

Title: Association of vitamin C, vitamin D, vitamin E and risk of bladder cancer: a dose-response meta-analysis

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Supplementary table 1 characteristics of the studies included in this meta-analysis

Author Country	Design, Study name	Age (mean, years)	Subjects (cases), sex	Follow -up (years)	Exposure (assessment method)	RR (95% CI) for the highest vs. lowest categories	Covariates adjusted
Helzlsouer et al. 1989, USA ¹	Cohort (NCC) Washington County project	58.9	105 (35), both	12	---	a-Tocopherol (circulating) 0.57 (0.12-2.71)	Sex, race, within 2 h for the interval between blood collection and the previous meal, cigarette smoking and vitamin supplements
Nomura et al. 1991, USA ²	Matched case-control (PCC)	66.0 (men) 70.4 (women)	522 (261), both	---	Interview	Vitamin C (diet) Men: 1.0 (0.6-1.7) Women: 0.6 (0.2-1.4) Vitamin C (supplement) Men: 1.2 (0.8-1.8) Women: 0.5 (0.3-1.1) Vitamin C (total) Men: 1.2 (0.8-2.1) Women: 0.4 (0.2-1.1)	Sex, age, ethnic group, and pack-years of cigarette smoking.
Riboli et al. 1991, Spain ³	Matched case-control (HCC)	---	1221 (432), men	---	Interview	Vitamin C (diet) 1.03 (0.72-1.48) Vitamin E (diet) 0.72 (0.48-1.09)	Age, area of residence
Shibata et al. 1992, USA ⁴	Cohort	74.9	11580 (71), men	70159 person- years	FFQ	Men: Vitamin C (diet) 0.94 (0.52-1.70) Vitamin C (supplement) 0.58 (0.36-0.93) Vitamin E (supplement)	Age and smoking

Bruemmer et al. 1996, USA ⁵	Case-control (PCC)	58.3	667	---	Interview (supplement)	0.74 (0.46-1.20)	Age, sex, county, smoking, and calories (for diet and total)
		(cases)	(262),			Vitamin C (diet)	
		57.1	both			0.50 (0.28-0.88)	
		(controls)				Vitamin C (supplement)	
						0.40 (0.21-0.76)	
						Vitamin C (total)	
						0.45 (0.26-0.79)	
						Vitamin E (diet)	
						0.59 (0.31-1.14)	
						Vitamin E (supplement)	
Michaud et al. 2000, USA ⁶	Cohort, HPFS	40-75	47909	12	FFQ	0.61 (0.34-1.08)	Age, energy, pack-years of smoking history, current smoking status, geographic region of the United States, total fluid intake, and cruciferous vegetable intake, and total fluid intake (for supplement)
		(320),	men			Vitamin C (total)	
						0.90 (0.62-1.31)	
						Vitamin E (total)	
						0.64 (0.45-0.92)	
						Vitamin D (total)	
						1.06 (0.75-1.50)	
						Vitamin C (supplement)	
						0.73 (0.48-1.10)	
						Vitamin E (supplement)	
Wakai et al. 2000, Japan ⁷	Matched case-control (HCC)	66.6	592	---	Interview	0.83 (0.45-1.52)	Sex, age, hospital, smoking and occupational history as a cook
		(cases)	(297),			Vitamin C (diet)	
		66.5	both			0.74 (0.43-1.26)	
		(controls)				Vitamin E (diet)	
						0.65 (0.39-1.09)	
						Vitamin C (total)	
		0.81 (0.49-1.35)					

