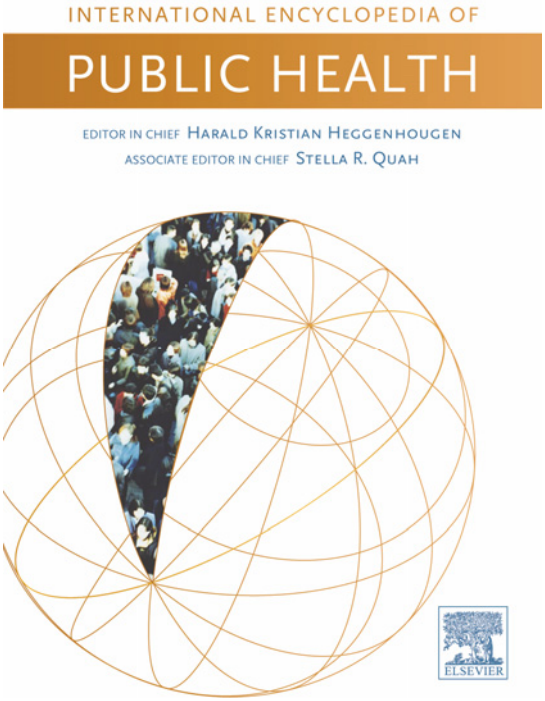

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The Epidemiology of Vitamin C

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Glossary

95% Confidence interval (CI) Estimated range of values that is 95% likely to include the true relative risk (RR).
Dietary vitamin C Intake of vitamin C from food sources (units: mg/day).
Prospective cohort study An observational study of a group of subjects with several common characteristics who vary in other characteristics, such as, vitamin C intake, and who are followed prospectively for development of and/or death from specific diseases.
Randomized controlled trial An experimental study of a specific intervention (such as, increased vitamin C intake) on a specific outcome (such as, death) based on comparing subjects randomly assigned to an 'intervention group' undergoing the intervention with subjects randomly assigned to a 'control group' undergoing no intervention.
Relative risk of death (RR) Death rate in the high-intake group relative to death rate in the low-intake group (generally determined by Cox proportional hazards regression).
Retrospective case-control study An observational study of 'cases' (patients with a common disease) who are compared with 'controls' (persons without the disease) in order to identify retrospectively measured risk factors (such as, vitamin C intake) that may contribute to the development of the disease.
Serum vitamin C or plasma ascorbic acid (PAA) Blood level of vitamin C (units: 1.0 mg/dl = 0.568 mmol/dl = 56.8 mol/l).
Vitamin C supplements Intake of vitamin C from vitamin supplements (units: mg/day).

Introduction

Vitamin C (ascorbic acid or ascorbate) is an essential nutrient for humans (Enstrom, 1997, 2001; Food and Nutrition Board, Institute of Medicine, 2000; Otten *et al.*, 2006). Ascorbate is required for many important metabolic reactions in all animals and is made internally in almost all of them, with humans being a notable exception. It has been long known that vitamin C deficiency causes scurvy in humans. Based on the most recent comprehensive assessment of the health effects of vitamin C by the U.S. National Academy of Sciences, the current U.S. recommended dietary allowance (RDA) for of vitamin C intake is 90 mg per day for adult males and 75 mg per day for adult females, with a tolerable upper intake level of 2000 mg per day in adults (Food and Nutrition Board, Institute of Medicine, 2000; Otten *et al.*, 2006).

Because of its antioxidant properties, dietary vitamin C and vitamin C supplements have been examined with regard to the prevention and treatment of cancer and the prevention of cardiovascular disease (Block, 1991; Byers and Guerrero, 1995; Carr and Frei, 1999; Levine *et al.*, 1999; Asplund, 2002; Knekt *et al.*, 2004; Stanner *et al.*, 2004; Coulter *et al.*, 2006; Bjelakovic *et al.*, 2007). The human body is under constant attack by reactive oxygen molecules (free radicals and singlet oxygen) that are formed as a natural consequence of normal biochemical activity. Reactive oxygen can damage the body in many ways by altering membrane structure and function. The hypothesis that free radicals may be involved in carcinogenesis is based primarily on observations that many carcinogens are free radicals, are the product of free radical reactions, are converted to free radicals *in vivo*, or stimulate the production of free radicals. Also, free radicals may be important in tumor initiation and/or promotion.

Because this damage can be life-threatening, the human body has evolved with antioxidant defense mechanisms to protect against free radical oxidation. Many antioxidants have been shown to inhibit carcinogenesis in a variety of animal models and antioxidant molecules may retard atherogenesis by interfering with this oxidation process. These defenses include small molecules like vitamin C that act as antioxidants or scavengers of reactive oxygen species. However, because human antioxidant defense systems are not completely efficient, it has been proposed that increasing the intake of dietary antioxidants such as vitamin C may be important in diminishing the cumulative effects of oxidative damage over the long human life span. Vitamin C is the major water-soluble antioxidant vitamin.

