OTHER DIETARY EXPOSURES AND THE RISK OF CANCER

WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	**Convincing**			High-dose beta-carotene supplements	Lung (in people who smoke or used to smoke tobacco) 2017[1]
	Probable	Calcium supplements	Colorectum 2017[2]	Glycaemic load[3]	Endometrium 2013
LIMITED EVIDENCE	**Limited – suggestive**	Healthy dietary patterns[4]	Mouth, pharynx and larynx 2018	Foods and drinks containing fructose[5]	Pancreas 2012
		Foods containing retinol	Lung 2017[6]	Foods containing saturated fatty acids	Pancreas 2012
		Vitamin D	Colorectum 2017[7]	Low plasma alpha-tocopherol concentrations	Prostate 2014
		Foods containing beta-carotene	Lung 2017[8]	Low plasma selenium concentrations	Prostate 2014
		Multivitamin supplements[9]	Colorectum 2017		
STRONG EVIDENCE	**Substantial effect on risk unlikely**	Beta-carotene: Prostate 2014[10] High-dose beta-carotene supplements: Skin (non-melanoma) 2017[11]			

1 The evidence for high-dose beta-carotene supplements and lung cancer (in people who smoke or used to smoke tobacco) is derived from studies using high-dose supplements (20 to 30 milligrams per day or 50 milligrams per day on alternate days for beta-carotene; 25,000 international units per day for retinol).

2 The evidence for calcium supplements and colorectal cancer is derived from studies using supplements at a dose >200 milligrams per day.

3 The glycaemic load of a food may be calculated by multiplying the glycaemic index of a food, expressed as a percentage, by the number of grams of carbohydrate in a serving of the food.

4 Judgements relate to healthy dietary patterns as marked by greater healthy dietary indices. These indices produce an integrated score to assess adherence to healthy eating or lifestyle recommendations or patterns. They are characterised by factors such as healthy weight management; engagement in physical activity; limiting intake of foods and drinks that promote weight gain; limiting intake of red and processed meat; limiting intake of alcoholic drinks; and a higher intake of wholegrains, vegetables and fruit.

5 The evidence for food and drinks containing fructose and pancreatic cancer includes both foods naturally containing fructose and foods that have had fructose added during preparation or processing.

6 The evidence for foods containing retinol and lung cancer is derived from studies on dietary intake and serum or plasma levels.

7 The evidence for vitamin D and colorectal cancer is derived from studies on dietary intake, supplements and serum or plasma levels.

8 The evidence for beta-carotene and lung cancer is derived from studies on dietary intake and serum levels.

9 Definitions and categorisation of multivitamin supplements are not standardised across studies.

10 The evidence for beta-carotene and prostate cancer is derived from studies on dietary intake and serum or plasma levels, as well as studies on high-dose supplement use (20, 30 and 50 milligrams per day).

11 The evidence for beta-carotene and non-melanoma skin cancer is derived from one study on plasma levels, as well as studies on high-dose supplement use (50 milligrams per day and 50 milligrams per day on alternate days).

Summary of published cohort studies of healthy dietary patterns and the risk of cancers of the mouth, pharynx and larynx

Cancer	Subtype	Study	Diet index	No. of cases	Risk estimate (95% CI)	Contrast	P trend	Conclusion[1]	Date of CUP cancer report[2]
Mouth, pharynx and larynx	Oral cavity	NIH-AARP [41]	ACS	862 men, 292 women	0.79 (0.64–0.97) 0.71 (0.48–1.06)	Quintile 5 vs quintile 1	0.06 0.03	Limited – suggestive: Decreases risk	2018
	Laryngeal			620	0.82 (0.64–1.05)		0.06		
	Head and neck	NIH-AARP [42]	HEI-2005	1466 men, 402 women	0.74 (0.61–0.89) 0.48 (0.33–0.70)	Quintile 5 vs quintile 1	0.0008 < 0.0001		
			aMED		0.80 (0.64–1.01) 0.42 (0.24–0.74)	7–9 vs 0–2	0.002 < 0.0001		
	Upper aerodigestive tract	EPIC [43]	WCRF/AICR	602	0.69 (0.50–0.95)	Quintile 5 vs quintile 1	< 0.0001		

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

2   Throughout this Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3   Judgements relate to healthy dietary patterns as marked by greater healthy dietary indices. These indices produce an integrated score to assess adherence to healthy eating or lifestyle recommendations or patterns. They are characterised by factors such as healthy weight management; engagement in physical activity; limiting intake of foods and drinks that promote weight gain; limiting intake of red and processed meat; limiting intake of alcoholic drinks; and a higher intake of wholegrains, vegetables and fruit.