Zeegers et al. 2001, Netherlands ⁸	Cohort, Netherlands Cohort Study	62.7 (cases) 61.4 (controls)	3692 (569), both	6.3	FFQ	Vitamin E (total) 0.68 (0.41-1.12) Vitamin C (diet) 0.81 (0.61-1.07) Vitamin E (diet) 0.98 (0.68-1.41) Vitamin C (supplement) 1.01 (0.69-1.48) Vitamin E (supplement) 1.05 (0.63-1.73)	Age, sex, cigarette smoking amount and cigarette smoking duration
Jacobs et al. 2002, USA ⁹	Cohort, Cancer Prevention Study II Cohort	Main (40-70)	991522 (1289), both	18	FFQ	Vitamin C (supplement) 1.25 (0.91-1.72) Vitamin E (supplement) 0.60 (0.37-0.96)	Age, sex (in combined-sex models), educational level, cigarette smoking (current or former status and number of pack-years), consumption of citrus fruits/juices, consumption of vegetables, and vitamin C and vitamin E supplement use
Michaud et al. 2002, Finland ¹⁰	Cohort, ATBC cohort	50-69	27111 (344), men smokers	11	FFQ	Vitamin C (diet) 1.35 (0.95-1.91) Vitamin E (diet) 0.79 (0.56-1.11)	Age, duration of smoking, smoking dose, total energy, and trial intervention (alpha-tocopherol and beta-carotene supplements)
Nomura et al. 2003, USA ¹¹	Cohort (NCC), none	73.2	219 (109), men	>20	---	α -Tocopherol (circulating): 0.90 (0.40-2.01) γ -Tocopherol (circulating): 1.20 (0.50-2.86) Total Tocopherol (circulating): 0.75 (0.33-1.72)	Age, pack-years of cigarette smoking, serum triglyceride and hours since last meal

Castelao et al. 2004, USA ¹²	Matched case-control (PCC)	56.3 (cases) 56.4 (controls)	3184 (1592), both	---	Interview	Vitamin C (diet) 0.73 (0.56-0.95)	Sex, date of birth, race, level of education, number of cigarettes smoked per day, number of years of smoking, smoking status in reference year, lifetime use of nonsteroidal anti-inflammatory drugs, and number of years employed as a hairdresser/barber
Holick et al. 2005, USA ¹³	Cohort, Nurses' Health Study	30-55	88796 (237), women	20	FFQ	Vitamin C (total) 1.03 (0.69-1.53) Vitamin E (total) 1.26 (0.85-1.89) Vitamin C (supplement) 1.09 (0.70-1.69) Vitamin E (supplement) 0.72 (0.37-1.42)	Age, pack-years of cigarette smoking, current smoking, and total caloric intake
Hung et al. 2006, USA ¹⁴	Case-control (PCC)	60.2	257 (84), both	---	---	α -Tocopherol (circulating): 0.91 (0.17-4.95) γ -Tocopherol (circulating): 1.81 (0.38-8.64)	Age, sex, pack-years and education
Kellen et al. 2006, Belgium ¹⁵	Case-control (PCC)	67.67 (cases) 64.24 (controls)	540 (178), both	---	Interview	Vitamin C (diet) 0.65 (0.39-1.11) Vitamin E (diet) 0.68 (0.41-1.13)	Sex, age, smoking status, number of cigarettes smoked per day, number of years smoking and occupational exposure to polycyclic aromatic hydrocarbons or aromatic amines
Liang et al. 2008, USA ¹⁶	Matched case-control (PCC)	63.1 (cases) 62.6 (controls)	675 (386), both	---	Interview	α -Tocopherol (circulating): 0.50 (0.3-0.78) γ -Tocopherol (circulating): 1.52 (0.95-2.44) α -Tocopherol (diet):	Age, sex, ethnicity, smoking status, number of cigarettes smoked per day, smoking duration, and plasma cholesterol (for circulating)

						0.85 (0.54-1.32)	
						γ -Tocopherol (diet):	
						1.18 (0.71-1.97)	
Roswall et al. 2009, Denmark ¹⁷	Cohort, Danish Diet, Cancer and Health Study	50-64	55557 (322), both	10.6	FFQ	Vitamin C (total)	Total intake of the three other micronutrients (vitamin C, vitamin E, folate and beta-carotene) as well as dietary intake for the supplemental intake and supplemental intake for the dietary intake and further for smoking status, smoking duration, smoking intensity, possible cessation and when, passive smoking, and work exposure
						1.23 (0.87-1.75)	
						Vitamin C (diet)	
						0.99 (0.70-1.39)	
						Vitamin C (supplement)	
						1.19 (0.86-1.66)	
						Vitamin E (total)	
						1.12 (0.78-1.59)	
						Vitamin E (diet)	
						1.07 (0.76-1.51)	
						Vitamin E (supplement):	
						0.97 (0.66-1.44)	
Brinkman et al. 2010, USA ¹⁸	Case-control (PCC)	62 (cases) 60.7 (controls)	661 (322), both	---	Interview	Vitamin D (total)	Age, sex, smoking status, pack years smoked, and total energy intake
						0.58 (0.31-1.06)	
						Vitamin E (total)	
						0.66 (0.36-1.20)	
						Vitamin C (total)	
						0.78 (0.45-1.38)	
Brinkman et al. 2011, Belgium ¹⁹	Case-control (PCC)	67.6 (cases) 64.2 (controls)	586 (200), both	---	FFQ	Vitamin D (total)	Age, sex, smoking status, number of cigarettes smoked per day, number of years of cigarette smoking and exposure to occupational carcinogens and energy intake
						1.03 (0.62-1.72)	
Amaral et al. 2012, Denmark ²⁰	Matched case-control (HCC)	68 (cases) 66 (controls)	2153 (1125), both	---	---	Vitamin D (circulating)	Age, sex, ethnic origin, region, smoking status, and season of blood collection
						0.55 (0.35-0.84)	

