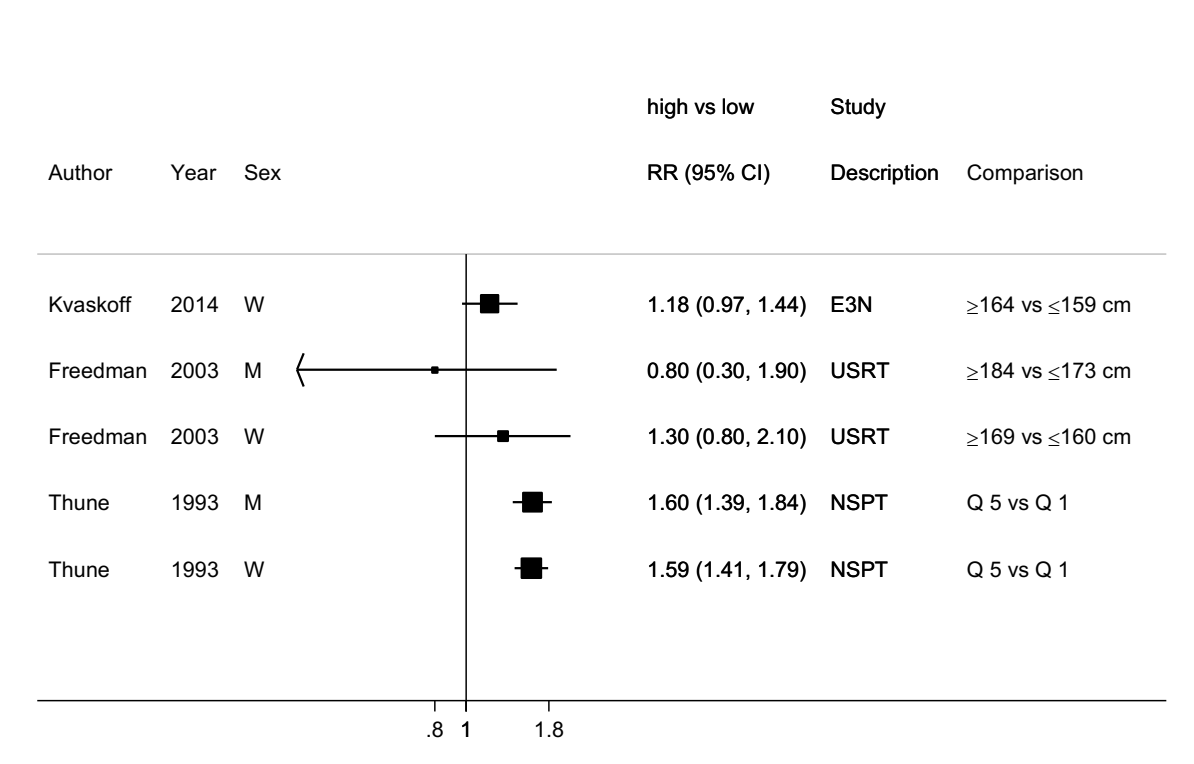


Figure 68 Relative risk of melanoma for 5 cm increase of height

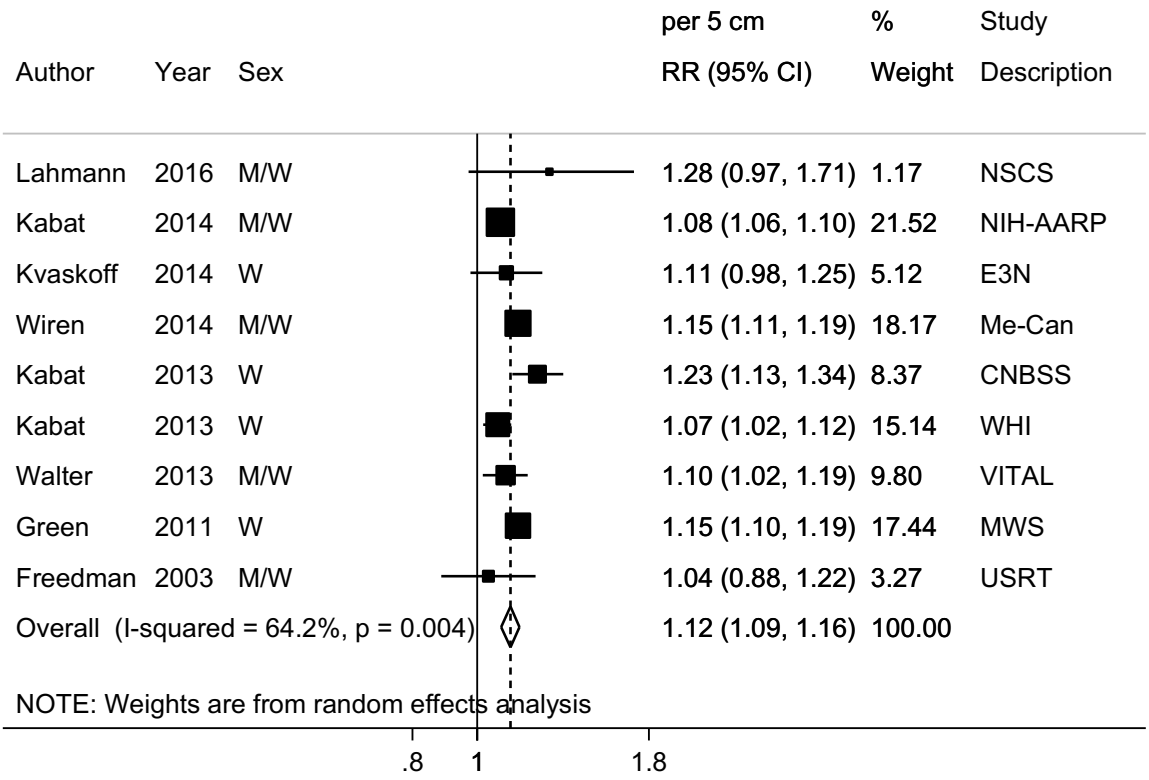


Figure 69 Funnel plot of studies included in the dose response meta-analysis of height and melanoma

