

2017	DIET, NUTRITION, PHYSICAL ACTIVITY AND LUNG CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		Arsenic in drinking water <sup>1</sup> High-dose beta-carotene supplements <sup>2</sup>
	Probable		
LIMITED EVIDENCE	Limited – suggestive	Vegetables <sup>3</sup> Fruit <sup>3</sup> Foods containing carotenoids Foods containing beta carotene Foods containing retinol Foods containing vitamin C <sup>4</sup> Foods containing isoflavones <sup>5</sup> Physical activity	Red meat Processed meat Alcoholic drinks
	Limited – no conclusion	Cereals (grains) and their products; starchy tubers; vegetables (never smokers); fruits (never smokers); dietary fibre; pulses (legumes); citrus fruits; poultry; fish; eggs; milk and dairy products; total meat; total fat; animal fats; plant oils; soft drinks; coffee; tea; carbohydrate; protein; vitamin A; thiamin; riboflavin; niacin; vitamin B6; folate; foods containing vitamin C (former and never smokers); vitamin E; selenium; calcium; copper; iron; zinc; beta-carotene supplements (never and former smokers); alpha-carotene; lycopene; beta-cryptoxanthin, lutein and zeaxanthin; foods containing isoflavones (current and former smokers); plasma hydroxyvitamin D; vitamin C supplements; retinol supplements; multivitamin supplements; patterns of diet; body fatness; energy intake; height	
STRONG EVIDENCE	Substantial effect on risk unlikely		

1
The International Agency for Research on Cancer (IARC) 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 high-dose supplements (20 mg/day for beta-carotene; 25,000 IU/day for retinol) in current and former smokers.

3
The evidence applies to current and former smokers only.

4
The evidence applies to current smokers only.

5
The evidence applies only to individuals who have never smoked.

Summary cohort studies – arsenic

Study description	No. cases (No. participants) years of follow-up	Sex	RR (95% CI)	Exposure / Contrast
HIGH-EXPOSURE AREAS				
Chung, 2013 (Taiwan, Arsenic Study) [26]	71 (1,563) 20 years	Mixed	1.47 (0.66-3.31)	≥ 19.5 vs. < 9.1 (µg/L * year)
	43 cases	Men	*SMR 6.05 (4.38–8.15)	
	28 cases	Women	*SMR 7.18 (4.77–10.38)	
Chen, 2010 Taiwan (North- eastern Taiwan cohort) [28]	178 (6,888) 11 years	Mixed	2.08 (1.33–3.27) Ptrend: < 0.01	≥ 10,000 vs. < 400 (µg/L year)
			2.25 (1.43–3.55) Ptrend: < 0.01	≥ 300 vs. < 10 µg/L
Chen, 2004 (South-western and north-eastern Taiwan) [34]	139 (10,591) 8 years	Mixed	3.29 (1.60–6.78)	≥ 700 vs. < 10 µg/L
Nakadaira, 2002 (Nakajo Town Study, Japan) [30]	7 (86) 34 years	Men	11.01	Observed deaths vs. expected
		Women	5.34	Observed deaths vs. expected
Chiou, 1995 (South-western Taiwan cohort) [35]	17 (2,256) 5 years	Mixed	4.01 (1.00–16.12)	High vs. unexposed mg/L
Tsuda, 1995 (Japan 1959-1992) [31]	9 (454) 33 years	Mixed	*SMR 15.69 (7.38–31.02)	≥ 1 ppm
Tsuda, 1989 (Nakajo Japan) [32]	6 (281) 28 years	Mixed	*SMR 1,641 (715–3,634)	≥ 0.5 ppm
Chen, 1988 (Taiwan study) [33]	27 (1,008) 16 years	Mixed	*SMR 1,049	***BFD patients vs. general population
			*SMR 284	***BFD patients vs. residents in BFD-endemic area
LOW-EXPOSURE AREAS				
Baastrup, 2008 (Danish Diet Cancer and Health cohort) [29]	402 (56,378) 10 years	Mixed	**IRR 0.99 (0.90–1.08)	Per 1 µg/L
			**IRR 1.00 (0.98–1.03)	Per 5 mg/L
ARSENIC IN FOODS				
Sawada, 2013 (Japan Public Health Centre study) [27]	685 men, 254 women (90,378) 11 years	Men	1.28 (1.00–1.62) Ptrend: 0.05	102.2 vs. 36.5 µg/day (inorganic arsenic)
		Women	1.37 (0.95–1.98) Ptrend: 0.08	107.6 vs. 37.1 µg/ day (inorganic arsenic)
* SMR: standardized mortality ratio. ** IRR: incident rate ratio. *** BFD: blackfoot disease.				

