

Carotenoids and cardiovascular health¹⁻³

Sari Voutilainen, Tarja Nurmi, Jaakko Mursu, and Tiina H Rissanen

ABSTRACT

Cardiovascular disease (CVD) is the main cause of death in Western countries. Nutrition has a significant role in the prevention of many chronic diseases such as CVD, cancers, and degenerative brain diseases. The major risk and protective factors in the diet are well recognized, but interesting new candidates continue to appear. It is well known that a greater intake of fruit and vegetables can help prevent heart diseases and mortality. Because fruit, berries, and vegetables are chemically complex foods, it is difficult to pinpoint any single nutrient that contributes the most to the cardioprotective effects. Several potential components that are found in fruit, berries, and vegetables are probably involved in the protective effects against CVD. Potential beneficial substances include antioxidant vitamins, folate, fiber, and potassium. Antioxidant compounds found in fruit and vegetables, such as vitamin C, carotenoids, and flavonoids, may influence the risk of CVD by preventing the oxidation of cholesterol in arteries. In this review, the role of main dietary carotenoids, ie, lycopene, β -carotene, α -carotene, β -cryptoxanthin, lutein, and zeaxanthin, in the prevention of heart diseases is discussed. Although it is clear that a higher intake of fruit and vegetables can help prevent the morbidity and mortality associated with heart diseases, more information is needed to ascertain the association between the intake of single nutrients, such as carotenoids, and the risk of CVD. Currently, the consumption of carotenoids in pharmaceutical forms for the treatment or prevention of heart diseases cannot be recommended. *Am J Clin Nutr* 2006;83:1265-71.

KEY WORDS Carotenoids, coronary artery disease, cardiovascular health, lycopene, β -carotene

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death in Western countries. Although CVD mortality has decreased in the past decades in many countries, these diseases still account for >40% of total mortality. Diets vary extensively between different populations (1). In the eastern part of Finland, the mortality rate was 10 times that found in Crete, where the population consumes a typical Mediterranean diet that is rich in plant foods and relatively poor in animal foods. A plant-dominated diet likely promotes health through multiple nutrients and mechanisms. Carotenoids, the pigments responsible for the yellow to red color of some fruit and vegetables, have been implicated as beneficial substances.

Carotenoids found in the human diet are primarily derived from plants and are found in roots, leaves, shoots, seeds, fruit, and flowers. More than 600 carotenoid compounds have been characterized; \approx 50 of these are consumed in the human diet (2, 3).

Approximately 12 carotenoids account for most of the dietary intake, and they are found in measurable concentrations in human blood and tissues (3, 4); the most common are lycopene, lutein, α -carotene, β -carotene, β -cryptoxanthin, and zeaxanthin (4). Carotenoids can also be present, to a lesser extent, in eggs, poultry, and fish because the animals are typically fed plant and algal products; eg, the zeaxanthin in chicken originates from maize in the poultry feed.

Various biological effects have been attributed to carotenoids. One possible mechanism of action of carotenoids is via their antioxidant activity, but other mechanisms may also contribute to their beneficial effects (5). Plasma concentrations of carotenoids are considered useful biomarkers of total dietary intake of vegetables and fruit (6).

Because carotenoids are a complex group of chemicals, and studies of the health effects of carotenoids are very heterogeneous, it is difficult to undertake a meta-analysis or even a detailed systematic review about the health effects of carotenoids. In the present review article, we collected all epidemiologic studies and clinical trials on the effects of carotenoids with CVD as a clinical endpoint.

CAROTENOIDS IN HUMAN HEALTH

Chemistry, metabolism, and bioavailability of main carotenoids

Most carotenoids, such as α -carotene, β -carotene, and β -cryptoxanthin, have provitamin A activity. In addition to their provitamin A activity, carotenoids have been considered to have many other biological functions (7, 8). They are proposed to be efficient scavengers of free radicals (7), and they have also been shown to protect low density lipoproteins (LDLs) against oxidation in vitro. Some (9, 10), but not all (11), dietary intervention studies of either lycopene-containing foods or lycopene supplementation have shown potential short-term improvement in LDL resistance to oxidation. However, the results are inconsistent, and some recent in vitro experiments have shown not only a loss

¹ From the Research Institute of Public Health and Department of Public Health and General Practice, University of Kuopio, Kuopio, Finland.