Abbreviations: aMED, alternate Mediterranean score [44]; EPIC, European Prospective Investigation into Cancer and Nutrition; HEI-2005, Healthy Eating Index-2005 [5]; NIH-AARP, National Institutes of Health-American Association of Retired Persons; ACS, American Cancer Society; WCRF/AICR, World Cancer Research Fund and the American Institute for Cancer Research Score [43].

CUP dose–response meta-analysis of glycaemic load[1] and the risk of endometrial cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[2]	Date of CUP cancer report[3]
Endometrium	6	6	3,869	1.15 (1.06–1.25)	50 units/ day	0	Probable: Increases risk	2013

1   The glycaemic load of a food may be calculated by multiplying the glycaemic index of a food, expressed as a percentage, by the number of grams of carbohydrate in a serving of the food.

2   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable'.

3   Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

CUP dose–response meta-analysis for consumption of foods and drinks containing fructose[1] and the risk of pancreatic cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I^2 (%)	Conclusion[2]	Date of CUP cancer report[3]
Pancreas[4]	7	6	2,831	1.22 (1.08–1.37)	25 g/day	0	Limited – suggestive: Increases risk	2012

1 Fructose comes from many sources (for example, soft drinks, fruit juices and sucrose), which may differ between population groups, and makes the evidence difficult to interpret. It is also unclear whether fructose may be acting as a marker for other linked exposures.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

4 The evidence for foods and drinks containing fructose and pancreatic cancer includes both foods naturally containing fructose and foods that have had fructose added during preparation or processing.

CUP dose–response meta-analysis of consumption of foods containing saturated fatty acids[1] and the risk of pancreatic cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[2]	Date of CUP cancer report[3]
Pancreas	6	5	2,740	1.11 (1.01–1.21)	10 g/day	43	Limited – suggestive: Increases risk	2012

1   It is not clear whether total fat intake has any effect independent of the association with saturated fatty acids. See CUP pancreatic cancer report 2012, Section 7.3, and CUP pancreatic cancer SLR 2011, Section 5.2.1, for further details.

2   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

3   Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

CUP dose–response meta-analysis for consumption of foods containing retinol and the risk of lung cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I^2 (%)	Conclusion[1]	Date of CUP cancer report[2]
Lung[3]	Dietary[4]	7	3	1,925	1.00 (1.00–1.00)	100 IU/day	97	Limited – suggestive: Decreases risk	2017
	Serum	15	8	2,855	0.97 (0.95–0.98)	10 µg/ 100 ml	0		

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3 The evidence for foods containing retinol and lung cancer is derived from studies on dietary intake and serum or plasma levels.

4 The dose–response meta-analysis for dietary retinol and the risk of lung cancer has not been updated, the result from 2007 Second Expert Report is presented.

CUP dose–response meta-analysis of vitamin D intake and the risk of colorectal cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Colorec-tum[3]	Dietary[4]	15	10	5,171	0.95 (0.93–0.98)	100 IU/day	11	Limited – suggestive: Decreases risk	2017
	Serum or plasma	12	11	4,801	0.92 (0.85–1.00)	30 nmol/L	54		
	Supple-ments[4,5]	3	2	415	0.93 (0.88–0.98)	100 IU/day	0		

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

2   Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3   The evidence for vitamin D and colorectal cancer is derived from studies on dietary intake, supplements and serum or plasma levels.

4   Dose–response meta-analyses for dietary vitamin D and vitamin D supplements and the risk of colorectal cancer have not been not updated. Results from the 2010 CUP colorectal cancer SLR are presented; see CUP colorectal cancer SLR 2016, Appendix 6.

5   The evidence for vitamin D supplements is for the risk of colon cancer only; no conclusion was drawn for rectal cancer.

CUP dose–response meta-analysis for low plasma alpha-tocopherol concentrations and the risk of prostate cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Prostate	12	9	4,989	0.99 (0.98–1.00)	1 mg/L	0	Limited – suggestive: Increases risk for low levels[3]	2014

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3 The Panel's interpretation of the available evidence was that there is an increased risk of prostate cancer at low levels of plasma alpha-tocopherol.