Epidemiologic studies of the relationship of vitamin C to cancer and other diseases consist of two types: Observational studies and intervention trials. Observational studies examine the association between vitamin C intake and disease or between blood levels of vitamin C and disease. However, these observational studies must be interpreted cautiously, since the effects observed may result from factors correlated with vitamin C rather that from vitamin C itself. Thus, supporting data from intervention studies are important for causal inference. Randomized controlled intervention trials, unlike the observational studies, generally are not subject to bias and/or confounding. However, these trials are extraordinarily expensive, difficult to conduct, and relatively short in duration.

There are well over 100 epidemiologic studies that have examined some aspect of the relationship between vitamin C and disease. The majority of these are case-control studies of cancer patients compared with appropriately matched control subjects without cancer. The case-control studies have been reviewed by Block (1991) and Byers and Guerrero (1995). The majority of these studies show an inverse relationship between vitamin C intake and risk of death from all causes, cancer, and cardiovascular disease. Many of these studies have focused on tobacco-related cancers, such as oral cavity, esophagus, and lung cancer. The observational studies have failed to find any consistent adverse effects associated with increased vitamin C intake. In addition, data from *in vitro* and animal carcinogenesis studies have been generally consistent with the observational studies.

This review focuses on prospective epidemiologic studies that involve vitamin C intake, an index of vitamin C intake, or serum vitamin C (plasma ascorbic acid). Most of these studies have been published during the past 20 years. These studies are generally methodologically superior to case-control studies since they obtain information about vitamin C and other characteristics before cancer or other diseases develop and are less subject to selection bias. Although not the focus of this review, there are several prospective studies that show an inverse relationship between fruit and/or vegetable intake and mortality. Many of these studies are relevant because citrus fruit intake is a reasonable measure of dietary vitamin C intake. This review incorporates findings from our previous reviews (Enstrom, 1997, 2001), other recent reviews (Block, 1991; Byers and Guerrero, 1995; Carr and Frei, 1999; Levine *et al.*, 1999; Asplund, 2002; Knekt *et al.*, 2004; Stanner *et al.*, 2004; Coulter *et al.*, 2006; Bjelakovic *et al.*, 2007), and recent randomized controlled trials (De Lorgeril *et al.*, 1998; Hercberg *et al.*, 2004; Jaxa-Chamiec *et al.*, 2005).

Methods

A complete presentation of all results on the relationship of vitamin C intake and mortality and incidence from all diseases is beyond the scope of this review. To provide information on the most important epidemiologic evidence, the essential characteristics are given for 26 major prospective studies that measured vitamin C intake in the diet or in blood samples and had mortality from all causes, cancer, and/or cardiovascular disease as an outcome (Bjelke, 1982; Kvale *et al.*, 1983; de Long and Hammond, 1985; Enstrom *et al.*, 1986; Gey *et al.*, 1987; Kromhout, 1987; Heilbrun *et al.*, 1989; Knekt *et al.*, 1991; Chow *et al.*, 1992; Enstrom *et al.*, 1992; Shibata *et al.*, 1992; Hunter *et al.*, 1993; Rohan *et al.*, 1993; Pandey *et al.*, 1995; Zheng *et al.*, 1995; Eichholzer *et al.*, 1996; Hertog *et al.*, 1996; Losonczy *et al.*, 1996; Sahyoun *et al.*, 1996; Bandera *et al.*, 1997; Ocke *et al.*, 1997; Jarvinen *et al.*, 1997; Young *et al.*, 1997; Enstrom, 1999; Botterweck *et al.*, 2000; Loria *et al.*, 2000; Khaw *et al.*, 2001; Jacobs *et al.*, 2002; Fletcher *et al.*, 2003; Genkinger *et al.*, 2004; Cho *et al.*, 2006; Jenab *et al.*, 2006). Vitamin C intake was determined for each subject based on their consumption of fruits and other foods containing vitamin C and/or supplements containing vitamin C. In addition, serum vitamin C (plasma ascorbic acid) was measured for the subjects in several cohorts.

Table 1 describes the study population, number of subjects, geographic location, age range, follow-up period, health status, and type of data collected for these 26 population cohorts cited in the previous paragraph. The studies are shown in chronological order, citing the first and/or most important publication associated with each cohort. Several small cohorts that examined vitamin C intake and total mortality during 1950–80 are described in a former review (Enstrom, 1997).

Table 2 describes the results of those studies that give all-cause mortality for males, females, and/or both sexes. The number of years of follow-up, the high and low vitamin C intake groups, and the variables controlled for are presented along with the total number of deaths in the cohort, relative risk (RR) of the high-intake group versus the low-intake group, and 95% confidence interval (CI) or statistical significance level (p-value) for the relative risk.

Table 3 describes the results of these same studies where results are presented for mortality or incidence from all cancer for males, females, and/or both sexes. Table 4 describes the results of these same studies where results are presented for mortality from all cardiovascular disease or coronary heart disease for males, females, and/or both sexes. The mortality or incidence results for the specific cancer sites of lung, breast, stomach, colorectum, and prostate are described in a former review (Enstrom, 2001). Finally, a summary is given regarding recent randomized controlled trials that have assessed the impact of vitamin C intake on subsequent cancer and/or cardiovascular disease (De Lorgeril *et al.*, 1998; Hercberg *et al.*, 2004; Jaxa-Chamiec *et al.*, 2005).