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³ Reprints not available. Address correspondence to S Voutilainen, Research Institute of Public Health, University of Kuopio, PO Box 1627, 70211 Kuopio, Finland. E-mail: sari.voutilainen@uku.fi.

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of antioxidant effectiveness, but also prooxidant effects of carotenoids at high concentrations (12). Other carotenoid functions, eg, enhancement of gap junctions, tumor-suppressive activity, immunomodulation, carcinogenesis, and protection of DNA against peroxidation have been described (8). To date, the pro-vitamin A function is the only physiologic function of carotenoids clearly demonstrated in humans.

The bioavailability of carotenoids appears to be dependent on several factors (13). In general, the absorption of carotenoids depends on their bioavailability from the food matrix and their solubility in micelles (2, 14). Many carotenoids are absorbed better in the presence of dietary fats and from heat processed foods than from unprocessed sources (15, 16). The nature of the isoforms of carotenoids also affects their bioavailability and absorption; ie, *trans*-isomers of lycopene are absorbed more poorly than are *cis*-isomers (16). Other factors that influence the absorption of carotenoids include the presence of dietary fiber, the health status of the person, and the physical form of the carotenoid (17).

Carotenoids share the same chylomicron absorption pathway as other lipid-soluble compounds. The blood concentration of carotenoid varies between persons. In a study conducted in 400 male and female participants in the United States, low serum concentrations of α -carotene, β -carotene, β -cryptoxanthin, and lutein plus zeaxanthin were generally associated with male sex, smoking, young age, high non-HDL cholesterol, high alcohol consumption, and high body mass index (18).

In addition to diet, carotenoid intake can be assessed by measuring biomarkers of carotenoid intake. Because adipose tissue is the major storage site for carotenoids in the human body, carotenoid concentrations in adipose tissue are supposed to be a better predictor of long-term intake than are concentrations in plasma or serum (19). It was also proposed that the usefulness of adipose tissue and plasma carotenoids as biomarkers of carotenoid intake is similar, although correlations for individual carotenoids vary substantially (20).

No recommended dietary allowances for carotenoids exist in the United States or in Europe. The amount of carotenoids in the diet is difficult to estimate, partly because the methods used to in preparation of food composition tables are not sufficiently specific or sensitive. The main sources of some carotenoids are presented in **Table 1**.

Although carotenoids are not essential for human health, they have biological actions that may be important in maintaining health and preventing the appearance of serious diseases such as cancer, pulmonary disorders, and cataract (8). Epidemiologic studies have also shown that a high intake of carotenoids is associated with a reduced risk of CVD, although the results of these studies are somewhat conflicting.

Epidemiologic studies of carotenoids and cardiovascular health

Many epidemiologic studies have detected an association between carotenoids and the risk of heart diseases or atherosclerosis (**Table 2**). In the present review, we categorized studies into 3 groups according to the source of carotenoids measured: dietary intake, serum or plasma concentrations, and adipose tissue concentration of carotenoids.

TABLE 1
Main sources of dietary carotenoids¹

Carotenoid	Source
Lycopene	Tomato and tomato products
	Watermelon
	Pink grapefruit
	Papaya
	Guava
β -Carotene	Rose hip
	Carrots
	Apricots
	Mangoes
	Red pepper
	Kale
	Spinach
α -Carotene	Broccoli
	Carrots
	Collard greens
	Pumpkin
	Corn
Lutein plus zeaxanthin	Yellow pepper
	Cloudberry
	Kale
	Spinach
	Broccoli
	Peas
	Brussels sprouts
	Collard greens
	Lettuce
	Corn
Egg yolk	
β -Cryptoxanthin	Avocado
	Oranges
	Papaya
	Passion fruit
	Pepper
Persimmon	

¹ From Osganian et al (22).

Dietary intake of carotenoids

Osganian et al (22) studied prospectively the relation between dietary intake of carotenoids and the risk of coronary artery disease (CAD) in 73 286 female nurses by using a semiquantitative food-frequency questionnaire. During the 12-y follow-up (803 590 person-years), they identified 998 incident cases of CAD. After adjustment for age, smoking, and other CAD risk factors, they observed modest, but significant, inverse associations between the highest fifths of β -carotene and α -carotene intakes and the risk of CAD, but not with lutein plus zeaxanthin, lycopene, or β -cryptoxanthin intakes. The association between the specific carotenoids and CAD risk did not vary significantly according to smoking status.