Mondul et al. 2012, Finland ²¹	Cohort (NCC), ATBC cohort	58.6	500 (250), men smokers	11	---	Vitamin D (circulating) 0.61 (0.36-1.05)	Age, date of baseline blood draw, number of cigarettes per day, years of smoking, and vitamin D binding protein
Mondul et al. 2012, USA ²²	Cohort (NCC), PLCO Cancer Screening Study	64	733 (369), both	13	---	Vitamin D (circulating) 1.19 (0.74-1.92)	Age, race, sex, and date of blood collection, smoking status, pack-years of smoking, dairy consumption, and use of aspirin or ibuprofen
Ros et al. 2012, Europe ²³	Cohort (NCC), EPIC	58.5	1712 (856), both	11.0	FFQ	Vitamin C (circulating) 0.85 (0.61-1.17) Vitamin C (diet) 1.11 (0.82-1.51)	Sex, age at baseline, study center, date and time of blood collection, fasting status, smoking status, duration, and intensity
Afzal et al. 2013, Denmark ²⁴	Cohort, Copenhagen City Heart Study	20-100	9791 (112), both	28	---	Vitamin D (circulating) 0.78 (0.65-0.94)	Age, sex, pack-years, BMI, alcohol consumption, leisure time and work-related physical activity, and duration of education
Park et al. 2013, USA ²⁵	Cohort, Multiethnic Cohort Study	Men: 60.2 Women: 59.7	Men: 83694 (429) Women: 102191 (152)	12.5	FFQ	Vitamin C (diet) Men: 0.83 (0.62-1.11) Women: 0.46 (0.28-0.73) Vitamin E (diet) Men: 0.97 (0.74-1.27) Women: (0.48 (0.29-0.78)	Age at cohort entry, ethnicity, total energy intake, first-degree family history of bladder cancer, employment in a high-risk industry, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), number of years since quitting (time dependent), interactions of ethnicity with smoking status, average number of cigarettes, and squared average number of cigarettes

ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, BMI: body mass index, EPIC: European Prospective Investigation into Cancer and Nutrition, FFQ: food frequency questionnaire, HCC: hospital-based case-control study, HPFS: Health Professionals Follow-Up Study, NCC: nested case-control study, PCC: population-based case-control study, PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Supplementary table 2 Pooled results on vitamin C and risk of bladder cancer