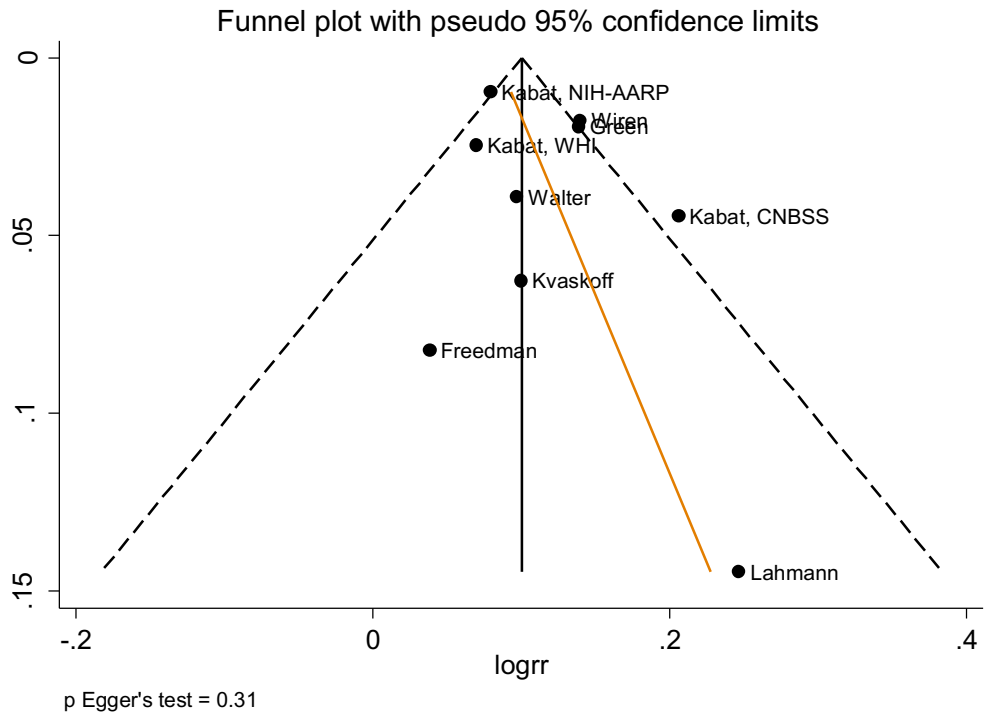


Figure 70 Relative risk of melanoma for 5 cm increase of height, by sex

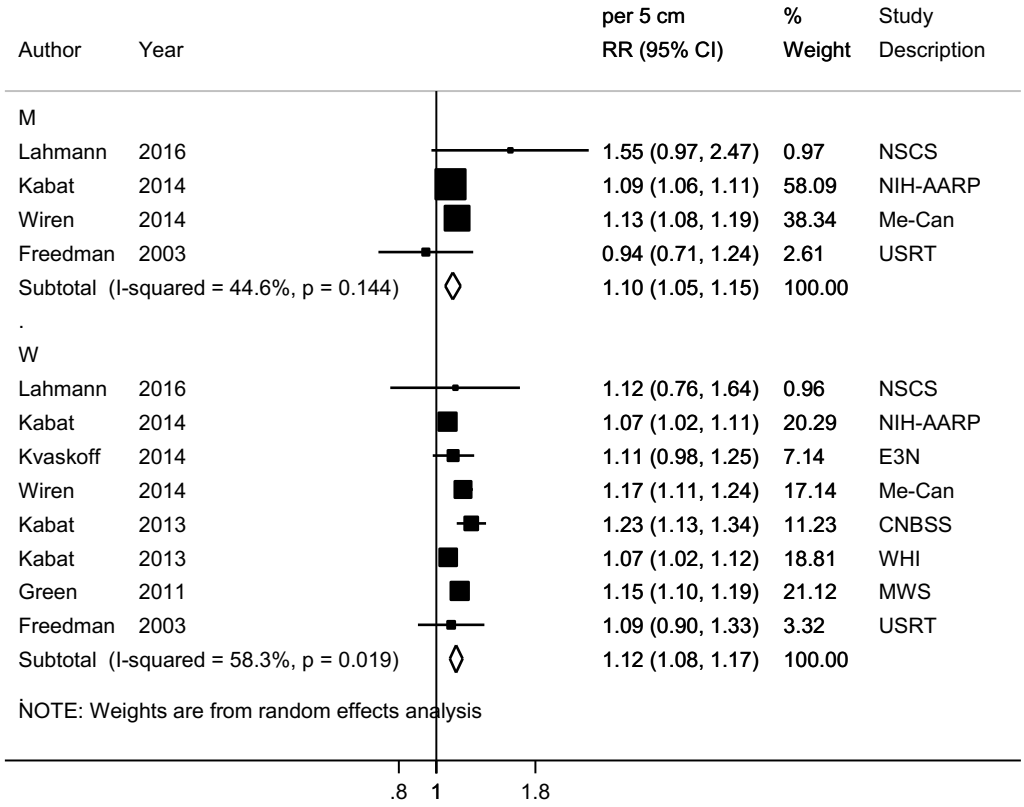
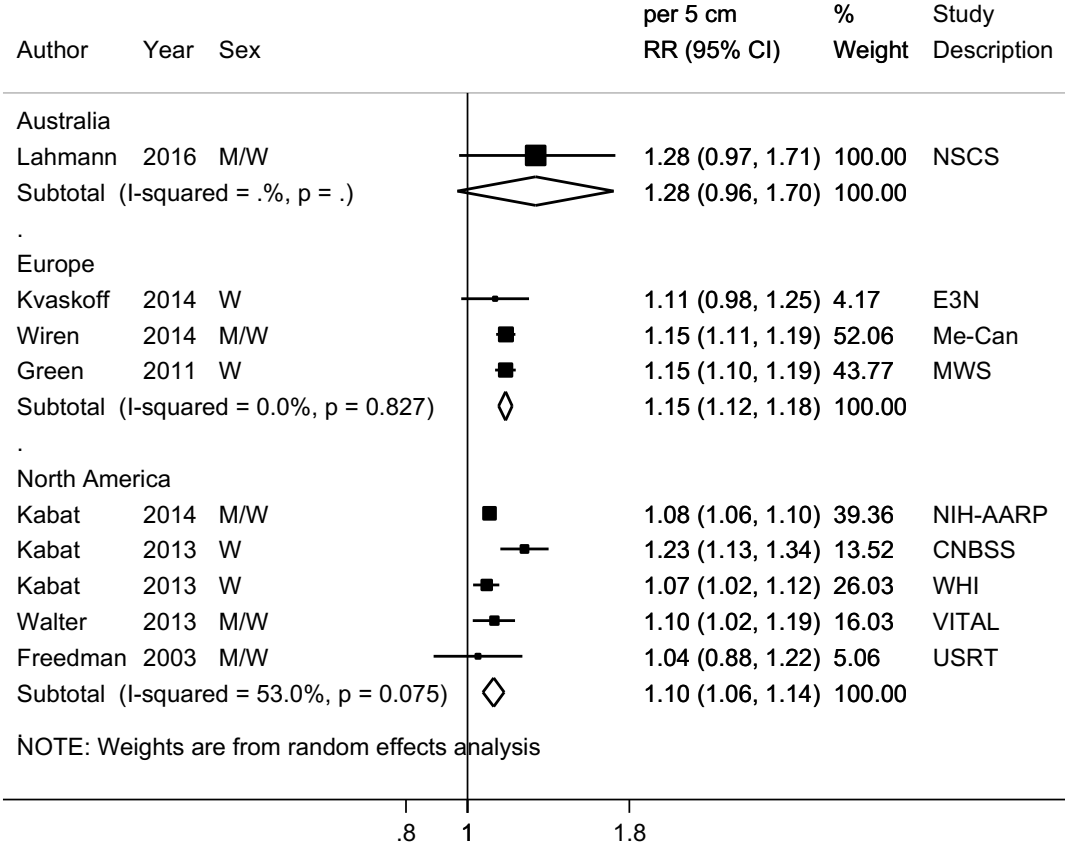


Figure 71 Relative risk of melanoma for 5 cm increase of height, by geographic location



8.4.1 Birthweight

Cohort studies

Summary

One study (one publication on melanoma) was identified in the 2005 SLR and five new studies (five publications on melanoma) were identified in the CUP.

Dose-response meta-analysis to examine association of birthweight and cutaneous melanoma was conducted.

Table 61 Birthweight and melanoma risk. Number of studies in the CUP SLR.

	Number
Studies identified	6 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	3 (3 publications) melanoma risk NMSC, BCC, SCC risk – no studies
Studies included in linear dose-response meta-analysis	5 (5 publications) melanoma risk NMSC, BCC, SCC risk – no studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

Cutaneous malignant melanoma

Summary

Main results:

Five studies out of 6 (6 publications) identified could be included in the dose-response meta-analysis on melanoma. A statistically significant positive association was observed (RR for 500 g increment: 1.06, 95% CI= 1.02-1.10). There was no evidence of heterogeneity, publication or small study bias.

One study was excluded from the dose-response meta-analysis. The study reported a statistically non-significant positive association comparing high birth weight, >90 percentile of 4 080 vs. no (Olesen, 2009).

Stratified analyses were limited by low number of studies.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis. The association ranged from 1.05 (95% CI=1.00-1.10) when Ahlgren, 2007 (35% weight) was omitted to 1.07 (95% CI=1.02-1.11) when (Spracklen, 2014) (21% weight) was omitted.

Nonlinear dose-response meta-analysis:

Nonlinear dose-response meta-analysis was not conducted due to low number of studies.

Study quality:

Two studies used self-reported birthweight (Spracklen, 2014; Yang, 2014).

One study adjusted only for age and calendar period (Ahlgren 2007) and all other studies used multivariate models. However, none of the studies adjusted for some indicator of skin colour and/or sun exposure.

Table 62 Birthweight and skin cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and 2016 CUP.

	2005 SLR*	**CUP**
Increment unit used	500 g	
Malignant melanoma		
Studies (n)	-	5
Cases	-	3 561
RR (95%CI)	-	1.06 (1.02-1.10)
Heterogeneity (I^2, p-value)	-	0%, 0.92
P value Egger test	-	0.49
Malignant Melanoma: stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	-	2
Cases	-	2 361
RR (95%CI)	-	1.05 (0.99-1.11)
Heterogeneity (I^2, p-value)	-	0%, 0.54
Geographic area	**Europe**	**North America**
Studies (n)	4	1
RR (95%CI)	1.07 (1.02-1.11)	1.02 (0.94-1.12)
Heterogeneity (I^2, p-value)	0%, 0.96	-
Adjusted for age, sex and some indicator of skin colour and/or sun exposure	**Adjusted**	**Not adjusted**
Studies (n)	-	5
RR (95%CI)	-	1.06 (1.02-1.10)
Heterogeneity (I^2, p-value)	-	0%, 0.92

Birthweight	**Self-reported**	**Measured/from records**
Studies (n)	2	3
RR (95%CI)	1.05 (0.99-1.11)	1.07 (1.01-1.13)
Heterogeneity (I^2, p-value)	0%, 0.54	0%, 0.86

*Dose-response meta-analysis was not conducted in the 2005 SLR.

Table 63 Birthweight and malignant melanoma risk. Results of meta-analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Meta-analyses							
Yang, 2014	5* cohort and 1 case-control study	4000	Sweden, Denmark, Norway, UK	Incidence, MM	Per 1kg increase	1.14 (1.05-1.24)	0.8

*The five cohort studies identified were included in the present review.

Table 64 Birthweight and skin cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Spracklen, 2014 SKI22202 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, W	566/ 56 526	Self-report verified by medical record	Self-reported birthweight	Incidence, MM	≥10 vs. <6 lbs	1.05 (0.66-1.67) Ptrend:0.37	Age, alcohol, BMI, educational level, race, smoking status, socio-economic status	Mid-points of exposure categories
Yang, 2014 SKI23429 UK	MWS, Prospective Cohort, Age: 50-64	1 795/ 453 023 9.2 years	Cancer registry	Self-reported birthweight	Incidence, MM	Per 1 kg	1.13 (0.97-1.32)	Age, age at first child, age at menarche, alcohol consumption, BMI, height, parity, region, smoking,	RR rescaled for an increment of 500g
		821/			<25 kg/m²		1.28 (1.01-1.63)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, W	857/			25.0+ kg/m^2		1.03 (0.83-1.29)	socio-economic status, strenuous exercise, use of HRT, year of birth, having been breastfed as an infant, maternal height, maternal smoking during pregnancy, paternal height	
O'Rorke, 2013 Northern Ireland	Northern Ireland Birth and Cancer Registries, Case-cohort study, M/W	276/ 440 612	Cancer registry	Child Health Database	Incidence, MM	4 500-6 000 vs. 3 000-3 499 g	1.60 (0.74-3.40)	Sex, year of birth, gestational age, number of previous miscarriages, breast feeding status, mode of delivery, maternal age at birth, birth order and social class.	
						Per 500 g	1.08 (0.97-1.21)		Nothing estimated
Olesen, 2009 Denmark	Danish Birth and Cancer Registries, Retrospective Cohort, M/W, born between 1950 and 2002 - nationwide	296/ 2 594 783	Danish cancer registry	Hospital and birth records	Incidence, MM	High birth weight >90 percentile of 4 080g (1973-2002) vs. no	1.19 (0.63-2.26)	Sex, age, calendar period, multiple birth, family size, sibling order, age of mother at birth of the child, age of the mother at first birth, family history of cutaneous malignant melanoma	Excluded, only two levels of exposure, used in the high vs. low analysis
Ahlgren, 2007 SKI22181	Danish Birth and Cancer Registries,	847/ 217 329 6 975 553	Danish cancer registry	School health records	Incidence, MM	4500-5999 vs. 3000-3499 g	1.02	Age, calendar period	
						Per 1000 g	1.14 (1.00-1.31)		RR rescaled for

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Denmark	Prospective Cohort, M/W, born between 1930 and 1975 in Copenhagen municipality	person-years							an increment of 500g
McCormack, 2005 Sweden	UBCoS, Prospective Cohort, Age: 31-45 years, M/W, Birth cohort	77/ 11 166 41 years	Cancer registry/ population register	All measurements made at birth by hospital staff recorded as obstetric notes	Incidence, MM, men	Per 502 g (men) and 498g (women)	1.01 (0.82-1.26)	Sex, birth order, gestational age, marital status, occupation, socio-economic status	Weighted average birthweight