Summary of RCTs – beta-carotene supplements

Study name and intervention	No. cases		Trial period RR (95% CI)	Post-trial period
	Intervention	Control		
Women’s Antioxidant Cardiovascular Study [38]  β-carotene 50 mg every other day vs. placebo	41	33	June 1995– Jan 2005	
			1.26 (0.80–1.99)	
ATBC study, lung cancer incidence [41]  Daily 20 mg β-carotene vs. no β-carotene in male smokers	242	209	Apr 1985– Apr 1993	May 1993– Apr 2011
			1.17 (1.02–1.33)	1.04 (0.96–1.11)
CARET study, lung cancer incidence [42]  Daily β-carotene (30 mg) and retinyl palmitate (25,000 IU) current or former smokers	5.92/ 1,000 person years	4.62/ 1,000 person years	1985–Jan 1996	Feb 1996– Dec 2001
			1.28 (1.04–1.57)	1.12 (0.97–1.31)
Australian cohort of asbestos workers [43]  30 mg/day β-carotene vs. 25,000 IU/day retinol	6	4	Jun 1990– May 1995	
			1.50 (0.43–5.28)	
Physicians Health Study (PHS) [44]  50 mg β-carotene on alternate days vs. placebo group	85	93	Jun 1982– Dec 1995	
			0.9 (0.7–1.2)	
Women’s Health Study [45]  50 mg of β-carotene every other day for 2 years (women)	30	21	Apr 1993– Jan 1996	Feb 1998
				1.43 (0.82–2.49)

## Summary of cohort studies – beta-carotene supplements

Study	Increment/ Contrast	RR (95% CI)	No. cases	Factors adjusted for
<b>Virtamo, 2014 ATBC [46]</b>	Beta-carotene vs. no beta-carotene	1.04 (0.96–1.11)	2,881	Age, smoking (number cigarettes/day), alcohol consumption, BMI
<b>Roswall, 2009 Denmark Cohort [39]</b>	Per 5,000 µg/day	1.64 (1.20–2.23)	721	Age; sex; supplements of folate, vitamin C and vitamin E; smoking status, intensity, duration; passive smoking; smoking cessation; work exposure to carcinogenic substances
	> 13,500 vs. 0 µg/ day	1.56 (0.58–4.25)		
<b>Satia, 2009 Vitamins And Lifestyle (VITAL) cohort Study [40]</b>	> 1,200 µg /day vs. no use men	1.10 (0.71–1.70)	297	Age; sex; BMI; years of smoking, pack-years and pack-years squared; fruit and vegetable intake; physical activity; supplemental vitamin E use
	> 1,200 µg /day vs. no use women	1.49 (0.76–2.58)	224	
<b>Michaud, 2000 Health Professionals Follow-up Study [47]</b>	Use vs. non-use	0.82 (0.36–1.85)	275	Age (5-year categories), smoking status, time since quitting, age at start of smoking quintiles of energy intake, time period
<b>Michaud, 2000 Nurses' Health Study [47]</b>		1.23 (0.55–2.76)	519	

