β-Carotene, Carotenoids and the Prevention of Coronary Heart Disease[1]

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ABSTRACT The importance of low density lipoprotein (LDL) oxidation to the atherosclerotic process has led to the examination of β-carotene as a possible preventive agent. Several epidemiologic studies show an inverse association between serum/adipose β-carotene levels and coronary heart disease risk. Randomized clinical trials, however, have not shown any benefit, and perhaps even an adverse effect, of β-carotene supplementation. A number of possible confounding factors may explain the inconsistency between the trials and epidemiologic evidence. Other carotenoids that are correlated with β-carotene both in the diet and in the blood might be important factors, as might other plant-derived compounds. Alternatively, low serum carotenoid levels may reflect either increased lipoprotein density or the presence of inflammation, both factors emerging as important novel risk factors for coronary heart disease. Whereas the trial results support no preventive role for β-carotene, the epidemiologic evidence does generally support the idea that a diet rich in high carotenoid foods is associated with a reduced risk of heart disease. J. Nutr. 129: 5–8, 1999.

KEY WORDS: • β-carotene • carotenoid • cardiovascular disease • epidemiologic studies • humans

A body of evidence indicating that the oxidation of low density lipoproteins (LDL) plays an important role in the development of atherosclerosis has led investigators to consider a preventive role for dietary constituents with antioxidant activity (Steinberg 1995). Early in vitro studies of LDL oxidation showed that β-carotene carried in LDL is oxidized prior to the onset of oxidation of LDL polyunsaturated fatty acids, suggesting a possible role in delaying the onset of LDL oxidation (Esterbauer et al. 1989). Subsequently, the antioxidant hypothesis has sparked a steady stream of conflicting research regarding β-carotene's role in the prevention of coronary heart disease.

Epidemiologic Studies of Serum or Adipose β-Carotene Levels. In general, epidemiologic studies have found inverse associations between serum or adipose β-carotene levels and cardiovascular disease outcomes (summarized in **Table 1**). In a majority of the studies, either β-carotene or total carotenes (including the α, β and other isomers) were associated with reduced risk of disease (Gey et al. 1993, Kardinaal et al. 1993, Kohlmeier et al. 1997, Riemersma et al. 1991, Street et al. 1994). The magnitude of the reduction has ranged from only small decreases in risk to >50% reductions. Two studies found cigarette smoking to be an important risk modifier with strong inverse associations found only in smokers (Kardinaal et al. 1993, Street et al. 1994). Two reports from the European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer of adipose β-carotene levels conflict with regard to smoking's role (Kardinaal et al. 1993, Kohlmeier et al. 1997). The earlier publication by Kardinaal et al. (1993), found that smokers with β-carotene levels above the 80th percentile had roughly half the risk of incident nonfatal myocardial infarction compared to those below the 80th percentile. Kohlmeier et al.'s (1997) later analysis found no such modification by smoking status. The later analysis included a slightly different subset of cases and controls, controlled for a larger set of confounders and modeled the risk relationship using conditional instead of unconditional logistic regression. It is unclear which of these differences explains the discrepancy between the two studies. Iribarren et al. (1997a) failed to find an association between β-carotene and extreme carotid artery initima-medial thickness (>90th percentile) using b-mode ultrasound in a population free of symptomatic coronary disease. This study may not be comparable to other studies because of the outcome examined. Initima-medial thickening is thought to reflect the earlier stages of the atherosclerotic process that precedes the formation of more complex arterial lesions such as plaque. Plaque rupture is thought to be a primary precipitant of acute coronary syndromes, such as myocardial infarction and sudden cardiac death (Pahor et al. 1999). Some evidence suggests that the carotenoids affect later stages in the atherogenic process, possibly involving the establishment or stabilization of arterial plaque (Kritchevsky et al. 1998). The null result of Iribarren et al.'s (1997a) study may reflect the focus on a stage of atherogenesis that β-carotene may not affect. Three studies (Evans et al. 1998, Morris et al. 1994, Sahyoun et al. 1996) looked at total carotenoids rather than β-carotene or total carotene levels . Morris et al. (1994) found a significant decrease in the risk of incident coronary heart disease associated with increased levels of total carotenoids [relative risk (RR) = 0.64 contrasting extreme quartiles, $P < 0.05$], but the two other studies did not. The interpretation of studies of total carotenoids is, however, problematic. Supposing that β-carotene does reduce disease risk in some fashion, it is unlikely that all other carotenoids would have a similar action in this regard. The carotenoids differ in their properties: only some have provitamin A activity, and they differ in tissue localization and in their antioxidant properties (summarized by Omenn 1998). Thus, using total carotenoids as an independent variable could mask an inverse association of a specific carotenoid, should one exist. Nor is it true that the total carotenoid level is a useful proxy measure for a particular carotenoid of interest. For total carotenoids to be a good proxy, the relative proportions of individual serum carotenoids should not vary greatly from person to person. Individual serum carotenoids are correlated with one another, but not to such a degree as to support the use of the measurement of total carotenoids as a proxy for an individual carotenoid (Ascherio et al. 1992).