Results

Among the 26 prospective cohorts described in Table 1, the relative risk (RR) for all-cause mortality as a function of vitamin C intake is presented in Table 2 for eight cohorts. Results based on dietary vitamin C and serum vitamin C are presented in separate parts of the table. Each relative risk is based on comparing persons with the highest and lowest vitamin C intake, generally values close to the RDA. The 12 RRs for males from five cohorts range between 0.48 and 0.95: All 12 are less than 1.00 and ten are significantly less than 1.0 ($p<0.05$). The nine RRs for females from four cohorts range between 0.77 and 1.03: Seven are less than 1.0 and four are significantly less than 1.0. The 18 RRs for both sexes from seven cohorts range between 0.43 to 0.97: 18 are less than 1.0 and 13 are significantly less. Of the RRs that control for confounding variables, five of six for males, one of three for females, and six of ten for both sexes are significantly less than 1.00.

Table 3 shows the RRs for mortality or incidence from all cancer sites: 27 of 27 RRs are less than 1.0, and 11 are significantly less than 1.0. Table 4 shows the RRs for mortality for cardiovascular disease mortality: 24 of 27 are less than 1.0 and 12 are significantly less than 1.0. The reviews by Block (1991) and Byers and Guerrero (1995) of the results of case-control studies for stomach, colorectal, lung, breast, and prostate cancer showed RRs that were less than 1.0. Of the studies in the Block review, 25 of 44 (57%) of the RRs are significantly ($p<0.05$) less than 1.0; of the studies in the Byers review, 38 of 49 (78%) of the RRs are less than 1.0. These results are consistent with the cohort results for specific cancer sites presented in our previous reviews (Enstrom, 1997, 2001). Thus, the vast majority of observational results from both case-control and cohort studies indicate a beneficial effect of increased vitamin C intake with respect to cancer and coronary heart disease. Also, it is obvious that the results in Tables 2–4 represent only a small fraction of the potential results that would be available if the cohorts in Table 1 were fully analyzed with respect to vitamin C intake and mortality.

Other compilations have yielded somewhat different findings. A recent study pooled nine prospective cohort studies with information on intakes of vitamin E, carotenoids, and vitamin C and coronary heart disease (CHD) incidence (Knekt *et al.*, 2004). During a 10-year follow-up of 293 172 subjects who were free of CHD at baseline, dietary intake of antioxidant vitamins was only weakly related to a reduced CHD risk after adjustment for potential nondietary and dietary confounding factors. Compared with subjects in the lowest dietary intake quintile for vitamin C, those in the highest intake quintile had a relative risk of CHD incidence of 1.23 (1.04–1.45). However, compared with subjects who did not take vitamin C supplements, those who took at least 700 mg per day of supplemental vitamin C had a relative risk of CHD incidence of 0.75 (0.60–0.93). However, this compilation is based on well-nourished cohorts and deals with CHD incidence and not the CVD mortality, making a direct comparison with results in Table 4 difficult.

Overall, there is substantial epidemiologic evidence that dietary vitamin C intake is consistently associated with moderately lower death rates from all causes, cardiovascular disease, and cancer, and particularly some types of tobacco-related cancer. This reduced mortality appears to be associated with diets rich in vitamin C, particularly the intake of citrus fruits, and with increased blood levels of ascorbic acid. The antioxidant hypothesis proposes that vitamin C and other antioxidant nutrients afford protection against chronic diseases by decreasing oxidative damage. Although scientific rationale and observational studies have been convincing, randomized primary and secondary intervention trials involving vitamin C have failed to show consistent benefit from the use of supplements on cardiovascular disease or cancer risk. Most of the major antioxidant trials have involved vitamin E and/or vitamin A given at relatively high doses and several of these trials suggest possible harm in certain subgroups.

Table 1 Description of populations for prospective vitamin C studies: Mortality and incidence