Figure 72 RR estimates of melanoma by levels of birthweight

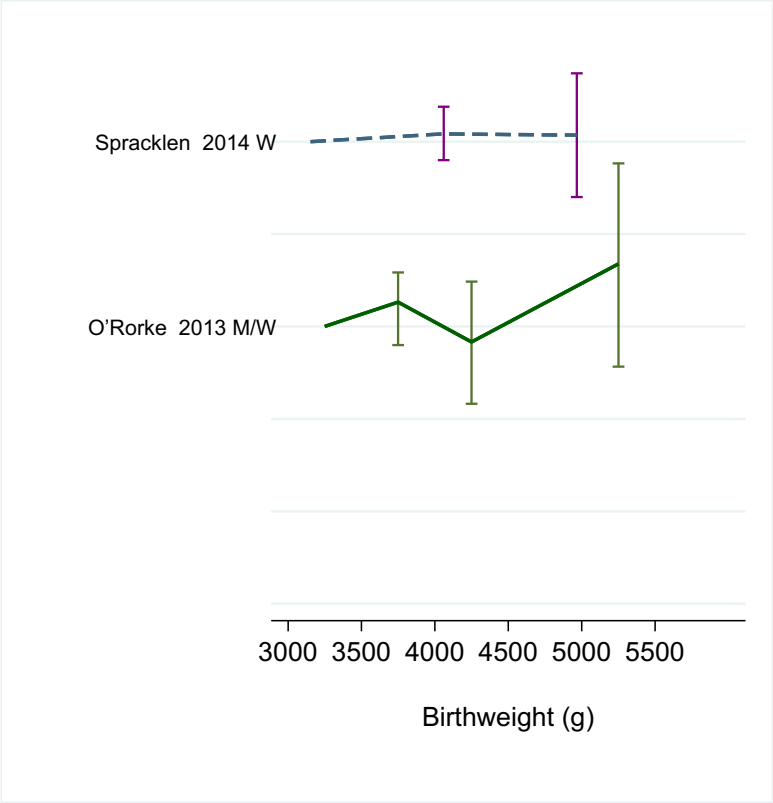


Figure 73 RR (95% CI) of melanoma for the highest compared with the lowest birthweight

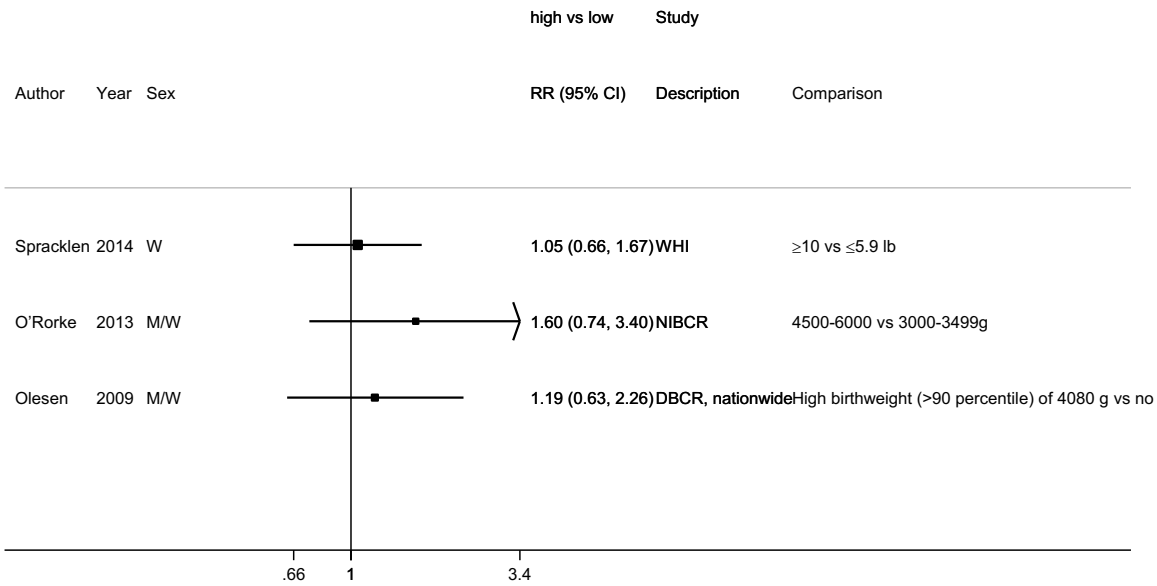


Figure 74 Relative risk of melanoma for 500 g increase of birthweight

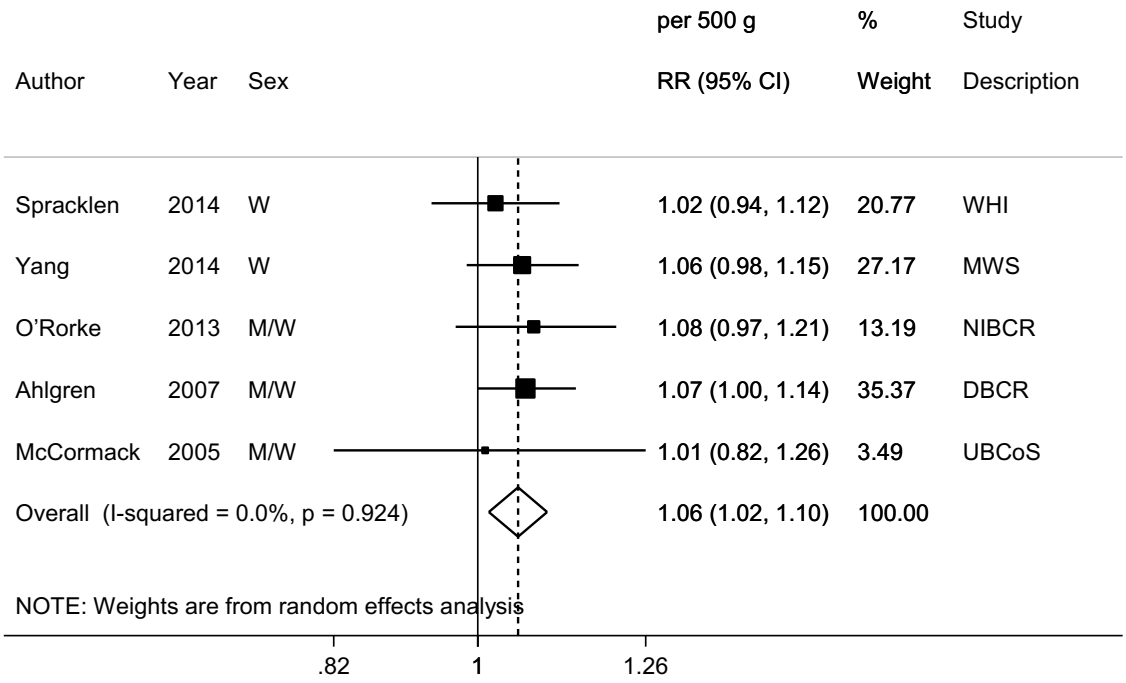


Figure 75 Funnel plot of studies included in the dose response meta-analysis of birthweight