## Summary of CUP 2015 stratified dose-response meta-analysis – vegetables

Analysis	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>Current smokers</b>	Per 100 g/day	0.88 (0.79–0.99)	81%	6	6,520
<b>Former smokers</b>	Per 100 g/day	0.97 (0.91–1.05)	25%	4	3,771
<b>Never smokers</b>	Per 100 g/day	1.00 (0.91–1.10)	0%	5	680

Summary of CUP 2015 meta-analysis and published pooled analysis – vegetables

Analysis	Increment/ Contrast	RR (95% CI)	I <sup>2</sup> or P- value	No. Studies	No. Cases	Sub-group
2015 CUP	Per 100 g/day	0.94 (0.89–0.98)	48%	20	12,563	
Pooling Project of cohort studies [61]	Q5 vs. Q1	0.88 (0.78–1.00)	0.76	7	3,206	
	Q4 vs. Q1	0.86 (0.74–1.00)	0.85	5	1,915	Current smokers
		0.97 (0.76–1.24)	0.30		981	Former smokers
		0.90 (0.58–1.40)	0.35		259	Never smokers
CUP additional analysis: pooled analyses of Pooling Project of cohort studies [61] combined with all studies from the CUP	Highest vs. lowest	0.93 (0.88–0.98)	0%	24*	18,927	
		0.88 (0.80–0.97)	32%	10	8,435	Current smokers
		0.98 (0.83–1.16)	55%	8	4,752	Former smokers
		0.96 (0.76–1.20)	0%	9	939	Never smokers

\*Three overlapping studies [62, 63] in CUP and pooled analysis.

## Summary of CUP 2015 meta-analysis – green leafy vegetables

Analysis	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>2015 CUP</b>	Per 50 g/day	0.89 (0.79–1.00)	50%	8	5,732
<b>Current smokers</b>	Per 50 g/day	0.83 (0.66–1.06)	44%	4	1,388
<b>Former smokers</b>	Per 50 g/day	0.63 (0.41–0.95)	28%	3	425
<b>Never smokers</b>	Per 50 g/day	0.96 (0.76–1.22)	0%	4	591

## Summary of CUP 2015 stratified dose-response meta-analysis – fruits

Analysis	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
Current smokers	Per 100 g/day	0.91 (0.85–0.98)	57%	9	7,141
Former smokers	Per 100 g/day	0.97 (0.92–1.02)	0%	5	3,828
Never smokers	Per 100 g/day	1.03 (0.97–1.09)	0%	8	1,260



Summary of CUP 2015 meta-analysis and published pooled analysis – fruit

Analysis	Increment/ Contrast	RR (95% CI)	I <sup>2</sup> or P- Value	No. Studies	No. Cases	Sub-group
2015 CUP	Per 100 g/ day	0.92 (0.88–0.95)	57%	23	14,506	
Pooling Project of cohort studies [61]	Q5 vs. Q1	0.77 (0.67–0.87)	0.56	7	3,206	
	Q4 vs. Q1	0.82 (0.68–0.99)	0.13	5	1,915	Current smokers
		0.85 (0.69–1.05)	0.49	5	981	Former smokers
		0.59 (0.34–1.04)	0.09	5	259	Never smokers
CUP additional analysis: pooled analyses of Pooling Project of cohort studies [61] combined with all studies from the CUP	Highest vs. lowest quantile	0.81 (0.75–0.87)	23%	28*	14,783	
		0.83 (0.75–0.92)	16%	13	6,280	Current smokers
		0.89 (0.81–0.99)	0%	9	3,790	Former smokers
		0.91 (0.71–1.17)	33%	12	2,184	Never smokers

\*Three overlapping studies [62, 63] in CUP and pooled analysis.