Author (year)	*Population description*	*Age at entry*	*Start*	*End*	*Initial health*	*Type of study*
Bjelke (1982)	13 785 Males, 2928 females; random sample of Norwegian men and their family members 10 602 males	35+	1967	1978	Average	Mailed dietary questionnaire
Kvale (1983)			1967	1978		
De Long (1985)	~350 000 white males from 25 states enrolled by ACS (Cancer Prevention Study I)	40–74	1960	1970	No history of cancer and not sick at entry	Mailed lifestyle and dietary questionnaire
Enstrom (1986)	1369 Males, 1654 females; representative sample of residents of Alameda County, CA	16+	1974	1983	Noninstitutionalized	Lifestyle and dietary interview
Gey (1987)	2975 Male employees of the three major Swiss pharmaceutical companies in Basel (Basel Study)	average 51	1971–73	1980	Apparently healthy	Exam with blood samples
Eichholzer (1996)	2975 Males		1971–73	1990		
Kromhout (1987)	878 Middle-aged males randomly sampled from Zutphen, Netherlands (Zutphen Study)	40–59	1960	1985	Average	Lifestyle and dietary interview of subjects and wives
Ocke (1997)	561 Males	52–71	1971	1990	No history of cancer	
Heilbrun (1989)	8006 Japanese men residing on Oahu, HI	45–67	1965–68	1985	Cancer-free	Clinical exam and dietary history
Knekt (1991)	4538 Males; participants in Finish multiphasic Mobile Clinic Health Examination Survey	20–69	1967–72	1986	Cancer-free	Dietary history interview and health exam
Jarvinen (1997)	4697 Females	15+	1967–72	1991		
Chow (1992)	17 818 White males; Lutheran Brotherhood Insurance Society policy holders from nine states	35+	1966	1986	Already insured	Mailed lifestyle and dietary questionnaire
Enstrom (1992)	4479 Males, 6869 females; national sample (NHANES I Epidemiologic Followup Study)	25–74	1971–74	1982–84	Average	lifestyle and dietary interview and exam with blood samples
Enstrom (1999)	4479 Males, 6869 females		1971–74	1992	Average	
Yong (1997)	3968 Males, 6100 females		1971–74	1992	Average, good dietary data	
Shibata (1992)	~4277 Males, ~7300 females; elderly residents of Leisure World, Laguna Hills, CA	>50	1981–85	1989	Cancer-free, 1st year	Mailed dietary questionnaire
Hunter (1993)	87 494 Female registered nurses from 11 large states (Nurses Health Study)	34–59	1980	1988	Cancer-free	Mailed dietary questionnaire
Rohan (1993)	56 837 Females enrolled in multicenter Canadian National Breast Screening Study (NBSS)	40–59	1982	1987	Cancer-free	Lifestyle and dietary questionnaire: nested case-control analysis

Pandey (1995)	1556 Male employees of Western Electric Company in Chicago, IL (Western Electric Study)	40–55	1958–59	1983	No history of CHD, cancer, or other serious illness	Lifestyle and dietary interview and numerous exams
Zheng (1995)	34 691 Females recruited from a random DMV sample in Iowa	55–69	1986	1992	no history of cancer	Mailed dietary questionnaire
Gale (1995)	359 Males, 307 females; stratified random sample from 8 areas in the UK	65+	1973	1993	No history of CHD, stroke, or arteriosclerosis	Detailed dietary interview, health exam, blood sample
Hertog (1996)	2112 Males recruited from all residents of Caerphilly, South Wales, UK (Caerphilly Study)	45–69	1979–83	~1995	Average	Baseline and follow-up exams with lifestyle and dietary questionnaire
Losonczy (1996)	~4095 Males, ~7083 females; free living persons from communities in MA, IA, CT and NC	67–105	1984–86	1993	Average	Medical history, lifestyle and dietary interview
Sahyoun (1996)	254 Males, 471 females; noninstitutionalized recruited from MA community groups	60–101	1981–84	1992	Free of terminal disease and severe disorders	Physical, medical, dietary, and biochemical exam
Bandera (1997)	27 544 Males, 20 456 females in New York State selected from DMV file (New York State Cohort)	~40–80	1980	1987		Mailed dietary questionnaire: nested case-control analysis
Botterweck (2000)	58 279 Males, 62 573 females in Netherlands Cohort Study	55–69	1986	1990	Average	Mailed dietary questionnaire: nested case-control analysis
Loria (2000)	3347 Males, 3724 females; national sample (NHANES II Mortality Follow-up Study)	30–75	1976–80	1992	No history of CHD, stroke, or cancer	Lifestyle and dietary interview and exam with blood samples
Kwaw (2001)	8860 Males, 10 636 females; general practices sample in Norfolk, UK (EPIC Study)	45–79	1993–97	1999	No history of CHD, stroke, or cancer	Lifestyle and dietary interview and exam with blood samples
Jacobs (2002)	460 737 Males, 585 186 females in 50 U.S. states enrolled by ACS (Cancer Prevention Study II)	30+	1982	1998	No history of cancer	Lifestyle and dietary questionnaire
Fletcher (2003)	552 Males, 662 females; randomly selected patients of 51British family practitioners (MRC Study)	75–84	~1995	~1999	Average	Health and nutrition interview and exam with blood samples
Genkinger (2004)	2299 Males, 3852 females; Washington County, MD, population sample (CLUE Study)	Mean 55	1974–89	2001	Average	Lifestyle and dietary interview and 1989 exam with blood samples
Jenab (2006)	153 451 Males, 368 032 females in 10 European countries (EPIC-EURGAST Study)	45–79	1992–98	~2001	Average	Lifestyle and dietary interview and exam with blood samples

Data from Enstrom JE (1997) Vitamin C in prospective epidemiologic studies. In: Packer L and Fuchs J (eds.) *Vitamin C in Health and Disease*, pp. 381–398. New York: Marcel Dekker; Enstrom JE (2001) Epidemiology and clinical aspects of ascorbate and cancer. In: Cadenas E and Packer L (eds.) *Handbook of Antioxidants*, 2nd edn., pp. 167–188. New York: Marcel Dekker.