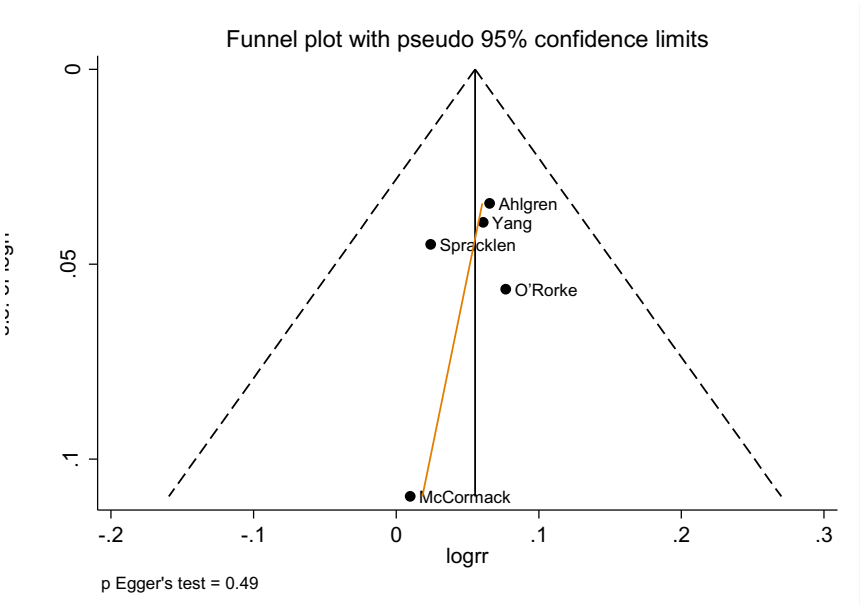


Figure 76 Relative risk of melanoma for 500g increase of birthweight, by sex

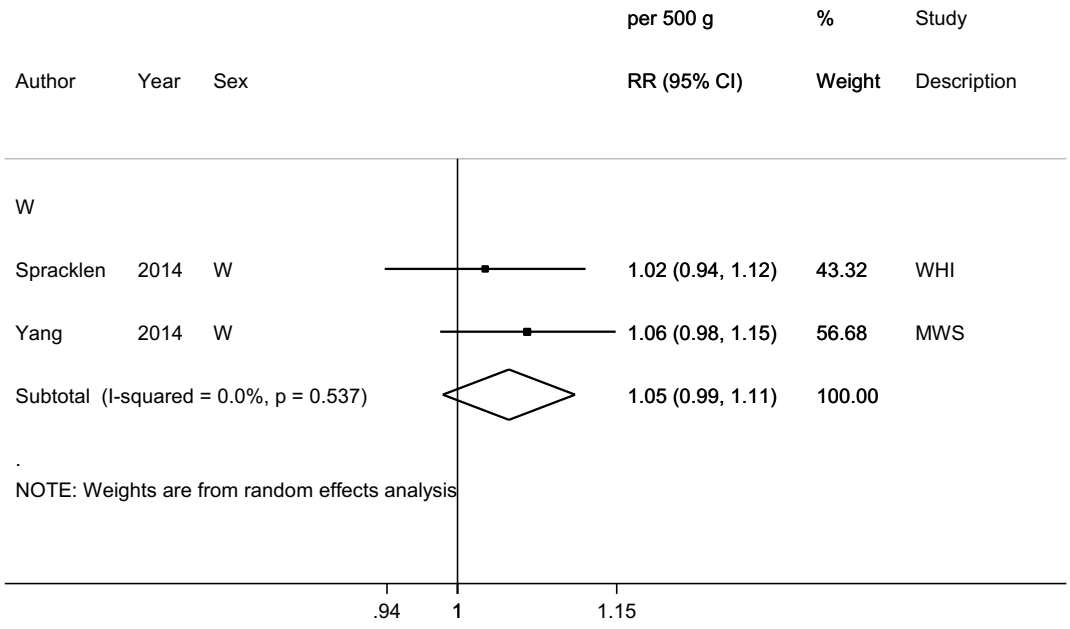
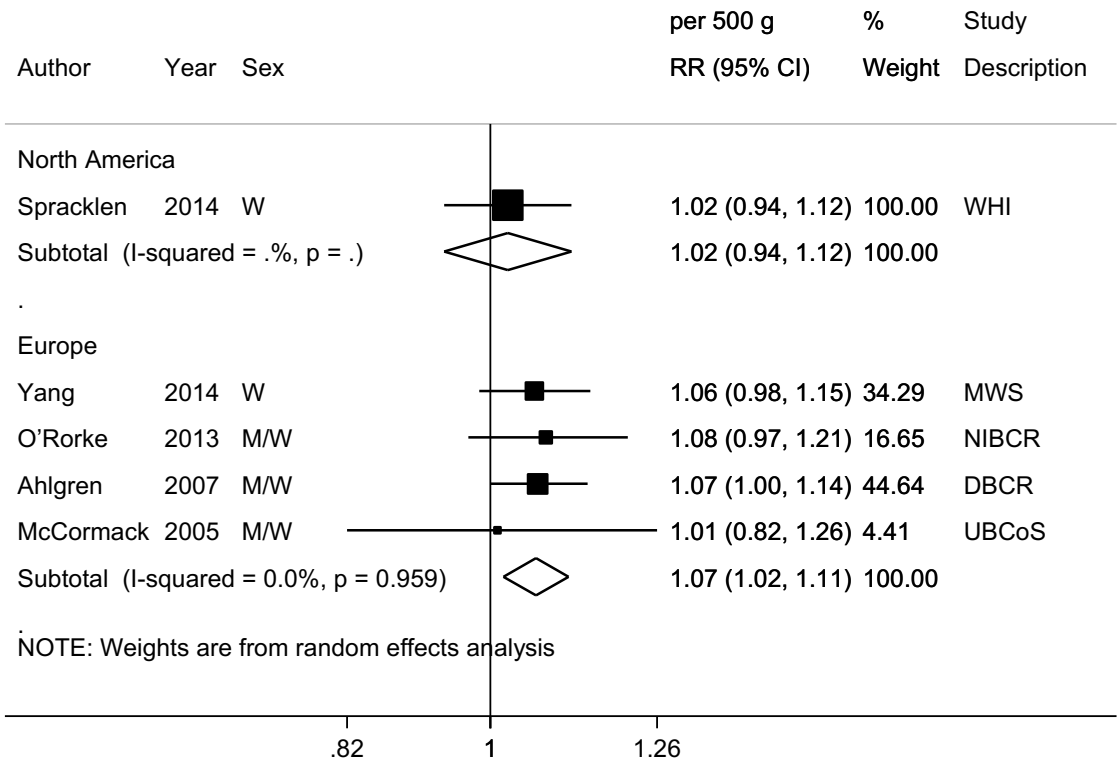


Figure 77 Relative risk of melanoma for 500g increase of birthweight, by geographic location



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Appendix 1 The protocol

Systematic Literature Review Protocol

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

University of Bristol

Date: 9 June 2005

1 Research question

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

2 Review team

Dr Trudy Bekkering, Research Associate in Epidemiology, University of Bristol
Contribution: Project manager, reviewer (100%)
Expertise: Epidemiology, Systematic Reviews

Ms Rebecca Beynon, Research Assistant, University of Bristol
Contribution: Administrative support (100%)

Ms Margaret Burke, Trials Search Coordinator, Cochrane Heart Group
Contribution: Specialist in search strategies (15%)
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Professor George Davey Smith, Professor of Epidemiology, University of Bristol
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Expertise: Epidemiology, Systematic Reviews and Meta-Analysis

Mr Ross Harris, Statistician, University of Bristol
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Dr David de Berker, Consultant dermatologist, United Bristol Health Care Trust
Contribution: Specialist in skin cancer
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3 Timeline

Protocol ready:	15 June 2005
Preliminary output from search strategy:	1 July 2005
Design of the data extraction sheets:	1 July 2005
List of all relevant papers included in the review:	1 September 2005
Results of the preliminary analyses:	1 November 2005
Report finished:	30 December 2005
Update review:	30 June 2006

All activities will be piloted in order to ensure the process runs smoothly and problems are identified and resolved before the main activities are undertaken. The Review Coordinator will be contacted if we identify any problems with respect to the review process or if we expect to be off target with regard to the timeline. Ongoing changes to the protocol may make it necessary to review the timeline of the review.

4 Background

The most common forms of skin cancer are usually divided into two types: melanoma and non melanoma skin cancer (NMSC).

Melanoma originates from pigment cells or melanocytes. In 2002, there were an estimated 160,116 new cases of melanoma reported worldwide and the standardised incidence rate was 100 (Globocan, 2002). Malignant melanoma of the skin occurs predominantly in white-skinned populations. Almost 80% of the new cases are in North America, Europe, Australia and New Zealand. In 2002, 23,039 new cases of melanoma of the skin were reported in Western Europe compared with 807 in Northern Africa (Globocan, 2002). Globocan figures are estimates based on data from cancer registries. It has to be noted that most cancer registries cannot be assumed to be complete for skin cancers and thus that the figures are likely to be underestimates. The most common histopathological type of melanoma is superficial spreading melanoma, which accounts for more than 50% of the melanoma. Next most common is nodular melanoma, which is said to share many of the epidemiological features of other types of melanoma. Lentigo malignana melanoma is relatively uncommon (Armstrong and English, 1996). Mortality rates from melanoma have been steadily increasing in most white populations for many years. There were 40,731 deaths from melanoma of the skin in 2002 (Globocan, 2002).

Five-year survival rate of melanoma in Europe is 81% (Sant, 2003). In the US it lies between 70 and 85%. These rates differ between races and thickness of the melanoma at diagnosis (Armstrong and English, 1996).
NMSC is the most common malignant neoplasm in Caucasian populations around the world. In the UK there are more than 62,000 new cases registered in 2001 (www.cancerresearchuk.org). However, this figure is an underestimate as registration is generally incomplete.
The most common types of NMSC are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Both originate from epidermal cells. The risks of BCC and SCC have shown to have a positive association with exposure to Solar UV radiation and a negative association with the degree of skin pigmentation. Thus, in the US, NMSC is more common among whites than blacks, Asians, Hispanics and Native Americans. Annual age-adjusted incidence rates (per 100,000) for BCC and SCC among US whites are 199 and 43 respectively (Scotto et al, 1996). Worldwide, the highest rates have been reported in the white populations of Australia and South Africa.
SCC is more invasive then BCC; it is estimated that less than 1 out of 500 patients with SCC die of this cancer (Preston and Stern, 1992). It has to be noted that the incidence figures of NMSC are not comparable with those of other cancers because most NMSC are seen and treated in offices of physicians whereas other cancers registers use figures from hospitals. Also, it is common for someone to have multiple NMSC, whereas that is rare for other neoplasms.

Recommendations for the prevention of skin cancer were not included in the expert report 'Food, Nutrition and the Prevention of Cancer: a global perspective' (WCRF, 1997).

5 Search strategy

The search aims to identify all types of evidence relevant to the research question. Therefore, epidemiological literature as well as mechanistic literature will be searched and reviewed. A separate search strategy will be used for the two types of literature.

A. Epidemiological literature

A systematic search will be carried out for the epidemiological literature. All search strategies will be generated with the consultation of a medical librarian. Searching will be carried out using the sources and time-periods as specified in the manual (WCRF, 2003):

- MEDLINE (1966-present)
- EMBASE (1980-present)
- ISI Web of Science
- BIOSIS (Previews) (1985-present)
- SciSearch
- MetaRegister
- LILACS
- The Cochrane Library (2005, Issue 2). Searches will include DARE (Database of Abstracts of Reviews of Effects); CDSR (Cochrane Database of Systematic Reviews) and HTA (Health Technology Assessment)
- CAB abstracts

- Follow-up of references from relevant papers / personal communication with experts
- Follow-up of references from recent systematic reviews
- Hand searching will be used to check on the completeness of initial electronic searches (only if a journal not included by the electronic databases shows up consistently in citation lists)

Search strategy for MEDLINE

Searching for all studies relating to food, nutrition and physical activity. Terms for the exposures as specified in the manual will be used (WCRF, 2003) (Appendix 1). These will be combined with terms for skin cancer as specified below.

Skin cancer

a) Searching for all studies relating to skin:

1. Exp Skin neoplasms
2. Exp Melanoma
3. Exp Basal cell carcinoma
4. Exp squamous cell carcinoma
5. skin adj4 (cancer$ or neoplasm$ or tumo?r$).tw
6. basal cell adj4 carcinoma$.tw
7. squamous cell adj4 carcinoma$ .tw
8. melanoma$.tw
9. text word for basal cell epithelioma
10. text word for squamous cell epithelioma

or/1-11

b) Additional search terms relating to exposure: arsenic is an important exposure with respect to skin cancer. However, this is already in the current search strategy.

The search strategy for MEDLINE will be adapted for other databases with the help of the information specialist.

B. Mechanistic literature

The following search strategy will be used to identify mechanistic reviews. These search terms will be combined with the search terms stated above for the cancer site and the relevant exposures.

1 exp Apoptosis/

2 exp Cell Transformation, Neoplastic/

3 proliferation.tw.

4 apoptosis.tw.

5 differentiation.tw.

6 mechanistic stud$.tw.

7 mechanism$.tw.

8 immun$ response$.tw.

9 Neoplasm Invasiveness/

10 invasion.tw.

11 or/324-333

12 review.pt.

13 editorial.pt.

14 or/12-13

6 Study selection criteria

An In-Out Form will be used to assess each paper's inclusion into the review. The inclusion criteria are as follows:

A. Epidemiological literature

Population

Inclusion: Studies of men, women and children.

Exposure

Papers reporting on the effect of at least one of the exposures as listed in section 20 of the SLR specification manual will be included (WCRF, 2003). Main categories include:

Patterns of diet, including regionally defined diets, socio-economically defined diets, culturally defined diets, individual level dietary patterns, other dietary patterns, breastfeeding and other issues

Foods, including starchy foods; fruit and (non-starchy) vegetables; pulses (legumes); nuts and seeds; meat, poultry, fish and egg; fats, oils and sugars; milk and dairy products; and herbs, spices, and condiments.