Several prospective and case-control studies have shown an association between low intakes of β -carotene and the risk of CVD, although the results of the studies are inconsistent (Table 2). In the Rotterdam Study ($n = 4802$), there was a significantly reduced risk of myocardial infarction (MI) after a 4-y follow-up in the subjects in the highest third of β -carotene intake compared with the subjects in the lowest third (23). In a case-control study conducted in Italy with 433 cases and 869 paired controls, the risk of nonfatal acute MI in women was inversely related to the intake of β -carotene-containing foods (24).

TABLE 2

Studies of the association of carotenoids with the risk of cardiovascular disease (CVD) and atherosclerosis¹

Assay or source of carotenoid	Study and nationality of subjects	Study setting, follow-up	Sex	n	Outcome	Main results
Dietary intake						
α - and β -Carotene, lutein plus zeaxanthin, lycopene, and β -cryptoxanthin	Nurses Health Study, American (22)	Prospective, 12 y	F	73 286	CAD	Inverse significant associations between the highest quintiles of intake of β -carotene and α -carotene and risk of CAD
β -Carotene	The Rotterdam Study, Dutch (23)	Prospective, 4 y	F, M	4802	MI	Significantly decreased risk of MI in highest β -carotene intake quartile
β -Carotene	Italian (24)	Case-control	F	433 + 869 ²	AMI	The risk of nonfatal AMI in women was inversely related to intake of β -carotene-containing foods
Carotenoids with provitamin A activity	Finnish Mobile Clinic Study, Finnish (25)	Prospective, 14 y	F, M	5133	Coronary mortality	Nonsignificant inverse association between dietary intake of carotenoids with provitamin A activity and the risk of coronary mortality in women
β -Carotene	Western Electric Study, American (26)	Prospective, 30 y	F, M	1843	Stroke	A modest decrease in the risk of stroke with higher intake of β -carotene
α - and β -Carotene, lutein, and lycopene	The Health Professionals Follow-up Study, American (27)	Prospective, 8 y		43 738	Stroke	High dietary intake of lutein was associated with a reduced risk of ischemic stroke
β -Carotene, lutein plus zeaxanthin, and lycopene	ATBC Study, Finnish (28)	Prospective, 6.1 y	M	26 593	Stroke	Dietary intake of β -carotene was inversely associated with the risk of cerebral infarction
Carotenoids with provitamin A activity	ARIC Study, American (29)	Cross-sectional	F, M	12 773	Prevalence of carotid plaques	Those in the highest quintile of carotenoid consumption had a lower prevalence of plaques
Plasma or serum						
Serum total carotenoids	LRC-CPPT Study, American (31)	Prospective, 13 y	M	1883 (placebo group)	CHD	Participants in the highest quartile of total carotene had the lowest risk of incident CHD
Plasma α - and β -carotene, β -cryptoxanthin, lutein, and lycopene	Physicians' Health Study, American (32)	Nested case-control, 13 y	M	531 + 531	MI	No evidence for a protective effect of a higher baseline plasma concentration of any of the carotenoids measured
Plasma α - and β -carotene, β -cryptoxanthin, lutein, and lycopene	Physicians' Health Study, American (33)	Nested case-control, 13 y	M	297 + 297	Stroke	Baseline plasma α - and β -carotene and lycopene tended to be inversely related to risk of ischemic stroke
Serum lycopene, β -carotene, lutein, and zeaxanthin	American (34)	Nested case-control, 14 y	F, M	123 + 246	MI	Low concentration of carotenoids were associated with increased risk of MIs in smokers
Plasma lycopene	Women's Health Study, American, 1994 (35)	Nested case-control, 4.8 y	F	483 + 483	CVD	Higher plasma concentrations of lycopene were associated with a significantly lower risk of CVD
Serum lycopene	KIHD Study, Finnish (36)	Prospective, 5.3 y	M	725	AMI, stroke	Men in the lowest quartile of serum lycopene had a risk of AMI or stroke 3.3-fold that of the other men
Plasma α - and β -carotene concentration	Basel Prospective Study, German (37)	Prospective, 12 y	M	2974	CVD and stroke mortality	Significantly increased mortality in subjects with initially low plasma carotenoid concentrations
Serum β -cryptoxanthin, lutein plus zeaxanthin, lycopene, and α -carotene	ARIC Study, American (38)	Cross-sectional, case-control	F, M	321 + 321	IMT	Serum β -cryptoxanthin and lutein plus zeaxanthin were inversely related to the extent of atherosclerosis
Plasma α - and β -carotene, lutein, lycopene, zeaxanthin, and β -cryptoxanthin	Bruneck Study, Italian (39)	Cross-sectional and prospective, 5 y	F, M	392	Prevalence and incidence of carotid plaques	α - and β -Carotene were inversely associated with the prevalence of atherosclerosis in the carotid and femoral arteries and with the 5-y incidence of atherosclerotic lesions
Serum α - and β -carotene, β -cryptoxanthin, lutein, lycopene, and zeaxanthin	The Rotterdam Study, Dutch (40)	Case-control	F, M	108 + 108	Plaques of the abdominal aorta	Serum lycopene was inversely associated with the risk of atherosclerosis
Serum lycopene	KIHD Study, Finnish (41)	Cross-sectional	M	1028	CCA-IMT	The mean and maximal CCA-IMT increased linearly across quartiles of serum lycopene concentration
Plasma lycopene	ASAP Study, Finnish (42)	Cross-sectional	F, M	520	IMT	Low plasma lycopene concentrations were associated with early atherosclerosis in men
Adipose tissue						
β -Carotene	EURAMIC Study, Multicenter (43)	Case-control	M	638 + 727	MI	High β -carotene concentrations within the normal range reduce the risk of a first MI
α - and β -Carotene and lycopene	EURAMIC Study, Multicenter (44)	Case-control	M	1379	MI	48% lower risk of MI in highest 10th percentile of lycopene than in the other subjects