	Diet plus supplement				Diet				Supplement			
	N	RR (95% CI)	I2 (%)	P ^a	N	RR (95% CI)	I2 (%)	P ^a	N	RR (95% CI)	I2 (%)	P ^a
Total	8	0.86 (0.67-1.10)	52.5		14	0.84 (0.73-0.98)	47.5		9	0.87 (0.69-1.11)	64.9	
By design				0.18				0.28				0.28
Cohort	3	1.05 (0.85-1.31)	0.00		7	0.91 (0.73-1.13)	61.5		6	0.97 (0.77-1.22)	51.9	
Case-control	5	0.71 (0.48-1.05)	56.0		7	0.77 (0.65-0.92)	7.50		3	0.64 (0.31-1.34)	80.5	
By age (years)				0.76				0.96				0.67
≥60	4	0.82 (0.56-1.19)	41.1		8	0.84 (0.73-0.98)	0.00		4	0.81 (0.55-1.20)	65.1	
<60	4	0.89 (0.62-1.27)	67.7		6	0.83 (0.61-1.12)	76.4		5	0.92 (0.66-1.28)	69.5	
Country				0.66				0.15				0.34
USA	6	0.79 (0.58-1.08)	54.8		7	0.72 (0.59-0.88)	27.3		7	0.80 (0.58-1.09)	70.4	
Europe	1	1.23 (0.87-1.74)	---		6	0.99 (0.83-1.18)	38.0		2	1.11 (0.87-1.42)	0.00	
Japan	1	0.81 (0.49-1.35)	---		1	0.74 (0.43-1.26)	000		-	---	---	
Assessment method				0.18				0.67				0.28
Interview	4	0.71 (0.48-1.05)	56.0		6	0.80 (0.68-0.95)	0.00		3	0.64 (0.31-1.34)	80.5	
FFQ	3	1.05 (0.85-1.31)	0.00		8	0.86 (0.69-1.07)	64.5		6	0.97 (0.77-1.22)	51.9	
Number of cases				0.44				0.28				0.22
≥300	3	1.00 (0.77-1.30)	63.2		8	0.89 (0.74-1.07)	62.3		4	1.05 (0.84-1.32)	35.8	
<300	5	0.76 (0.52-1.13)	16.8		6	0.74 (0.58-0.93)	0.00		5	0.72 (0.47-1.10)	71.4	
Number of covariates ^b				0.42				0.01				0.89
≥4	5	0.80 (0.62-1.03)	33.4		6	0.69 (0.58-0.82)	13.7		4	0.84 (0.55-1.29)	74.4	
<4	3	0.96 (0.57-1.61)	66.2		8	1.01 (0.88-1.15)	0.00		5	0.89 (0.65-1.23)	63.9	

a: P values were obtained from meta-regression

b: Number of covariates adjusted including 7 covariates: age, sex, smoking, dietary factors, occupational factors and others (education and physical activity)

Supplementary table 3 Pooled results on vitamin E and risk of bladder cancer

	Diet plus supplement				Diet				Supplement			
	N	RR (95% CI)	I2 (%)	P ^a	N	RR (95% CI)	I2 (%)	P ^a	N	RR (95% CI)	I2 (%)	P ^a
Total	6	0.82 (0.62-1.08)	55.2		9	0.80 (0.68-0.94)	33.0		7	0.78 (0.64-0.94)	0.60	
By design				0.22				0.14				0.18
Cohort	3	0.96 (0.64-1.45)	73.1		5	0.86 (0.69-1.08)	51.3		6	0.82 (0.67-1.01)	0.00	
Case-control	3	0.65 (0.47-0.90)	0.00		4	0.67 (0.52-0.86)	0.00		1	0.51 (0.29-0.89)	---	
By age (years)				0.43				0.65				0.48
≥60	2	0.67 (0.46-0.99)	68.1		5	0.85 (0.72-1.01)	0.00			0.87 (0.62-1.24)	0.00	
<60	4	0.88 (0.61-1.27)	0.00		4	0.74 (0.52-1.04)	60.9			0.73 (0.57-0.93)	9.70	
Country				0.96				0.84				0.10
USA	4	0.77 (0.53-1.13)	61.0		3	0.68 (0.42-1.11)	71.0			0.66 (0.52-0.85)	0.00	
Europe	1	0.68 (0.41-1.12)	---		5	0.86 (0.73-1.02)	0.00			1.00 (0.73-1.36)	0.00	
Japan	1	1.12 (0.78-1.59)	---		1	0.65 (0.39-1.09)	---		--	---	---	
Assessment method				0.22				0.29				0.18
Interview	3	0.65 (0.47-0.90)	0.00		3	0.69 (0.53-0.90)	0.00		1	0.51 (0.29-0.89)	--	
FFQ	3	0.96 (0.64-1.45)	73.1		6	0.84 (0.67-1.04)	48.2		6	0.82 (0.67-1.01)	0.00	
Number of cases				0.88				0.03				0.24
≥300	3	0.80 (0.54-1.19)	62.2		5	0.92 (0.79-1.06)	0.00		4	0.85 (0.67-1.09)	5.30	
<300	3	0.83 (0.52-1.34)	64.6		4	0.59 (0.46-0.77)	0.00		3	0.65 (0.47-0.90)	0.00	
Number of covariates ^b				0.31				0.25				0.13
≥4	5	0.76 (0.56-1.02)	49.8		5	0.69 (0.52-0.92)	47.1			0.64 (0.48-0.85)	0.00	
<4	1	1.12 (0.78-1.59)	---		4	0.89 (0.74-1.07)	0.00			0.92 (0.71-1.19)	0.00	