Beverages, including total fluid intake, water, milk, soft drinks, fruit juices, hot drinks and alcoholic drinks.

Food production, preservation, processing and preparation.

Dietary constituents, including carbohydrate, lipids, protein, alcohol, vitamins, minerals, phytochemicals and other bioactive compounds.

Physical activity, including total physical activity, physical inactivity and surrogate markers for physical activity.

Energy balance, including energy intake and energy expenditure.

Anthropometry, including markers of body composition, markers of distribution of fat, skeletal size and growth in fetal life, infancy or childhood.

Outcome measures

Inclusion: Studies reporting on incidence or prevalence of and/or death from cancer of the skin. We will include all malignancies that are in or go through the epidermis. Cancers of the sweat, sebaceous and follicular glands will be included. Studies of associations in transplant patients will be included.

Exclusion: Studies that focus on pre-malignant cancer (actinic keratoses, intra epidermal carcinoma) and cancer that does not arise from the epidermis, dermis or cornified skin. Therefore, lymphoma of the skin, liposarcoma, melanoma of female genital tract, eye, inner mouth, and central nervous system will be excluded. Kaposi sarcoma of the skin will be excluded because this relates to HIV infection. Any secondary primaries will be excluded. Patients with 'syndromes' such as Gorlin's and Li Fraumeni syndrome will be excluded because these patients are genetically pre-disposed to (skin) cancer.

Type of studies

Inclusion: All types of epidemiological studies relevant to the research question in all languages.

Exclusion: published abstracts, grey (non-peer-reviewed) literature and unpublished material.

The selection of papers and will be performed according to the specifications in the manual section 13.10, 13.11 (WCRF, 2003). In short, all obtained references will be archived in a Reference Manager Database and duplicates will be removed. A preliminary MEDLINE search found more than 5,000 references, the majority of which are mechanistic studies. For example, in a detailed study of the titles and abstracts 200 references two were found to be definitely relevant and two more to be potentially relevant. It is therefore not practical to screen all titles and abstracts of identified references. Instead, the initial screening of the references will be done using the title only. This will be done by selecting papers whose titles contain key words such as "apoptosis" or "cell line", and then rapidly scanning these titles to confirm that they are not relevant to the review. Once the titles have been screened using this method, the titles and abstracts of remaining papers will be assessed by one reviewer using the inclusion criteria. The results of the search and the first selection will be sent to WCRF. Full papers of all studies that are not clearly ineligible will then be obtained. Two independent reviewers will assess all obtained papers. Disagreements between these reviewers will be resolved by discussion with one of the principle reviewers. The excluded papers and reasons for exclusion are recorded in a second file, and the included papers and study type is recorded in the third file. The second and third file will also be sent to the WCRF.

If a retrieved paper reports outcomes for more than one cancer site, the Review Coordinator will be informed. However, this will only be done for the less obvious

papers, which is the case if the name of the other cancer site is not in the title or in the abstract.

B. Mechanistic data

Will be described after consultation of the Mechanisms Working Group.

7 Data extraction

Data-Extraction Forms will be designed for the review with reference to the Access Database from Leeds. For each study design, a separate form will be made. A study design algorithm will be used for allocating study designs to papers, or, if necessary, for allocating study designs to a particular exposure. Data extraction will include study characteristics that are potential sources of heterogeneity, such as study design, type of cancer and methods of exposure measurement. The country and/or region from which the study population was drawn will be recorded. Data extraction will further include results related to the life course approach; example variables are: birth weight, weight at one year, age at menarche, pubertal status, age at first birth, parity, age of menopause.

Case series will only be extracted if this study design is the only one available for a particular review. Results related to gene-nutrient interactions available in the data are extracted and reported in the report.
One researcher will perform data extraction and a second researcher will check the extraction against the original paper (allocating study designs will be done in duplicate) and differences between reviewer's results will be resolved by returning to the relevant literature, discussion, and when necessary consultation with a third reviewer. The data-extraction forms will be entered into the Access database that was developed by the Leeds team.
Duplicate publication will be identified by cross-checking the study population and location for all studies reporting associations of the same dietary component with the specified cancer. When duplicates are identified, the following rules will be used to decide which results to include in the analysis:

1) Longest follow up if a cohort / biggest sample if a case-control study
2) Most extractable according to order in Table 11 in Manual i.e. categories are to be preferred above means
3) Whole group is reported, not subgroups
4) The best adjustments
5) Combining less subgroups (e.g. combining men and women is to be preferred over male smokers, female smokers, male non-smokers and female non-smokers)

We can take different parts of the results from different studies to cover these issues e.g. unadjusted results from one paper and adjusted results from another paper.

8 Data analysis

For each study where this is possible, we will derive estimates (and their standard errors) of the log odds ratio per unit increase in exposure, and log odds ratio per standard deviation increase in exposure, with and without controlling for confounding

variables. This will be done as described in the SLR specification manual, and the paper by Zwahlen et al. on which this is based. We will record whether analyses controlled for the potential confounders listed in Table 1.

Within each forest plot (for each type of study), results will be presented separately for melanoma skin cancer, basal cell carcinoma and squamous cell carcinoma. Where the study does not differentiate these subtypes, broader definitions such as 'NMSC' and 'skin cancer' will be used. Additionally, overall associations combining these will be presented.

When analysing the data, potential effect modifiers in diet-cancer studies, as listed in Table 7 of the SLR specification manual (age, sex, obesity, ethnicity, smoking) will be considered. If there is clear evidence of effect modification, a stratified analysis will be presented.

Table 1. Potential confounding factors in diet-cancer studies

Cancer in general	Site-specific
• Age • Sex • Smoking habits (current and history) • Social class/living conditions/income • Physical activity • BMI • Total energy intake • Alcohol consumption • Ethnicity • Supplement use • Family history of specific cancer (1rst degree relatives) • Other components of diet	• Treatment for other conditions (e.g. immunosuppressive medication) • Exposure to sunlight • Occupation • Latitude/location • Genetic diseases (Xeroderma pigmentosa, Gorlin's syndrome • Skin type, eye colour, hair colour, presence of freckles • Diseases of skin pigmentation

Number of melanocytic naevi (ie moles) and diagnosis with "dysplastic naevus syndrome". Removed from list of potential confounders because it may lie on the causal pathway between diet and disease.

Information on the study characteristics and results of each study will be tabulated using the recommended format for this table as specified in the manual (WCRF, 2003). We will quantify the amount of between-study heterogeneity using I^2 statistics (Higgins and Thompson, 2002). We will use forest plots to display results from different studies that estimated associations between each component of diet and the specified cancer. Separate plots will display results before and after control for confounding factors.

Where studies are sufficiently homogeneous (I^2 statistic<0.3 or P value for heterogeneity >0.01), a summary estimate of the log odds ratio per unit, or standardised log odds ratio, will be estimated using fixed-effect meta-analysis. In the presence of heterogeneity, the focus of analyses will be on explanations for between-study variation, but we will also present results from both fixed and random-effects meta-analyses. Dose-response plots will be produced for meta-analysed studies with quantile or category data.

When sufficient number of studies estimate the same association, we will also use sensitivity analysis and meta-regression methods to investigate whether between-study heterogeneity is explained by the study characteristics listed in Box 3 of the SLR specification manual (exposure characteristics, exposure range, sex ratio, adjustment for confounders (Table 1), age at recruitment, follow-up, geographical region, study design and outcome). Experience with previous reviews suggests that such analyses will be appropriate only rarely.

Funnel plots will be used to assess whether evidence of small-study effects (Sterne et al, 2000). If funnel plot asymmetry is observed, careful consideration will be given to its causes as well as the possible impact on the overall estimate of association (Sterne et al, 2001).

9 References

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http://www.cancerresearchuk.org/aboutcancer/specificcancers/non_melanoma_skincancer?version=1 Accessed 31 May 2005

APPENDIX 1.

Terms for the search strategy for epidemiological literature as specified in the manual (WCRF, 2003):

#1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]

#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab] OR breastfeed*[tiab] OR breast feed*[tiab] OR breastfed[tiab] OR breast fed[tiab] OR breastmilk[tiab] OR breast milk[tiab]

#3 food and beverages[MeSH Terms]

#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR seeds[tiab] OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR fat[tiab] OR fats[tiab] OR fatty[tiab] OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR oils[tiab] OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab]

#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR ethanol[tiab] OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]

#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]

#8 food preservation[MeSH Terms]

#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab]

OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR microwave[tiab] OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab]

#12 dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR sweetening agents[MeSH Terms]

#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR sodium[tiab] OR iron[tiab] OR calcium[tiab] OR selenium[tiab] OR iodine[tiab] OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab]

#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] OR walking[MeSH Terms]

#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]

#18 growth[MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms]

#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab]

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

Optional:
Apply "Limits: Human" to set #20
[NB - see main report for details on the risks involved in using this option]

KEY:

[tiab] searches the title and abstract fields only
[MeSH Terms] searches the Medical Subject Headings field only
NB - explosion of MeSH terms is automatic

* truncation symbol - searches all words with this combination of letters at the beginning

Appendix 2 Modifications to the protocol

Continuous update of the WCRF-AICR report on diet and cancer

Modifications to the protocol on Skin Cancer.

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

June 2016

Introduction for the reviewers:

The most common forms of skin cancer are usually divided into two types: melanoma and non-melanoma skin cancer (NMSC).

The most common types of NMSC are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Both originate from epidermal cells.

The risks of BCC and SCC have shown to have a positive association with exposure to Solar UV radiation and a negative association with the degree of skin pigmentation.

It is common for someone to have multiple NMSC, whereas that is rare for other neoplasms. It will be possible to find studies in which the NMSC is not the first diagnosed (e.g. prevalence).