¹ CAD, coronary artery disease; MI, myocardial infarction; AMI, acute MI; CHD, coronary heart disease; CCA-IMT, intima-media thickness of common carotid arteries; ATBC, The Alpha-Tocopherol, Beta-Carotene Cancer Prevention; ARIC, Atherosclerosis Risk in Communities; LRC-CPPT Study, Lipid Research Clinics Coronary Primary Prevention Trial and Follow-up; KIHD, Kuopio Ischaemic Heart Disease Risk Factor; ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; EURAMIC, European Community Multicentre Study on Antioxidants, Myocardial Infarction, and Breast Cancer.

² Case subjects + control subjects (all such values).

In 1994, Knekt et al (25) found an inverse nonsignificant association between dietary intake of carotenoids with provitamin A activity and the risk of coronary mortality in women in their longitudinal cohort study of 5133 Finnish men and women aged 30–69 y. Similar findings were published in 1997 for β -carotenoid intake and the risk of stroke in the Chicago Western Electric Study, which evaluated 1843 middle-aged men (26). In the prospective Health Professionals Study (27), a high dietary

intake of lutein had a modest association with a reduced risk of ischemic stroke, whereas the dietary intake of lycopene and α - or β -carotene measured by food-frequency questionnaire had no association with stroke risk. In the α -Tocopherol, β -Carotene Cancer Prevention (ATBC) Study conducted in Finland, the dietary intake of β -carotene was inversely associated with the risk of cerebral infarction [relative risk (RR) of highest compared with the lowest quartile: 0.74; 95% CI: 0.60, 0.91], lutein plus



zeaxanthin was associated with the risk of subarachnoid hemorrhage (RR: 0.47; 95% CI: 0.24, 0.93), and lycopene was associated with the risk of cerebral infarction (RR: 0.74; 95% CI: 0.59, 0.92) and intracerebral hemorrhage (RR: 0.45; 95% CI: 0.24, 0.86) (28). This Finnish study cohort consisted of 26 593 male smokers aged 50–69 y with no previous history of stroke.

In 1998, Kritchevsky et al (29) published results from a cross-sectional study assessing intake of carotenoids with provitamin A activity and size of carotid artery plaques in 12 773 participants of the Atherosclerosis Risk in Communities cohort. They noted that both women and men in the highest fifth of carotenoid consumption had a lower prevalence of plaques than did those in the lowest fifth. In women, this inverse association was particularly strong for current smokers; in men, no such effect modification by smoking was seen. The inverse association was somewhat stronger in men aged 55–64 y than in men aged 45–54 y, whereas age made little difference in the women.

Recently, Knekt et al (30) published results of a cohort study pooling 9 prospective studies that included information on intakes of vitamin E, carotenoids, and vitamin C. During a 10-y follow-up, a major incident coronary heart disease (CHD) event occurred in 4647 of the 293 172 subjects who were free of CHD at baseline. The investigators found a lower risk of major CHD events at higher total intakes of β -carotene and at higher dietary intakes of several carotenoids after adjustment for only age and energy intake. The relations were considerably reduced after additional adjustment for potential nondietary confounding factors, and the investigators concluded that the CHD risk reductions at high carotenoid intakes appeared to be small.