CUP dose–response meta-analysis of low plasma selenium concentrations and the risk of prostate cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Prostate	17	9	3,559	0.95 (0.91–1.00)	10 µg/l	29	Limited – suggestive: Increases risk for low levels[3]	2014

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3 The Panel's interpretation of the available evidence was that there is an increased risk of prostate cancer at low levels of plasma selenium.

Summary of CUP dose–response meta-analyses for consumption of foods containing beta-carotene and the risk of cancer

Cancer	Type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Lung[3]	Dietary	15	13	7,560	0.99 (0.98–1.00)	700 µg/day	5	Limited – suggestive: Decreases risk	2017
	Serum	17	13	2,958	0.92 (0.87–0.97)	10 µg/ 100 ml	40		
Pros-tate[4]	Dietary	11	10	12,219	1.00 (0.99–1.00)	700 µg/day	0	Substantial effect on risk unlikely	2014
	Serum or plasma	14	9	3,449	0.99 (0.95–1.04)	10 µg/ 100 ml	38		
	Supple-ments[5]	8	0	–	No statistically significant association in 8 studies	–	–		

1   See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'substantial effect on risk unlikely' and 'limited – suggestive'.

2   Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3   The Panel made two separate conclusions on lung cancer and beta-carotene: one on 'beta-carotene', which is based on evidence on dietary intake and serum levels, and another on 'high-dose beta-carotene supplements'. The evidence for beta-carotene is presented here. For information on high-dose beta-carotene supplements, see **Section 5.10**.

4   The Panel made one conclusion for prostate cancer and beta-carotene, which is based on evidence derived from studies on dietary intake and serum or plasma levels, as well as studies on high-dose supplement use (20, 30 and 50 milligrams per day).

5   A dose–response meta-analysis could not be conducted in the CUP for prostate cancer and beta-carotene supplements. Evidence is from five cohort studies and three randomised controlled trials (RCTs) which all reported no statistically significant association.

Summary of published randomised controlled trials for consumption of beta-carotene supplements and the risk of prostate cancer

Trial name	No. of participants	Intervention	Intervention length (years)	Follow up (years)	RR (95% CI)
Beta-carotene and Retinol Efficacy Trial (CARET) [81, 82]	18,314 at high risk of developing lung cancer	30 mg beta-carotene and 25,000 IU retinyl palmitate	4 (trial ended early)	5	1.01 (0.80–1.27)
Physicians' Health Study (PHS) [83]	22,071	50 mg beta-carotene taken on alternate days	13		1.00 (0.90–1.10)
Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study (men who smoke tobacco) [84, 85]	29,133	20 mg of beta-carotene only or with 50 mg of *alpha-tocopherol*	5–8	6–8	1.26 (0.98–1.62) for the 1985–1993 follow-up period

Summary of published studies of high-dose beta-carotene supplements and the risk of cancer

Cancer	Total no. of studies	RCT	Cohort studies	Conclusion[1]	Date of CUP cancer report[2]
Lung (people who smoke/ used to smoke tobacco)[3]	11	6	5	Convincing: Increases risk[4]	2017
Skin cancer (non-melanoma)[5]	3	2	1	Substantial effect on risk unlikely	2017

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'convincing'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3 The evidence for high-dose beta-carotene supplements and lung cancer (people who smoke or used to smoke tobacco) is derived from studies using high-dose supplements (20 to 30 milligrams per day or 50 milligrams per day on alternate days for beta-carotene; 25,000 international units per day for retinol).

4 The Panel made two separate conclusions on lung cancer and beta-carotene: one based on evidence on dietary intake and serum levels, and another on high-dose beta-carotene supplements. The evidence based on high-dose beta-carotene supplements is presented here. For information on dietary intake and serum levels, see **Section 5.9**.

5 The evidence for beta-carotene and non-melanoma skin cancer is derived from one study on plasma levels, as well as studies on high-dose supplement use (50 milligrams per day and 50 milligrams per day on alternate days).