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

- Probable: arsenic in drinking water (search if updated review has been published)
- Limited suggestive decreases: retinol
- Limited suggestive increases: selenium supplements

1. Research question

The research topic is:

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

The main objective is:

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

2. Review team

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Snieguole Vingeliene	Research Assistant	Supervisor of data extraction and report preparation. Reviewer
Elli Polemiti	Research Assistant	Reviewer
Christophe Stevens	Database manager	Systematic search, article selection, data extraction

3. Timeline

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

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

4. Search strategy

Search strategy for skin cancer

a) Pubmed

Searching for all studies relating to skin:

1. Exp Skin neoplasms
2. Exp Melanoma
3. Exp Basal cell carcinoma
4. Exp squamous cell carcinoma
5. skin adj4 (cancer$ or neoplasm$ or tumo?r$).tw
6. basal cell adj4 carcinoma$.tw
7. squamous cell adj4 carcinoma$ .tw

8. melanoma$.tw
9. text word for basal cell epithelioma
10. text word for squamous cell epithelioma
11. or/1-11

b) Hand searching for cited references

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

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

5. Study selection criteria for the update

5.1 Inclusion criteria

The articles to be included in the review:

- Have to present results on an exposure/intervention relevant to the CUP
- Must have as outcome of interest incidence or mortality for skin cancer*
- Have to present results from an epidemiologic study in men and women of one of the following types†:
  - Randomized controlled trial
  - Group randomized controlled trial (Community trial)
  - Prospective cohort study
  - Nested case-control study
  - Case-cohort study
  - Historical cohort study
- Have any publication date

* In the 2005 SLR the most frequent skin cancers identified were:

1) basal cell carcinoma, basal cell epithelioma
2) squamous cell carcinoma of skin, squamous cell epithelioma
3) melanoma, cutaneous melanoma (sometimes subdivided in inasive melanoma and melanoma in situ)
4) skin cancer, skin neoplasms, skin tumour, skin tumour, non melanoma skin cancer (usually melanoma is not included in this category).

5.2 Exclusion criteria

Studies with cases of anatomical localisations other than to skin cancer. Example: ocular melanoma.

Studies of skin cancer in patients with Aids (e.g. Kaposi's sarcoma and AIDs)

6. Article selection

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

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

The article selection will follow three steps:

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

6.1 Reference Manager Files

Five customized fields will be created in the reference manager database. They will be used to indicate if the study was selected upon reading of title, abstract, or entire article, the study design of included articles, the status of data extraction of the included article, the WCRF code assigned and for excluded articles, the reason for exclusion (**Table 1**)

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

Field	**Use**	**Terms used**	**Notes**
User Def 1	Indicate if article is relevant to the CUP review	Excludedabti; Included; excluded;	Excludedabti means excluded basing on abstract and title of the article. Without "abti" means full text is reviewed.
User Def 2	If excluded, reasons	No associations of interest; No original data/duplicates; Commentary; Foreign article in [*language*]	No associations of interest include situations such as "out of the research topic", "no measure of relationship", "no specific outcome"

		Not adequate study design Pooled studies/meta-analyses	
User Def 3	Study design	Randomized controlled trial (RCT) Prospective cohort study Retrospective cohort study Nested case-control study Case cohort study Population-based case-control study Hospital-based case-control study Case-control study- other type of controls or control type unclear	The CUP only extract data from RCT, cohort/cohort based studies. Case-control studies are identified but the data is not extracted to the database.
User Def 4	WCRF code of the article	This is done during the data extraction	WCRF codes are assigned automatically in the application when performing extraction.
User Def 5	Other notes, name of study	Indicate if includes more than one anatomical localization	

7. Data extraction

(Due to time limitations, the review team may use an alternative quick data extraction, in which the study author, publication year, study name, exposures investigated –one per column- will be extracted in an excel file. This is because the CUP review will be only narrative. No meta-analysis will be included. In this case the data extraction will be done after the report is prepared.

Meta-analysis of case-control studies, cohort studies and RCT will be included in the CUP review)

The IC team will update the WCRF-AICR central database.

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

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

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

When indicated, the reviewer should also extract for each result:

- Type of cancer:

Basal cancer

SCC

NMSC

Melanoma

All skin cancer

-Whether the skin cancer is the first (incident) or not

(This is based in the 2005 SLR. Other classifications may be identified and the protocol amended correspondingly)

Note on adjustment factors: vary important not to miss any data related to sun exposure or skin colour.

7.1 Study identifier

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

Appendix 3 Exposure codes

1 Patterns of diet

1.1 Regionally defined diets

*1.1.1 Mediterranean diet

Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and "western type".

1.2 Socio-economically defined diets

To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).

1.3 Culturally defined diets

To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.

1.4 Individual level dietary patterns

To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes) that do not fit into the headings above.

1.5 Other dietary patterns

Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.

1.6 Breastfeeding

1.6.1 Mother

Include here also age at first lactation, duration of breastfeeding, number of children breast-fed

1.6.2 Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7 Other issues

For example results related to diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here. Eating out of home should be reported here.

2 Foods

*2.0.1 Plant foods

2.1 Starchy foods

2.1.1 Cereals (grains)

* 2.1.1.0.1 Rice, pasta, noodles

* 2.1.1.0.2 Bread

* 2.1.1.0.3 Cereal

** Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)*

2.1.1.1 Wholegrain cereals and cereal products

* 2.1.1.1.1 Wholegrain rice, pasta, noodles

* 2.1.1.1.2 Wholegrain bread

* 2.1.1.1.3 Wholegrain cereal

2.1.1.2 Refined cereals and cereal products

* 2.1.1.2.1 Refined rice, pasta, noodles

* 2.1.1.2.2 Refined bread

* 2.1.1.2.3 Refined cereal

2.1.2 Starchy roots, tubers and plantains

* 2.1.2.1 Potatoes

2.1.3 Other starchy foods

**Report polenta under this heading*

2.2 Fruit and (non-starchy) vegetables

Results for "fruit and vegetables" and "fruits, vegetables and fruit juices" should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.

2.2.1 Non-starchy vegetables

This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported they should be recorded under one of the sub-headings below or if not covered, they should be recorded under '2.2.1.5 other'.

2.2.1.1 Non-starchy root vegetables and tubers

*2.2.1.1.1 Carrots

2.2.1.2 Cruciferous vegetables

2.2.1.3 Allium vegetables

2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)

2.2.1.5 Other non-starchy vegetables

*2.2.1.5.13 Tomatoes

*2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas

Other non-starchy vegetables' should include foods that are botanically fruits but are eaten as vegetables, e.g. courgettes. In addition vegetables such as French beans that do not fit into the other categories, above.

If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. If in doubt, enter the exposure more than once in this way.

2.2.1.6 Raw vegetables

This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 –2.2.1.5.

2.2.2 Fruits

*2.2.2.0.1 Fruit, dried

*2.2.2.0.2 Fruit, canned

*2.2.2.0.3 Fruit, cooked

2.2.2.1 Citrus fruit

2.2.2.1.1 Oranges

2.2.2.1.2 Other citrus fruits (e.g. grapefruits)

2.2.2.2 Other fruits

*2.2.2.2.1 Bananas

*2.2.2.2.4 Melon

*2.2.2.2.5 Papaya

*2.2.2.2.7 Blueberries, strawberries and other berries

*2.2.2.2.8 Apples, pears

*2.2.2.2.10 Peaches, apricots, plums

*2.2.2.2.11 Grapes

If results are available that consider other groups of fruit or a particular fruit please report under 'other', specifying the grouping/fruit used in the literature.

2.3 Pulses (legumes)

*2.3.1 Soya, soya products

*2.3.1.1 Miso, soya paste soup

*2.3.1.2 Soya juice

*2.3.1.4 Soya milk

*2.3.1.5 Tofu

*2.3.2 Dried beans, chickpeas, lentiles

*2.3.4 Peanuts, peanut products

Where results are available for a specific pulse/legume, please report under a separate heading.

2.4 Nuts and Seeds

To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts, please report under a separate heading.

2.5 Meat, poultry, fish and eggs

Wherever possible please differentiate between farmed and wild meat, poultry and fish.

2.5.1 Meat

This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.

Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.

2.5.1.1 Fresh Meat

2.5.1.2 Processed meat

*2.5.1.2.1 Ham

*2.5.1.2.1.7 Burgers

*2.5.1.2.8 Bacon

*2.5.1.2.9 Hot dogs

*2.5.1.2.10 Sausages

Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of 'processed meat' used by each study.

2.5.1.3 Red meat

*2.5.1.3.1 Beef

*2.5.1.3.2 Lamb

*2.5.1.3.3 Pork

*2.5.1.3.6 Horse, rabbit, wild meat (game)

Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.

Show any data on wild meat (game) under this heading as a separate sub-category.

2.5.1.4 Poultry

Show any data on wild birds under this heading as a separate sub-category.

*2.5.1.5 Offals, offal products (organ meats)

2.5.2 Fish

*2.5.2.3 Fish, processed (dried, salted, smoked)

*2.5.2.5 Fatty Fish

*2.5.2.7 Dried Fish

*2.5.2.9 White fish, lean fish

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats

*2.6.1.1 Butter

*2.6.1.2 Lard

*2.6.1.3 Gravy

*2.6.1.4 Fish oil

2.6.2 Plant oils

2.6.3 Hydrogenated fats and oils

*2.6.3.1 Margarine

Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation

2.6.4 Sugars

This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.

2.7 Milk and dairy products

Results concerning milk should be reported twice, here and under 3.3 Milk

*2.7.1 Milk, fresh milk, dried milk

*2.7.1.1 Whole milk, full-fat milks

*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk

*2.7.2 Cheese

*2.7.2.1 Cottage cheese

*2.7.2.2 Cheese, low fat

*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks

*2.7.3.1 Fermented whole milk

*2.7.3.2 Fermented skimmed milk

*2.7.7 Ice cream

2.8 Herbs, spices, condiments

*2.8.1 Ginseng

*2.8.2 Chili pepper, green chili pepper, red chili pepper

2.9 Composite foods

Eg, snacks, crisps, desserts, pizza. Also report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.

*2.9.1 Cakes, biscuits and pastry

*2.9.2 Cookies

*2.9.3 Confectionery

*2.9.4 Soups

*2.9.5 Pizza

*2.9.6 Chocolate, candy bars

*2.9.7 Snacks

3 Beverages

3.1 Total fluid intake

3.2 Water

3.3 Milk

For results concerning milk please report twice, here and under 2.7 Milk and Dairy Products.

3.4 Soft drinks

Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.

3.4.1 Sugary (not carbonated)

3.4.2 Carbonated (not sugary)

The precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.

*3.5 Fruit and vegetable juices

*3.5.1 Citrus fruit juice

*3.5.2 Fruit juice

*3.5.3 Vegetable juice

*3.5.4 Tomato juice

3.6 Hot drinks

3.6.1 Coffee

3.6.2 Tea

Report herbal tea as a sub-category under tea.