Plasma or serum concentrations of carotenoids

In 1994, Morris et al (31) examined the relation between total serum carotenoid concentrations and the risk of subsequent CHD events in a cohort from the Lipid Research Clinics Coronary Primary Prevention Trial and Follow-up Study. They found that men in the highest quartile of serum carotenoids had an adjusted RR of 0.64 (95% CI: 0.44, 0.92) compared with those in the lowest quartile. For men who never smoked, the RR was 0.28.

The large prospective Physicians' Health Study found no evidence for a protective effect of higher baseline plasma concentrations of α - and β -carotene, β -cryptoxanthin, lutein, or lycopene against MI (32). In current and former smokers, but not in persons who never smoked, higher baseline plasma concentrations of β -carotene tended to be associated with a reduced risk of MI. In the same study, baseline plasma concentrations of α -carotene and β -carotene and lycopene tended to be inversely related to the risk of ischemic stroke (33). In a nested case-control study from Washington County (34), low serum concentrations of β -carotene, lycopene, lutein and zeaxanthin were associated with an increased risk of subsequent MI in smokers but not in nonsmokers.

Few studies have examined the associations between higher circulating concentrations of lycopene and the risk of heart diseases. Sesso et al (35) recently described an association between plasma lycopene and the risk of CVD in middle-aged and elderly women in their prospective, nested, case-control Women's Health Study, which was conducted in 39 876 women who were free of CVD at study baseline. For CVD, the women in the upper 3 quartiles of lycopene concentration had a significant 50% risk reduction compared with those in the lowest quartile. The Kuopio Ischemic Heart Disease Risk Factor Study also examined the

role of serum lycopene with regard to the risk of acute coronary events and ischemic strokes (36). The subjects were 725 middle-aged men free of CHD disease and stroke at the study baseline. Men with a low serum concentration of lycopene (ie, the lowest quarter) had a >3-fold risk of experiencing an acute coronary event or stroke compared with the other men. After 12 y of follow-up in the Basel Prospective Study, CVD and stroke mortalities were significantly increased in the subjects who initially had low plasma concentrations of carotene, vitamin C, or both independent of vitamin E concentrations and the traditional CVD risk factors (37).

In their observational study conducted in 231 asymptomatic, age-, sex-, race-, and field center-matched case-control pairs from the Atherosclerosis Risks in Communities Study, Iribarren et al (38) observed an association between concentrations of serum β -cryptoxanthin, lutein plus zeaxanthin, lycopene, and α - and β -carotene and carotid atherosclerosis. They noted that serum β -cryptoxanthin and lutein plus zeaxanthin concentrations were inversely related to the extent of atherosclerosis. Increases in α -carotene and lycopene were associated with nonsignificant lower odds of being a case subject. In the Bruneck study (39), high plasma concentrations of α - and β -carotene were also associated with a reduced risk of atherosclerosis. The Dutch Rotterdam Study provided evidence of a modest inverse association between the concentration of serum lycopene and the presence of atherosclerosis, with the association being most pronounced in current and former smokers (40). They found no association between other carotenoids and atherosclerosis.

The Kuopio Ischemic Heart Disease Risk Factor Study also examined the association between serum concentration of lycopene and the intima-media thickness of the common carotid artery wall (CCA-IMT) in 1028 middle-aged men (41). Men with low serum lycopene concentrations (ie, the lowest quarter) had the greatest increment in the adjusted mean CCA-IMT as well as in maximal CCA-IMT compared with the other subjects. Another Finnish study also examined the role of blood concentrations of lycopene with regard to cardiovascular health in women and men living in the eastern part of Finland (42). The study examined the association between the plasma concentration of lycopene and CCA-IMT in a cross-sectional analysis of 520 high risk men and women in the Antioxidant Supplementation in the Atherosclerosis Prevention Study. A low plasma concentration (ie, lower than the median) of lycopene was associated with an 18% increase in the IMT in men compared with the men whose plasma concentrations of lycopene were higher. In the women, the difference in the increase in IMT was not significant.