Summary of published randomised controlled trials for high-dose beta-carotene supplements and the risk of lung cancer

Study name and intervention	No. of cases		Trial period RR (95% CI)	Post-trial period
	Intervention	Control		
Women's Antioxidant Cardiovascular Study [87] **Beta-carotene 50 mg every other day vs placebo**	41	33	June 1995– January 2005 1.26 (0.80–1.99)	
ATBC study, lung cancer incidence [84] **Daily 20 mg beta-carotene vs no beta-carotene in men who smoke**	242	209	April 1985– April 1993 1.17 (1.02–1.33)	May 1993– April 2011 1.04 (0.96–1.11)
CARET study, lung cancer incidence [81] **Daily beta-carotene (30 mg) and retinyl palmitate (25,000 IU) in people who smoke or used to smoke**	5.92/ 1,000 person years	4.62/ 1,000 person years	1985– January 1996 1.28 (1.04–1.57)	February 1996– December 2001 1.12 (0.97–1.31)
Australian cohort of asbestos workers [88] **30 mg/day beta-carotene vs 25,000 IU/day retinol**	6	4	June 1990– May 1995 1.50 (0.43–5.28)	
Physicians Health Study (PHS) [83] **50 mg beta-carotene on alternate days vs placebo group**	85	93	June 1982– December 1995 0.9 (0.7–1.2)	
Women's Health Study [89] **50 mg of beta-carotene every other day for 2 years (women)**	30	21	April 1993– January 1996	February 1998 1.43 (0.82–2.49)

Summary of published cohort studies for high-dose beta-carotene supplements and the risk of lung cancer

Study	Increment/contrast	RR (95% CI)	No. of cases
Virtamo, 2014 ATBC [91]	Use vs no use	1.04 (0.96–1.11)	2,881
Roswall, 2009 Denmark Cohort [90]	Per 5,000 µg/day	1.64 (1.20–2.23)	721
	> 13,500 vs 0 µg/day	1.56 (0.58–4.25)	
Satia, 2009 Vitamins And Lifestyle (VITAL) Cohort Study [92]	> 1,200 µg/day vs no use men	1.10 (0.71–1.70)	297
	> 1,200 µg/day vs no use women	1.49 (0.76–2.58)	224
Michaud, 2000 Health Professionals Follow-up Study [93]	Use vs no use	0.82 (0.36–1.85)	275
Michaud, 2000 Nurses' Health Study [93]		1.23 (0.55–2.76)	519

Summary of published randomised controlled trials for beta-carotene supplements and the risk of non-melanoma skin cancer

Study	Length of intervention (years)	Total no. participants	Cases treatment/ placebo	Gender	Contrast	RR (95% CI)
PHS [100]	12	22,071	1,786/ 1,821	M	50 mg every other day vs placebo	0.98 (0.92–1.05)
Beta Carotene Trial 1983–89 [101]	5	1,805	362/340	M/W	50 mg/day vs placebo	1.04 (0.89–1.21)

CUP highest versus lowest meta-analysis of calcium supplements and the risk of colorectal cancer

Cancer	Total no. of studies	No. of studies in highest vs lowest plot	No. of cases	Risk estimate (95% CI)	Contrast	I² (%)	Conclusion[1]	Date of CUP cancer report[2]
Colorectum[3]	10	7	9,115	6 studies reported decreased risk, which was significant in 2 studies[4]	Highest vs lowest[5]	–	Probable: Decreases risk	2017
	1	–	–	No significant effect in one RCT[6]	–	–		

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3 The evidence for calcium supplements and colorectal cancer is derived from studies using supplements at a dose >200 milligrams per day.

4 No summary estimate is provided as the dose of calcium supplement varied between the studies.

5 The highest versus lowest meta-analysis for calcium supplements and the risk of colorectal cancer has not been not updated; results from the 2010 CUP colorectal cancer SLR are presented (see CUP colorectal cancer SLR 2016, Appendix 5).

6 Evidence is from an RCT of calcium and vitamin supplements with a dose of 1,000 milligrams elemental calcium carbonate plus 400 international units of vitamin D_3 daily in 36,282 postmenopausal women in the USA [103]. No significant effect was observed compared with placebo (RR 1.06 [95% CI 0.85–1.32]).

CUP highest versus lowest meta-analysis of users versus non-users of multivitamin supplements[1] and the risk of colorectal cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Contrast	Conclusion[2]	Date of CUP cancer report[3]
Colorectum	11	11	8,072	0.88 (0.79–0.98)	Users vs non-users	Limited – suggestive: Decreases risk	2017
	1	–	–	No significant effect in one RCT[4]	–		

1 Definitions and categorisation of multivitamin supplements are not standardised across studies.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Other dietary exposures and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

4 Evidence is from an RCT of multivitamin supplementation with vitamin E (400 international units of synthetic tocopherol), vitamin C (500 milligrams of synthetic ascorbic acid) and beta-carotene (50 milligrams of lurotin) in 14,641 male physicians in the USA [114]. No significant effect was observed compared with placebo (RR 0.89 [95% CI 0.68–1.17]).