Table 2 Results for prospective vitamin C studies: All-cause mortality

					Males			*Females*			*Both sexes*		
Author (year)	*Low vitamin C (Group L)*	*High vitamin C (Group H)*	*Control variables*	*Years of FU*	*Total deaths*	*RR (H vs L)*	*CI of RR*	*Total deaths*	*RR (H vs L)*	*CI of RR*	*Total deaths*	*RR (H vs L)*	*CI of RR*
Results based on dietary vitamin C													
Enstrom (1986)	VC<250 mg/day	VC>250 mg/day	Age	10	134	0.95	0.61–1.42	130	1.03	0.68–1.51	264	0.97	0.67–1.38
Enstrom (1992)	VC<50 mg/day	VC>50 mg/d and reg supps	Age	5	473	0.52	0.35–0.73	276	0.77	0.53–1.06	749	0.66	0.53–0.82
Enstrom (1992)	VC<50 mg/day	VC>50 mg/d and reg supps	Age, 10 confounders	5	473	0.61	0.43–0.86				749	0.68	0.52–0.89
Enstrom (1992)	VC<50 mg/day	VC>50 mg/d and reg supps	Age	Mean 10	1,069	0.59	0.47–0.72	740	0.90	0.74–1.09	1809	0.74	0.64–0.85
Enstrom (1992)	VC<50 mg/day	VC>50 mg/d and reg supps	age, 10 confounders	Mean 10	1,069	0.78	0.62–0.97				1809	0.86	0.73–1.02
Enstrom (1999)	VC<50 mg/day	VC>50 mg/d and reg supps	Age	Mean 19	2,132	0.67	0.57–0.77	1,876	0.86	0.76–0.98	4008	0.79	0.72–0.87
Enstrom (1999)	VC<50 mg/day	VC>50 mg/d and	Age, 10 confounders	Mean 19	1,883	0.90	0.78–1.04	1,652	1.01	0.88–1.17	3535	0.95	0.85–1.05
Pandey (1995)	VC = 21–82 mg/day	VC = 113–393 mg/day	age, 11 confounders	Mean 24	667	0.73	0.58–0.91						
Sahyoun (1996)	VC < 90 mg/day	VC > 388 mg/day	Age, sex	Mean 10							217	0.53	0.33–0.84
Sahyoun (1996)	VC < 90 mg/day	VC > 388 mg/day	Age, sex, 3 confounders	Mean 10							217	0.55	0.34–0.88

Fletcher (2003)	Med VC = 52.1 mg/day	Med VC = 103.5 mg/day	Age, sex	4.4							258	0.88	0.54–1.39
Genkinger (2004)	Med VC = 39.4 mg/day	Med VC = 175.6 mg/day	Age, sex, energy								910	0.88	0.72–1.07
Results based on serum vitamin C (plasma ascorbic acid)													
Sahyoun (1996)	PAA < 0.91 mg/dl	PAA > 1.56 mg/dl	Age, sex, 3 confounders	Mean 10							217	0.56	0.34–0.91
Loria (2000)	PAA < 0.50 mg/dl[a] PAA < 0.70 mg/dl[b]	PAA > 1.30 mg/dl[a] PAA > 1.50 mg/dl[b]	Age, sex	Mean 14	242	0.52	0.41–0.67	127	0.68	0.51–0.92	369	0.58	0.48–0.70
Loria (2000)	PAA < 0.50 mg/dl[a] PAA < 0.70 mg/dl[b]	PAA > 1.30 mg/dl[a] PAA > 1.50 mg/dl[b]	age, sex, 8 confounders	Mean 14	242	0.64	0.49–0.83	127	0.84	0.60–1.16	369	0.71	0.58–0.87
Khaw (2001)	Mean PPA = 0.37[a] Mean PPA = 0.53[b]	Mean PPA = 1.28[a] Mean PPA = 1.50[b]	Age, sex	Mean 4	309	0.48	0.33–0.70	187	0.50	0.32–0.81	496	0.49	0.36–0.65
Khaw (2001)	Mean PPA = 0.37[a] Mean PPA = 0.53[b]	Mean PPA = 1.28[a] Mean PPA = 1.50[b]	Age, sex, 6 confounders	Mean 4	309	~0.50	0.34–0.72	187	~0.58	0.37–0.94	496	~0.53	0.39–0.71
Fletcher (2003)	PAA < 0.19 mg/dl	PAA > 1.40 mg/dl	age, sex	4.4							258	0.43	0.29–0.64
Fletcher (2003)	PAA < 0.19 mg/dl	PAA > 1.40 mg/dl	Age, sex, 11 confounders	4.4							258	0.54	0.34–0.84

[a]Male values.

[b]Female values.

a = Male values; b = Female values; VC, vitamin C intake in mg/day; reg supps, daily use of vitamin C and/or multivitamin supplements; PAA, plasma ascorbic acid in mg/dl (1.0 mg/dl = 0.568 mmol/dL = 56.8 μmol/l).