Adipose tissue concentration of carotenoids

In the European Study of Antioxidants, Myocardial Infarction and Cancer of the Breast (EURAMIC), which was a European, multicenter, case-control study, α -tocopherol and β -carotene concentrations were measured in adipose-tissue samples that were collected from 1991 to 1992 from 683 persons with acute MI and from 727 control subjects (43). The age-adjusted and center-adjusted odds ratio (OR) for the risk of MI in the lowest compared with the highest fifth of adipose tissue β -carotene concentrations was 2.62 (95% CI: 1.79, 3.83). Additional control for body mass index and smoking reduced the OR to 1.78 (95% CI: 1.17, 2.71), whereas other established risk factors did not substantially change this ratio. The increased risk was mainly confined to current smokers: the multivariate OR in the lowest

TABLE 3
Clinical trials of carotenoids in cardiovascular disease (CVD)¹

Source and dose of carotenoids	Study and nationality of subjects	Follow-up	Sex and characteristics	n	Outcome	Main results
Primary prevention studies						
β -Carotene, 20 mg/d	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finnish (46)	6.5 y	M; smokers	29 133	IHD and stroke mortality	Nonsignificant increase in IHD and stroke mortality in the β -carotene-supplemented group
β -Carotene, 20 mg/d	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finnish (48)	6.0 y	M; smokers	29 133	First major coronary event	β -Carotene supplementation increased the post-trial risk of a first-ever nonfatal MI
β -Carotene, 50 mg/d	The Physicians' Health Study, American (49)	12.0 y	M	22 071	CVD mortality	No evidence for CVD mortality in the β -carotene-supplemented group
β -Carotene, 30 mg/d	The Beta-Carotene and Retinol Efficacy Cancer Prevention Trial, American (50)	4.0 y	M; smokers and asbestos workers	18 314	CVD mortality	β -Carotene supplementation had an adverse effect on the incidence of CVD mortality
β -Carotene, 50 mg/d	Skin Cancer Prevention Study, American (51)	8.2 y	F, M	532 + 1188 ²	CVD mortality	No evidence for increased CVD mortality in the β -carotene group
Secondary prevention studies						
β -Carotene, 20 mg/d	Heart Protection Study, British (52)	5.0 y	F, M; CHD, occlusive arterial disease, or diabetes	20 536	Fatal or nonfatal vascular event	No evidence for an association between β -carotene intake and the 5-y mortality from, or incidence of, any type of CVD
β -Carotene, 20 mg/d	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finnish (53)	5.3 y	M; smokers, previous MI	1862	Major coronary event	Significantly increased risk of fatal coronary event in the β -carotene-supplemented group

¹ IHD, ischemic heart disease; CHD, coronary heart disease; MI, myocardial infarction.² Case subjects + control subjects.

fifth of β -carotene intake in smokers was 2.39 (95% CI: 1.35, 4.25), whereas it was 1.07 for people who had never smoked.

In the same EURAMIC study, researchers examined the association between the lycopene concentration in fat tissue and the risk of MI in ten countries (44). They found that men with the highest concentrations of lycopene in adipose tissue had a 48% reduction in the risk of developing CVD compared with men with the lowest lycopene concentrations. The model was adjusted for CVD risk factors and adipose tissue concentrations of α - and β -carotene. In a part of the EURAMIC study conducted in the Malaga center (45), there was a 60% lower risk of MI in the participants in the highest compared with those in the lowest fifth of lycopene concentration in adipose tissue.

Clinical trials on carotenoids and CVD health

Although a higher plasma β -carotene concentration has been associated with a reduced risk of heart disease in several cross-sectional and prospective studies, 4 large randomized trials did not reveal any reduction in cardiovascular events with β -carotene use, and, in fact, there may even be an increase in heart disease and total mortality in male smokers (Table 3) (46, 49).

In the ATBC Study, 29 133 male smokers aged 50 to 69 y received α -tocopherol (50 mg), β -carotene (20 mg), both α - and β -carotene, or placebo daily for 5 to 8 y (46). Total mortality was 8% higher in the participants who received β -carotene than in those who did not, primarily because there were more deaths from lung cancer and ischemic heart disease. The beneficial and adverse effects of supplemental α -tocopherol and β -carotene disappeared during the postintervention follow-up (47). The authors concluded that smokers should avoid β -carotene supplementation. A recently published article in which the 6-y post-trial effects of α -tocopherol and β -carotene supplementation on CHD in the ATBC study was evaluated concluded that β -carotene seemed to increase the post-trial risk of a first-ever nonfatal MI,

although there is no plausible mechanism to explain this finding (48).