3.6.2.1 Black tea

3.6.2.2 Green tea

3.6.3 Maté

3.6.4 Other hot drinks

3.7 Alcoholic drinks

3.7.1 Total

3.7.1.1 Beers

3.7.1.2 Wines

3.7.1.3 Spirits

3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation

4.1 Production

4.1.1 Traditional methods (*to include 'organic')*

4.1.2 Chemical contaminants

Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:

4.1.2.1 Pesticides

4.1.2.2 DDT

4.1.2.3 Herbicides

4.1.2.4 Fertilisers

4.1.2.5 Veterinary drugs

4.1.2.6 Other chemicals

4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)

4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)

4.1.2.6.3 Polychlorinated biphenyls (PCBs)

4.1.2.7 Heavy metals

4.1.2.7.1 Cadmium

4.1.2.7.2 Arsenic

4.1.2.8 Waterborne residues

4.1.2.8.1 Chlorinated hydrocarbons

4.1.2.9 Other contaminants

Please also report any results that cover the cumulative effect of low doses of contaminants in this section.

4.2 Preservation

4.2.1 Drying

4.2.2 Storage

4.2.2.1 Mycotoxins

4.2.2.1.1 Aflatoxins

4.2.2.1.2 Others

4.2.3 Bottling, canning, vacuum packing

4.2.4 Refrigeration

4.2.5 Salt, salting

4.2.5.1 Salt

4.2.5.2 Salting

4.2.5.3 Salted foods

4.2.5.3.1 Salted animal food

4.2.5.3.2 Salted plant food

4.2.6 Pickling

4.2.7 Curing and smoking

4.2.7.1 Cured foods

4.2.7.1.1 Cured meats

4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, stomach and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-*nitrososamines should also be covered here.*

4.3 Processing

4.3.1 Refining

Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.

4.3.2 Hydrogenation

Results concerning hydrogenated fats and oils should be reported twice, here and under 2.6.3 Hydrogenated fats and oils

4.3.3 Fermenting

4.3.4 Compositional manipulation

4.3.4.1 Fortification

4.3.4.2 Genetic modification

4.3.4.3 Other methods

4.3.5 Food additives

4.3.5.1 Flavours

Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.

4.3.5.2 Sweeteners (non-caloric)

4.3.5.3 Colours

4.3.5.4 Preservatives

4.3.5.4.1 Nitrites and nitrates

4.3.5.5 Solvents

4.3.5.6 Fat substitutes

4.3.5.7 Other food additives

Please also report any results that cover the cumulative effect of low doses of additives.

Please also report any results that cover synthetic antioxidants

4.3.6 Packaging

4.3.6.1 Vinyl chloride

4.3.6.2 Phthalates

4.4 Preparation

4.4.1 Fresh food

4.4.1.1 Raw

Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).

4.4.1.2 Juiced

4.4.2 Cooked food

4.4.2.1 Steaming, boiling, poaching

4.4.2.2 Stewing, casseroling

4.4.2.3 Baking, roasting

4.4.2.4 Microwaving

4.4.2.5 Frying

4.4.2.6 Grilling (broiling) and barbecuing

4.4.2.7 Heating, re-heating

Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.

Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.

5 Dietary constituents

Food constituents' relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.

5.1 Carbohydrate

5.1.1 Total carbohydrate

5.1.2 Non-starch polysaccharides/dietary fibre

5.1.2.1 Cereal fibre

5.1.2.2 Vegetable fibre

5.1.2.3 Fruit fibre

5.1.3 Starch

5.1.3.1 Resistant starch

5.1.4 Sugars

*5.1.5 Glycemic index, glycemic load

This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for intrinsic and extrinsic sugars should be presented

separately. Count honey and sugars in fruit juices as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.

5.2 Lipids

5.2.1 Total fat

5.2.2 Saturated fatty acids

5.2.3 Monounsaturated fatty acids

5.2.4 Polyunsaturated fatty acids

5.2.4.1 n-3 fatty acids

Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.

5.2.4.2 n-6 fatty acids

5.2.4.3 Conjugated linoleic acid

5.2.5 Trans fatty acids

5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.

5.3 Protein

5.3.1 Total protein

5.3.2 Plant protein

5.3.3 Animal protein

5.4 Alcohol

This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.

*5.4.1 Total Alcohol (as ethanol)

*5.4.1.1Alcohol (as ethanol) from beer

*5.4.1.2Alcohol (as ethanol) from wine

*5.4.1.3Alcohol (as ethanol) from spirits

*5.4.1.4Alcohol (as ethanol) from other alcoholic drinks

* 5.4.1.5 Total alcohol (as ethanol), lifetime exposure

* 5.4.1.6 Total alcohol (as ethanol), past

5.5 Vitamins

*5.5.0 Vitamin supplements

*5.5.0.1 Vitamin and mineral supplements

*5.5.0.2 Vitamin B supplement

5.5.1 Vitamin A

5.5.1.1 Retinol

5.5.1.2 Provitamin A carotenoids

5.5.2 Non-provitamin A carotenoids

Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.

5.5.3 Folates and associated compounds

*5.5.3.1 Total folate

*5.5.3.2 Dietary folate

*5.5.3.3 Folate from supplements

Examples of the associated compounds are lipotropes, methionine and other methyl donors.

5.5.4 Riboflavin

5.5.5 Thiamin (vitamin B1)

5.5.6 Niacin

5.5.7 Pyridoxine (vitamin B6)

5.5.8 Cobalamin (vitamin B12)

5.5.9 Vitamin C

5.5.10 Vitamin D (and calcium)

5.5.11 Vitamin E

5.5.12 Vitamin K

5.5.13 Other

If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under 'other'.

5.6 Minerals

5.6.1 Sodium

5.6.2 Iron

5.6.3 Calcium (and Vitamin D)

5.6.4 Selenium

5.6.5 Iodine

5.6.6 Other

Results are likely to be available on other minerals e.g. magnesium, potassium, zinc, copper, phosphorus, manganese and chromium for certain cancers. These should be reported at the end of this section when appropriate under 'other'.

5.7 Phytochemicals

5.7.1 Allium compounds

5.7.2 Isothiocyanates

5.7.3 Glucosinolates and indoles

5.7.4 Polyphenols

5.7.5 Phytoestrogens eg genistein

5.7.6 Caffeine

5.7.7 Other

Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading 'other bioactive compounds'. Eg flavonoids, isoflavonoids, glycoalkaloids, cyanogens, oligosaccharides and anthocyanins should be reported separately under this heading.

5.8 Other bioactive compounds

6 Physical activity

6.1 Total physical activity (overall summary measures)

6.1.1 Type of activity

6.1.1.1 Occupational

6.1.1.2 Recreational

6.1.1.3 Household

6.1.1.4 Transportation

6.1.2 Frequency of physical activity

*6.1.2.1 Frequency of occupational physical activity

*6.1.2.2 Frequency of recreational physical activity

6.1.3 Intensity of physical activity

*6.1.3.1 Intensity of occupational physical activity

*6.1.3.2 Intensity of recreational physical activity

6.1.4 Duration of physical activity

*6.1.4.1Duration of occupational physical activity

*6.1.4.2Duration of recreational physical activity

6.2 Physical inactivity

6.3 Surrogate markers for physical activity e.g. occupation

7 Energy balance

7.1 Energy intake

*7.1.0.1 Energy from fats

*7.1.0.2 Energy from protein

*7.1.0.3 Energy from carbohydrates

*7.1.0.4 Energy from alcohol

*7.1.0.5 Energy from all other sources

7.1.1 Energy density of diet

7.2 Energy expenditure

8 Anthropometry

8.1 Markers of body composition

8.1.1 BMI

8.1.2 Other weight adjusted for height measures

8.1.3 Weight

8.1.4 Skinfold measurements

8.1.5 Other (e.g. DEXA, bio- impedance, etc)

8.1.6 Change in body composition (including weight gain)

8.2 Markers of distribution of fat

8.2.1 Waist circumference

8.2.2 Hips circumference

8.2.3 Waist to hip ratio

8.2.4 Skinfolds ratio

8.2.5 Other e.g. CT, ultrasound

8.3 Skeletal size

8.3.1 Height (and proxy measures)

8.3.2 Other (e.g. leg length)

8.4 Growth in fetal life, infancy or childhood

8.4.1 Birthweight,

8.4.2 Weight at one year

Appendix 4 Arsenic from diet and skin cancer risk. Main characteristics of case-control and ecologic studies.

Case-control studies

Author, Year, WCRF Code, Country	Study characteristics	Cases/ Controls	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Gilbert-Diamond,2013 USA	Population-based case-control study in New Hampshire, a region with moderate arsenic exposure through private well water and diet	470 invasive SCC, 447 controls	Urinary arsenic Median 4.76 µg/L	Histologically confirmed incident SCC (2003-2009)	For 1 ln-transformed μ/L increase	1.37 (1.04-1.08)	Uurinary creatinine, sex, age, BMI, education, smoking, skin reaction to chronic sun exposure (excluded participants who consumed seafood 2 days prior to urine collection)
Leonardi, 2012 Hungary, Romania, and Slovakia	ASHRAM study Hospital-based case-control SCC study in 3 countries, a region with moderate arsenic exposure through drinking water	529 BCC, 540 controls	Arsenic in drinking water based on national registries and residence of study participants Median 1.2 (0.7–13.8) µg/L	Histologically confirmed, consecutively diagnosed BCC (2003–2004)	For each 10 µg/L increase	Lifetime concentration 1.18 (1.08-1.28) Cumulative dose 1.10 (1.01-1.19)	Matched on sex, age, and area of residence; adjusted for sex, age, education, area of residence, skin response to 1 hour of midday sun, skin complexion
Rosales-Castillo, 2004 Mexico	Hospital-based case-control study. Controls recruited from dermatology clinics	42 NMSC, 48 controls	Cumulative exposure derived from 1 urine arsenic measure and participant's residential history	Prevalent, clinically diagnosed NMSC	High vs. low	4.53 (0.63–32.76)	Sex, age, sun exposure; association modified by HPV infection; arsenic exposure
Chen, 2003 Southwest Taiwan	Hospital-based case-control study January 1996 - December 1999	76 NMSC, 224 controls	Cumulative arsenic from artesian well water concentration and duration of drinking mean=8.14 (SD 15.48) mg/L-year	Pathologically diagnosed, incident skin cancer (1996–1999)	mg-L/year 0–2 >2–15 >15	1.00 (reference) 1.87 (0.79–4.45) 2.99 (1.30–6.87) P for trend=0.007	Age, sex, BMI, sun exposure, cigarette smoking, alcohol consumption, and education