Data from Enstrom JE (1997) Vitamin C in prospective epidemiologic studies. In: Packer L and Fuchs J (eds.) *Vitamin C in Health and Disease*, pp. 381–398. New York: Marcel Dekker; Enstrom JE (2001) Epidemiology and clinical aspects of ascorbate and cancer. In: Cadenas E and Packer L (eds.) *Handbook of Antioxidants*, 2nd edn., pp. 167–188. New York: Marcel Dekker.

Table 3 Results for prospective vitamin C studies: All-cancer mortality or incidence

					Males			*Females*			*Both sexes*		
Author (year)	*Low vitamin C (Group L)*	*High vitamin C (Group H)*	*Control variables*	*Years of FU*	*Total deaths*	*RR (H vs. L)*	*CI of RR*	*Total deaths*	*RR (H vs. L)*	*CI of RR*	*Total deaths*	*RR (H vs. L)*	*CI of RR*
Results based on dietary vitamin C													
Kromhout (1987)	VC < 63 mg/day	VC=83–103 mg/day	Age, smoking	25	155	<1.00	$P > 0.05$						
Enstrom (1992)	VC < 50 mg/day	VC>50 mg/d and reg supps	Age	Mean, 10	228	0.79	0.51–1.18	169	0.93	0.60–1.40	397	0.85	0.63–1.14
Enstrom (1994)	VC < 50 mg/day	VC>50 mg/d and reg supps	Age	Mean, 14	346	0.69	0.47–.97	269	0.92	0.65–1.27	615	0.78	0.60–0.98
Shibata (1992)	VC < 145 mg/day	VC>210 mg/day	Age, smoking	Mean, 7	645[c]	0.90	0.74–1.09	690[c]	0.76	0.63–0.91	1335[c]	0.83	0.71–0.95
Pandey (1995)	VC = 21–82 mg/day	VC = 113–393 mg/day	Age, 11	Mean, 24	155	0.61	0.40–0.94						
Sahyoun (1996)	VC < 90 mg/day	VC > 388 mg/day	Age, sex, 2 confounders	Mean, 10							57	0.94	0.36–2.44
Genkinger (2004)	Med VC = 39.4 mg/day	Med VC = 175.6 mg/day	Age, sex	~2.5							307	0.82	0.58–1.15
Results based on serum vitamin C (plasma ascorbic acid)													
Eichholzer (1996)	PAA < 0.4 mg/dl	PAA > 0.4 mg/dl	Age, smoking, lipids	17	290	0.81	0.59–1.12						
Sahyoun (1996)	PAA < 0.91 mg/dl	PAA > 1.56 mg/dl	Age, sex, 3 confounders	Mean, 10							57	0.68	0.25–1.83
Loria (2000)	PAA < 0.50 mg/dl[a] PAA < 0.70 mg/dl[b]	PAA > 1.30 mg/dl[a] PAA > 1.50 mg/dl[b]	Age, sex	Mean, 14	228	0.49	0.31–0.76	155	0.83	0.51–1.35	383	0.62	0.45–0.87
Loria (2000)	PAA < 0.50 mg/dl[a] PAA < 0.70 mg/dl[b]	PAA > 1.30 mg/dl[a] PAA > 1.50 mg/dl[b]	Age, sex, 8 confounders	Mean, 14	228	0.62	0.39–0.99	155	0.94	0.53–1.67	383	0.73	0.51–1.05
Khaw (2001)	Mean PPA = 0.37[a] Mean PPA = 0.53[b]	Mean PPA = 1.28[a] Mean PPA = 1.50[b]	Age, sex	Mean, 4	116	0.47	0.26–0.88	84	0.73	0.38–1.40	200	0.58	0.37–0.90
Khaw (2001)	Mean PPA = 0.37[a] Mean PPA = 0.53[b]	Mean PPA = 1.28[a] Mean PPA = 1.50[b]	Age, sex, 6 confounders	Mean, 4	116	~0.43	0.25–.80	84	~0.85	0.44–1.64	200	~0.58	0.38–0.90

a = Males values; b = Female values; c = Cancer incidence was measured in Shibata (1992) and cancer mortality was measured in all other studies. VC, vitamin C intake in mg/day; reg supps, daily use of vitamin C and/or multivitamin supplements; PAA, plasma ascorbic acid in mg/dl (1.0 mg/dl = 0.568 mmol/dL = 56.8 μmol/l).

Data from Enstrom JE (1997) Vitamin C in prospective epidemiologic studies. In: Packer L and Fuchs J (eds.) *Vitamin C in Health and Disease*, pp. 381–398. New York: Marcel Dekker; Enstrom JE (2001) Epidemiology and clinical aspects of ascorbate and cancer. In: Cadenas E and Packer L (eds.) *Handbook of Antioxidants*, 2nd edn., pp. 167–188. New York: Marcel Dekker.