## Summary of CUP 2015 meta-analysis and published pooled analysis – foods containing beta-carotene

Study	Increment/ Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP Lung SLR 2015</b>	700 µg/day	0.99 (0.98–1.00)	5%	13	7,560
<b>Männistö 2004 [79]</b>	Q5 vs. Q1	0.98 (0.87–1.11)	-	7	3,155

Summary of CUP 2015 stratified dose-response meta-analysis – foods containing vitamin C

Analysis	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
Current smokers	Per 40 mg/day	0.87 (0.79–0.96)	62%	4	1,664
Former smokers	Per 40 mg/day	0.96 (0.87–1.05)	0%	3	582
Never smokers	Per 40 mg/day	0.93 (0.79–1.08)	0%	3	225

Summary of CUP 2015 meta-analysis and published pooled-analysis – foods containing vitamin C

Study	Increment/ Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
CUP Lung SLR 2015 (smokers)	Per 40 mg/day	0.87 (0.79–0.96)	62%	4	1,664
Pooling Project (smokers) [82]	Highest vs. lowest	0.85 (0.70–1.02)	-	8*	1,915

\*Three studies were included in both the CUP highest vs. lowest analysis and Pooling Project [63, 71, 83].

## Summary of CUP 2015 stratified highest vs. lowest analysis – foods containing isoflavones

Analysis	Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP 2015</b>	Highest vs. lowest	0.88 (0.79–0.99)	0%	4	2,919
<b>CUP 2015 current and former smokers</b>	Highest vs. lowest	1.02 (0.84–1.25)	0%	2	1,054
<b>CUP 2015 never smokers</b>	Highest vs. lowest	0.66 (0.51–0.84)	0%	3	714

## Summary of CUP 2015 meta-analysis and published meta-analyses – red meat

Study	Increment/ Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP Lung SLR 2015</b>	Per 100 g/day	1.22 (1.02–1.46)	66%	7	9,765
<b>Xue (2014) [102]</b>	Per 120 g/day	1.21 (1.14–1.28)	-	6	7,070
<b>Yang (2012b) [103]</b>	Highest vs. lowest	1.20 (1.10–1.30)	0%	5	9,174

## Summary of CUP 2015 meta-analysis and published meta-analyses – processed meat

Study	Increment/ Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP Lung SLR 2015</b>	Per 50 g/day	1.14 (1.05–1.24)	0%	7	10,292
<b>Xue (2014) [102]</b>	Per 50 g/day	1.09 (0.99–1.19)	-	5	7,070
<b>Yang (2012b) [103]</b>	Highest vs. lowest	1.05 (0.92–1.19)	49%	4	9,174

## Summary of CUP 2015 meta-analysis and published pooled-analysis – ethanol

Study	Increment/ Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP</b>	Per 10 g/day	1.03 (1.01–1.05)	67%	26	21,940
<b>CUP Lung SLR 2015 + pooled analysis</b>	Per 10 g/day	1.03 (1.02–1.05)	67%	32	24,630
<b>Pooled analysis of cohort studies [132]</b>	≥ 30 g/day vs. none – men	1.21 (0.91–1.61)	-	7	3,137
	≥ 30 g/day vs. none – women	1.16 (0.94–1.43)	-		



Summary of CUP dose-response meta-analyses – other alcohol exposures,  
as ethanol

Analysis	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
CUP 2015 Beer	Per 10 g/day	1.04 (0.93–1.16)	64%	7	3,481
CUP 2015 Wine	Per 10 g/day	0.87 (0.76–0.98)	62%	5	2,701
CUP 2015 Spirits	Per 10 g/day	1.03 (0.98–1.10)	0%	6	2,920

# Summary of CUP highest vs. lowest meta-analysis – other physical activity exposures

Analysis	Contrast	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
Occupational physical activity	Highest vs. lowest	1.12 (0.99–1.28)	0%	5	3,773
Recreational physical activity	Highest vs. lowest	0.86 (0.81–0.92)	41%	18	17,655
	Highest vs. lowest, current smokers	0.81 (0.71–0.91)	65%	6	6,596
	Highest vs. lowest, former smokers	0.68 (0.51–0.90)	50%	3	3,647
	Highest vs. lowest, never smokers	0.99 (0.76–1.31)	19%	3	894