Author, Year, WCRF Code, Country	Study characteristics	Cases/ Controls	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Karagas, 2001 USA	Population –based case-control study in New Hampshire	587 BCC, 284 invasive SCC - BD excluded, 524 controls	Histologically confirmed incident BCC and SCC (1993-1995)	Toenails Geometric mean=0.094 (range=0.01–0.81) µg/g [any source of exposure to arsenic]		No increased risk of SCC or BCC	Matched on sex and age
Hsueh, 1995 Southwest Taiwan		1081 persons (66 skin cancer cases, including BD)	Prevalent skin cancer (90 % BD, and 91 % BCC and SCC histologically confirmed) (1988-1989)	Water (Median range= 0.70-0.93 ppm)	Average (ppm) 0 0.1-0.7 >0.7 Cumulative (ppm-yrs) <4 5-24 >24	1.00 (reference) 3.45 (0.70–17.0) 5.04 (1.07–23.8) P for trend <0.05 1.00 (reference) 8.90 (1.07–73.75) 13.74 (1.69-111.64)	Age, sex

Ecologic and cross-sectional studies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Cheng, 2016, Taiwan	Retrospective study in black foot disease endemic (BFDEA) areas in Taiwan	11 191 cases SCC, 13 684 cases BCC	Cases with pathology diagnosis, National Taiwan Cancer Registry	Exposure: living in BFDE area. Levels of arsenic in water were not assessed. Arsenic-containing well-water drinking stopped in the 1970s. Cases identified from 1979-2007	Skin SCC, BCC	Living in BFDEA vd Taiwan	SMR (morbidity) SCC (all period) 4.42 (3.94–4.96) SCC (1979–1983) 5.50 (3.26–8.69) SCC (2004-2007) 3.80 (3.04–4.70) BCC (all period) 3.20 2.83–3.60 BCC (1979–1983) 4.82 (2.20–9.15) BCC (2004-2007) 1.73 (1.30–2.27)	SMR of cutaneous SCC and BCC declined gradually following water source replacement and the withdrawal of arsenic exposure from artesian well water
Navoni, 2012 Argentina	Study in Buenos Aires			Arsenic levels assessed in 152 samples from 52 counties in Buenos Aires 2003–2008 Range 0,3- 187 μg/L, median 40 μg/L		Area with medium/high arsenic concentration compared to low arsenic concentration area	SMR Women 3.9 (2.9–5.2) Men 3.1 (2.5–3.9)	
Wheeler, 2013 UK	326 areas of England 2006-2008	216 497 NMSC		Mean stream arsenic sediments	NMSC rates	Mean ppm in stream 11-14 15-19 20+	Regression coefficient 0 (ref) 0.32 (8.99- 9.64) 5.85 (17.90, 6.19)	Age, sex, UV levels

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Knoleboch, 2006 USA	6,669 residents Wisconsin's Fox River Valley, which contains a large vein of arsenic-rich minerals in a bedrock layer	74 cases	Self reported history of skin cancer	Arsenic in samples of 2,233 household wells of study participants during July 2000 to January 2002	Skin cancer	µg/L >10 1.0–9.9 lg/l <1 (referent)	1.92 (1.01-3.68) 1.81(1.10–3.14) 1	Age, gender, smoking
Corey, 2005 Argentina (grey literature cited by Bardach, 2015)	Study in 1999, Santa Fe			Arsenic in public water	Skin cancer	> 50 µg//L compared to < 50 µg/	Mortality Rate Ratio 1.89 (1.15–3.09)	
Guo, 2001 SKI01124 Taiwan	Taiwan 1980-1989, 243 townships in Taiwan	1415 men, 954 women	National cancer Registry	**Nationwide census survey Arsenic in drinking water**	Basal cell carcinoma Men	Arsenic level (mcg/L) 0.05-0.08 0.09-0.16 0.17-0.32 0.33-0.64 >0.64	Rate difference with population size 0.004 -0.017 0.006 -0.024 0.128**	Age, urbanization index Note ** indicates p<0.01
					Basal cell carcinoma Women	0.05-0.08 0.09-0.16 0.17-0.32 0.33-0.64 >0.64	-0.012 0.018 0.04 0.016 0.027	
					Squamous cell carcinoma Men	0.05-0.08 0.09-0.16 0.17-0.32 0.33-0.64 >0.64	0.024 -0.026 0.073** -0.100 ** 0.155 **	
					Squamous	0.05-0.08	-0.006	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cell carcinoma Women	0.09-0.16 0.17-0.32 0.33-0.64 >0.64	0.006 0.016 -0.064** 0.212**	
					Melanoma Men	0.05-0.08 0.09-0.16 0.17-0.32 0.33-0.64 >0.64	0.008 -0.10 0.008 -0.004 -0.008	
					Melanoma Women	0.05-0.08 0.09-0.16 0.17-0.32 0.33-0.64 >0.64	0.000 -0.001 0.002 -0.009 -0.003	
Tsai, 1999 SKI14389 Taiwan	Taiwan 1971-1994, four townships Area endemic for Blackfoot disease	66 men 68 women			Mortality, skin cancer, women	Standard: Local National Local National	SMR (95% CI) 4.8 (3.7–6.2) 5.97 (4.6–7.6) 5.7 (4.4–7.2) 6.8 (5.3–8.6)	Age, sex
Hopenhayn-Rich, 1998 SKI02070 Argentina	Cordoba province	56 men, 35 women		Arsenic in drinking water (surveys)	Mortality skin cancer Men	Low Medium High	SMR 2.04 (1.38-2.89) 1.49 (0.83-2.45) 1.49 (0.71-2.73)	Reference: All Argentinian population Mean in high exposure group: 178 mcg/L
					Mortality skin cancer Women	Low Medium ~178 mcg/L	0.85 (0.42-1.51) 0.82 (0.32-1.68) 2.78 (1.61-4.44)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Smith, 1998 SKI02164 Chile	Northern Chile Mortality 1989–93, age ≥ 30	20 men 7 women		Annual average arsenic concentrations	Mortality skin cancer	Ranging 43–569 µg/L in 1950–94	SMR Men 7.7 (4.7–11.9) Women 3.2 (1.3–6.6)	Age-standardized to the national rates of Chile in 1991
Guo, 1998 Taiwan	243 townships, 11.4 million residents	952 men 595 women		Arsenic concentration in wells	Incidence skin cancer 1980–87	Risk difference per 1% increase in arsenic concentration >640 vs. 50 µg/L	Risk difference 0.34/100 000 ($p < 0.01$) RR 14.21 in men 19.25 in women	Rates standardized using the 1976 world standard population. Model assumes that same number of individuals use each well.
Wong, 1992 USA	Four counties in Montana	Around 2300 in the 4 counties		Two contaminated counties (copper smelter and copper mines); two control counties	Incidence skin cancer 1980–86		Age-adjusted skin cancer incidence higher in control counties	
Chen and Wang 1990 Taiwan	314 precincts and townships				Mortality rate of skin cancer per 100 000 1972–83	Increase in mortality rate per 0.1 µg/L increase: Men 0.9 (SE 0.2); Women 1.0 (SE 0.2)		Multiple regression adjusted for age and indices of urbanization and industrialization. Mortality rates standardized to the 1976 world standard population
Wu 1989 SKI03805 Taiwan	42 villages in region endemic for Blackfoot disease	19 men 17 women	Death certificates	Median arsenic concentrations of well-water in village of residence in 1964–66	Mortality skin cancer 1973–86	ppm < 30 30–59 > =60	SMR (Men) 2.03 14.01 32.41 ($p < 0.001$) Women	Age-standardized to the 1976 world standard population

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						< 30 30–59 > =60	1.73 14.75 18.66 ($p < 0.001$)	
Chen, 1988 Taiwan	Region endemic for Blackfoot disease (SW)			Arsenic concentrations of well-water	Mortality skin cancer 1973–86	Median (µg/L) Men < 300 300–600 > 600 Women < 300 300–600 > 600	SMR (per 100 000)_1.6 10.7 28.0 1.6 10.0 15.1	Age
Chen, 1985 SKI04411 Taiwan	Areas hyperendemic (21 villages), endemic (25 villages) and not endemic (38 villages) for Blackfoot disease	46 men 49 women		Areas with high, medium and low exposure to arsenic in Blackfoot disease areas compared to Taiwan population	Mortality skin cancer 1968–82		SMR Men 534 (379–689) Women 652 (469–835)	Mortality rates in all Taiwan as standard
Cebrian, 1983 Mexico	Two rural populations in Lagunera region; 2486 residents	4 cases in area of high exposure; 0 case in area of low exposure	Epidermoid or basal-cell carcinomas detected on physical exam of every 3rd household		Prevalence (time frame not specified)	Prevalence	High exposure arsenic (410 µg/L):1.4% Low exposure (5 µg/L): 0%	
Morton, 1976, SKI05213 USA	Oregon county, an area known to contain an arsenic-rich layer	~165 000 people		Water samples collected in 1958–1971 Range arsenic 0- 2150 ppb	Incidence rates of NMSC 1958-1971	Correlation IR and level of arsenic	SCC Men 0.15 Women -0.02 BCC Men -0.64	Age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
							Women 0.10	
Zaldivar , 1974 Chile	City of Antofagasta			Concentration of arsenic fell from 580 µg/L in 1968–69 to 8 µg/L in 1971	Incidence of cutaneous lesions of chronic arsenic poisoning, 1968–71	Incidence rates, skin cancer before and after arsenic fell	Incidence rates per 100 000 Men: 145.5in 1968–69, 9.1in 1971 Women: 168.0 in 1968–69; 10 in 1971	
Berg and Burbank, 1972 USA				Trace metals in water supplies from 10 basins throughout the USA; concentration of arsenic in water, Oct. 1962–Sept. 1967	Mortality skin cancer 1950–67		No correlation of mortality rate with arsenic concentration in water	
Tseng, 1968 SKI22098 Taiwan	40 421 residents from 37 villages (South west) ≥ 20 years of age	428 cases	Prevalence based on clinical examination of all households	Arsenic concentrations of wells in village of residence (range, 1–1820 µg/L; most wells contained 400–600 µg/L arsenic)	Prevalence skin cancer	Median (µg/L) < 300 300–600 > 600	Prevalence (per 1000) 2.6 10.1 21.4	
Rivara, 1967 Chile	Two regions, Antofagasta			Antofagasta arsenic concentration in drinking water in 1950-1992 40–860 µg/L.	Mortality 1976–92	Antofagasta vs. region with no arsenic contamination	SMR (95% CI) 3.2 (2.1–4.8)	Age

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