Table 4 Results for prospective vitamin C studies: Cardiovascular disease mortality

					Males			*Females*			*Both sexes*		
Author (year)	*Low vitamin C (Group L)*	*High vitamin C (Group H)*	*Control variables*	*Years of FU*	*Total deaths*	*RR (H vs. L)*	*CI of RR*	*Total deaths*	*RR (H vs. L)*	*CI of RR*	*Total deaths*	*RR (H vs. L)*	*CI of RR*
Results based on dietary vitamin C													
Enstrom (1992)	VC < 50 mg/day	VC > 50 mg/day and reg supps	Age	Mean, 10	588	0.55	0.39–0.74	371	0.75	0.55–0.99	929	0.64	0.51–0.80
Knekt (1994)	VC < 61 mg/day	VC > 85 mg/day	Age, sex, 5 confounders	16	186	1.00	0.68–1.45	58	0.49	0.24–0.98	244	0.85	0.61–1.19
Gale (1995)	VC < 27.9 mg/day	VC > 44.9 mg/day	Age, sex	20							182	0.80	0.60–1.20
Kushi (1996)	VC < 87 mg/day	VC > 196 mg/day	Age, 12 confounders	7				122	1.43	0.75–2.70			
Sahyoun (1996)	VC < 90 mg/day	VC > 388 mg/day	Age, sex, 2 confounders	Mean, 10							101	0.38	0.19–0.75
Fletcher (2003)	Med VC=52.1 mg/day	Med VC = 103.5 mg/day	Age, sex	4.4							113	0.91	0.54–1.57
Genkinger (2004)	Med VC=39.4 mg/day	Med VC = 175.6 mg/day	Age, sex, energy	~2.5							378	1.05	0.76–1.50
Studies based on serum vitamin C (plasma ascorbic acid)													
Gey (1993)	PAA < 0.4 mg/dl	PAA > 0.4 mg/dl	Age, smoking	Mean, 7	132	0.80	0.50–1.30						
Sahyoun (1996)	PAA < 0.91 mg/dl	PAA > 1.56 mg/dl	Age, sex, 3 confounders	Mean, 10							75	0.53	0.27–1.06
Loria (2000)	PAA < 0.50 mg/dl[a] PAA < 0.70 mg/dl[b]	PAA > 1.30 mg/dl[a] PAA > 1.50 mg/dl[b]	Age, sex	Mean, 14	293	0.58	0.36–0.91	213	0.82	0.52–1.30	506	0.69	0.50–0.96
Loria (2000)	PAA < 0.50 mg/dl[a] PAA < 0.70 mg/dl[b]	PAA > 1.30 mg/dl[a] PAA > 1.50 mg/dl[b]	Age, sex, 8 confounders	Mean, 14	293	0.69	0.43–1.11	213	1.08	0.65–1.75	506	0.85	0.61–1.20
Khaw (2001)	Mean PPA = 0.37[a] Mean PPA = 0.53[b]	Mean PPA = 1.28[a] Mean PPA = 1.50[b]	Age, sex	Mean, 4	123	0.29	0.15–0.59	57	0.41	0.20–1.00	180	0.34	0.20–0.56
Khaw (2001)	Mean PPA = 0.37[a] Mean PPA = 0.53[b]	Mean PPA = 1.28[a] Mean PPA = 1.50[b]	Age, sex, 6 confounders	Mean, 4	123	~0.31	0.16–0.64	57	~0.46	0.23–1.13	180	~0.37	0.22–0.62
Fletcher (2003)	PAA < 0.19 mg/dl	PAA > 1.40 mg/dl	Age, sex	4.4							113	0.46	0.26–0.83
Fletcher (2003)	PAA < 0.19 mg/dl	PAA > 1.40 mg/dl	Age, sex, 11 confounders	4.4							113	0.57	0.29–1.12

a = Males values; b = Female values; VC, vitamin C intake in mg/day; reg supps, daily use of vitamin C and/or multivitamin supplements; PAA, plasma ascorbic acid in mg/dl (1.0 mg/dl = 0.568 mmol/dL = 56.8 μmol/l).

Data from Enstrom JE (1997) Vitamin C in prospective epidemiologic studies. In: Packer L and Fuchs J (eds.) *Vitamin C in Health and Disease*, pp. 381–398. New York: Marcel Dekker; Enstrom JE (2001) Epidemiology and clinical aspects of ascorbate and cancer. In: Cadenas E and Packer L (eds.) *Handbook of Antioxidants*, 2nd edn., pp. 167–188. New York: Marcel Dekker.

The definitive trial investigating the effect of a dietary level of vitamin C has not been done.

A recent review of 68 randomized controlled trials of antioxidants assessed their safety and efficacy (Bjelakovic *et al.*, 2007). Very few trials have involved vitamin C supplements. There were no consistent adverse effects of multivitamin and mineral supplements. The evidence thus far shows that vitamin C supplements have had no significant effect on mortality from any cause. The evidence is insufficient to prove the presence or absence of benefits from use of multivitamin and mineral supplements to prevent cancer and chronic disease. Thus, there is a need for further evaluation of this issue.