In a randomized, double-blind, placebo-controlled trial of β -carotene (50 mg on alternate days), Hennekens et al (49) enrolled 22 071 male physicians aged 40 to 84 y in the United States; 11% of participants were current smokers and 39% were former smokers at the beginning of the study. They concluded that 12 y of supplementation with β -carotene produced neither benefit nor harm in the incidence of malignant neoplasms, CVD, or death from all causes.

The effects of a combination of β -carotene and vitamin A on lung cancer and heart disease were studied in the Beta Carotene and Retinol Efficacy Trial, which was a multicenter, randomized, double-blind, placebo-controlled primary prevention trial that involved a total of 18 314 smokers, former smokers, and workers who were exposed to asbestos (50). The authors found that in the active treatment group, the risk of death from any cause was 1.17 (95% CI: 1.03, 1.33), that of death from lung cancer was 1.46 (95% CI: 1.07, 2.00), and that of death from CVD was 1.26 (95% CI: 0.99, 1.61). On the basis of these findings, the randomized trial was stopped 21 mo earlier than planned.

Greenberg et al (51) examined the relation between β -carotene supplementation and risk of death from major disease causes in the randomized, placebo-controlled Skin Cancer Prevention Study, which used supplementation with 50 mg β -carotene/d for a median of 4.3 y. During a median follow-up period of 8.2 y, there were 285 all-cause deaths. No evidence of lower mortality was observed after supplementation in patients with initial β -carotene concentrations below the median for the study group. The subjects that were randomly assigned to β -carotene supplementation showed no reduction in relative mortality rates from all causes (adjusted RR: 1.03; 95% CI: 0.82, 1.30) or from CVD (adjusted RR: 1.16; 95% CI: 0.82, 1.64).

In the Heart Protection Study, a secondary prevention trial, 20 536 British adults aged 40–80 y with CHD, other occlusive



arterial disease, or diabetes were randomly assigned to receive antioxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg β -carotene daily) or placebo (52). Although this regimen increased blood vitamin concentrations substantially, it did not produce any significant reductions in the 5-y mortality or in the incidence of any type of vascular disease, cancer, or any other major outcome. In the ATBC Study, which was conducted in 1862 male smokers aged between 50 and 69 who had had a previous MI, the risk of fatal CHD increased in the groups that received either β -carotene or the combination of α -tocopherol and β -carotene compared with the group that received placebo (53).


Clinical trials have only focused on the effects of β -carotene among the carotenoids thus far; additionally, doses of β -carotene and compliance varied and the risk factor profiles of subjects were very different across studies. β -carotene and other carotenoids are often found in the same foods, and it is possible that the serum or adipose tissue β -carotene concentration is only an indicator of the consumption of other carotenoids or vitamins. Thus, β -carotene can be a marker of favorable dietary or lifestyle factors associated with a reduced risk of CVD. As mentioned before, however, it is also possible that high doses of carotenoids could have a prooxidant effect (12). Thus, it is possible that carotenoids could prevent cellular damage at physiologic concentrations, but that their ability to protect against cellular damage disappears at the higher doses used in the supplementation studies.

FUTURE DIRECTIONS AND CONCLUSIONS

A higher intake of fruit and vegetables can help prevent heart diseases and their associated mortality (54). More information is needed to clarify the relation between the intake of single nutrients, such as carotenoids, and the risk of heart diseases. Because carotenoids are a complex group of nutrients with different chemical structures and biological actions and because studies of the health effects of carotenoids are heterogeneous, it is difficult to undertake a meta-analysis or conduct a detailed systematic review about the health effects of carotenoids.

Note that all the evidence from clinical trials on the effects of carotenoids on heart diseases is based only on β -carotene. Although there have been null findings for β -carotene in these clinical trials, many observational studies investigating single or total carotenoids have shown that carotenoids are associated with a reduced risk of heart diseases.

Clinical trials are also warranted to evaluate the antioxidative and other health effects of other carotenoids, such as lycopene. Despite a plausible theory that antioxidants can prevent diseases triggered by oxidative damage, trials thus far have not substantiated this theory. At the moment, no reason exists to recommend carotenoids in pharmaceutical form for the treatment or prevention of CHD. When studying associations between nutrients and diseases, it is important to include not only traditional risk factors, but also other factors which are a part of a healthy lifestyle such as exercise and nonsmoking, into the statistical models.

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