a: P values were obtained from meta-regression

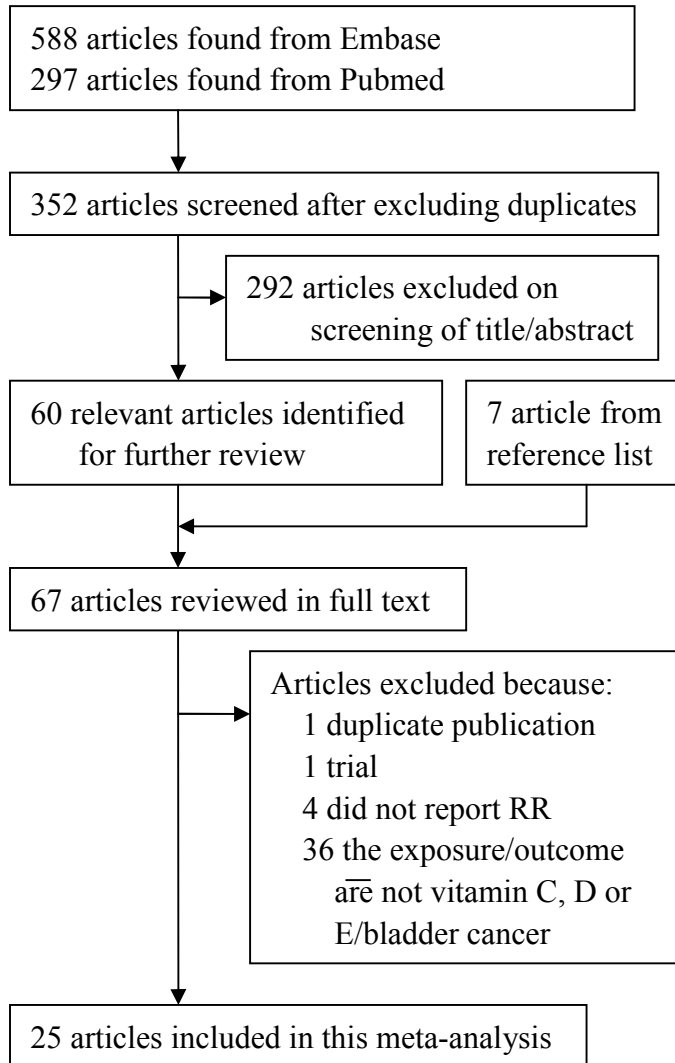
b: Number of covariates adjusted including 7 covariates: age, sex, smoking, dietary factors, occupational factors and others (education and physical activity)

Supplementary table 4 Subgroup analysis by smoking status and sex^a

Subgroup	Vitamin C			Vitamin D			Vitamin E		
	N ^b	RR (95% CI)	I2 (%)	N ^b	RR (95% CI)	I2 (%)	N ^b	RR (95% CI)	I2 (%)
Among smokers	10	0.92 (0.80-1.05)	67.7	4	0.72 (0.55-0.93)	0.00	9	0.77 (0.64-0.92)	68.8
Among non-smokers	5	0.94 (0.73-1.20)	36.4	1	1.04 (0.50-2.16)	---	4	1.00 (0.94-1.05)	0.00
Among men	9	0.95 (0.79-1.14)	43.1	2	0.84 (0.49-1.43)	---	9	0.75 (0.65-0.86)	0.00
Among women	4	0.74 (0.43-1.27)	75.1	---	---	---	4	0.74 (0.42-1.32)	69.2

a: We combined the result from diet and/or supplement and circulating levels (α -Tocopherol for vitamin E) to increase the number of studies in each subgroup analysis, and the summary estimates were presented in highest vs. lowest levels.

b: number of studies



Supplementary figure 1 Flow chart for study inclusion

Supplementary references

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