Three recent trials involving a vitamin C intervention are noteworthy. One intervention trial among acute myocardial infarction (AMI) patients in France showed that a Mediterranean-type diet with vitamin C intake of about 130 mg per day resulted in a lower cancer death rate (De Lorgeril *et al.*, 1998). In a randomized, double-blind, multicenter trial, 800 Polish patients (mean age, 62) with acute myocardial infarction (AMI) were randomly allocated to receive, on top of routine medication, one of two treatments: Vitamin C (1000 mg/12 h infusion followed by 1200 mg/24 h orally) and vitamin E (600 mg/24 h) or matching placebo for 30 days (Jaxa-Chamiec *et al.*, 2005). This randomized pilot trial shows that supplementation with antioxidant vitamins is safe and seems to positively influence the clinical outcome of patients with AMI.

The Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) study is a randomized, double-blind, placebo-controlled primary prevention trial of nutritional doses of supplementation among 13 017 French adults (7876 women aged 35–60 years and 5141 men aged 45–60 years) (Hercberg *et al.*, 2004). All participants took a single daily capsule of a combination of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 mug of selenium, and 20 mg of zinc, or a placebo. Median follow-up time was 7.5 years. The outcome of intervention versus placebo for total cancer incidence showed RR = 0.69 (0.53–0.91) in men and RR = 1.04 (0.85–1.29) in women. The outcome for total mortality showed RR = 0.63 (0.42–0.93) in men and 1.03 (0.64–1.63) in women.

Recently, the evidence of vitamin C supplements for treatment and prevention of cancer has been reviewed (Coulter *et al.*, 2006). Results for intervention studies involving vitamin C supplements and cancer have been inconclusive. There have been two small randomized controlled trials of terminal cancer patients (median survival of seven weeks) and neither of these showed any benefit from 10 g of vitamin C supplements. However, one small trial of bladder cancer patients showed a significant benefit for 2 g of vitamin C. In general, the potential role of vitamin C supplements in the treatment of human cancer has not been fully investigated. Systematic review of the literature does not support the hypothesis that the use of supplements of vitamin C in the doses tested helps prevent and/or treat cancer in the populations tested. The isolated findings of benefit require confirmation. Further details about these trials are presented in a former review (Enstrom, 2001) and a number of other studies (Creagan *et al.*, 1979; Moertel *et al.*, 1985; Blot *et al.*, 1993; Lamm *et al.*, 1994; Hercberg *et al.*, 1998).

Conclusions

A large majority of epidemiologic studies show a modest decrease in mortality from all causes, cancer, and cardiovascular disease with an increase of vitamin C intake, particularly for levels of vitamin C intake around the current U.S. RDA of 75–90 mg per day for adults. This inverse relationship is strongest for males, next strongest for both sexes combined, and weakest for females. However, several studies show no significant relationship after controlling for confounding variables and others do not properly control for confounding variables. Indices of varying quality have been used and they have usually been based on dietary sources alone. There does not appear to be a relationship between mortality and vitamin C supplement intake *per se*. The strongest inverse relationship has been observed in those studies that have analyzed serum vitamin C and total mortality. The vast majority of available prospective data remain unanalyzed and there is a need for comprehensive analysis in this area.

There have been relatively few intervention trials involving dietary vitamin C and vitamin C supplements. However, there are suggestions from the trials summarized above that there are benefits associated with interventions involving dietary levels of vitamin C. The beneficial results thus far should not be overinterpreted and probably apply only to populations with similar baseline nutritional status and risk factors and to the specific intervention used. But the potential benefit of vitamin C may have been minimized in these trials if the intervention was given too late in the disease process, given for an inadequate duration, or given to an already well-nourished population.

Although the specific antioxidant mechanism by which vitamin C may be causally related to reduced mortality has not yet been clearly established, the available epidemiologic evidence indicates there is continuing value in understanding this mechanism. This relationship can be substantially refined by complete analysis of the available prospective cohort data. Additional well-designed trials can measure the impact of specific vitamin C interventions, particularly in populations with poor nutrition. It is important to further examine the role of vitamin C in

reducing mortality, because it is a component of the diet that can be easily and inexpensively changed and one where even a small benefit can have a large population impact. While the existing epidemiologic evidence is not conclusive, it strongly suggests that increased levels of dietary vitamin C and serum vitamin C are associated with reduced mortality. Further studies are certainly warranted in order to conclusively determine the health benefits of vitamin C.

Acknowledgments

This review has been supported in part by the Wallace Genetic Foundation.

See also: Diet and Heart Disease; Functions and Deficiencies of B-vitamins (and Their Prevention); Vitamin A Deficiency and its Prevention; Vitamin D.

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http://www.iom.edu/Object.File/Master/7/296/webtablevitamins.pdf– Health benefits, food sources, side effects, and recommended daily intakes of vitamin C.

Epidemiology, Historical

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Background

Usually, great achievements and breakthroughs in most aspects of medical care, such as procedures in diagnostics and therapy, are highly esteemed over extended periods of time, because the disease for which the procedures were introduced is still prevalent. In epidemiology, this is not necessarily the case. Here, successes, often followed by equally successful achievements in preventive medicine, may permanently eliminate the medical problem that was solved by epidemiological research, thereby relegating successes in epidemiology and preventive