Trials of Supplementary β-Carotene. In contrast to the encouraging, albeit inconsistent, results from epidemiologic

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TABLE 1

Epidemiological studies of blood/tissue carotenoids and coronary disease

Study	Outcome[1]	Analyte[2]	Adjusted relative risk[3]
Riemersma et al. 1991	Angina	Carotene (P)	↓[4]
Kardinaal et al. 1993	Non-fatal MI	β-carotene (A)	↓ ↓[5,6]
Gey et al. 1993	CHD death	Carotene (P)	↓[5]
Morris et al. 1994	CHD	Total carotenoids (S)	↓[5]
Street et al. 1994	MI	β-carotene (S)	↓ ↓ ↓[5,6]
		Lycopene (S)	↓ ↓ ↓[5,6]
		Lutein (S)	↓ ↓ ↓[5,6]
		Zeaxanthin (S)	↓ ↓[5,6]
Sahyoun et al. 1996	CHD death	Carotenoids (S)	↔
Iribarren et al. 1997a	Carotid intima-media thickening > 90th percentile	α-carotene (S)	↔
		β-carotene (S)	↔
		β-cryptoxanthin (S)	↔
		lutein/zeaxanthin (S)	↓
		lycopene (S)	↔
Kohlmeier et al. 1997	Non-fatal MI	α-carotene (A)	↓[5,7]
		β-carotene (A)	↓ ↓[5,7]
		Lycopene (A)	↓ ↓[5]
Evans et al. 1998	CHD death	Total carotenoids (S)	↓
	Non-fatal MI		↔

[1] MI is myocardial infarction, CHD is Coronary Heart Disease.
[2] Measured in serum (S), plasma (P) or adipose tissue (A).
[3] Relative risk (RR) contrasting the highest carotenoid category to the lowest adjusting for confounders except for Iribarren et al (1997a) where the relative risk is for a 1-SD difference in serum level.
[4] ↓ denotes an RR <0.8 but >0.5, ↓ ↓ an RR between 0.5 and 0.33, ↓ ↓ ↓ an RR <0.33, and ↔ an RR between 0.8 and 1.25.
[5] Significant, $P < 0.05$.
[6] Results for cigarette smokers only.
[7] Not significant after adjusting for lycopene.

studies of serum β-carotene, four randomized, placebo, controlled clinical trials in which β-carotene was given without other antioxidants found no evidence that supplementation prevents cardiovascular disease. The trials were conducted in diverse populations: male Finnish smokers [The Alpha-Tocopherol Beta Carotene Prevention Study Group (ATBC)1994], patients at high risk for recurrent nonmelanoma skin cancer (Greenberg et al. 1996), U.S. male physicians (Hennekens et al. 1996), and a population at high risk for lung cancer because of a history of asbestos exposure or heavy smoking (Omenn et al. 1996). Three of the four studies found increases in cardiovascular disease mortality in the supplemented groups ranging from 12 to 26% (The Alpha-Tocopherol Beta Carotene Prevention Study Group 1994, Greenberg et al. 1996, Omenn et al. 1996). The Physicians Health Study found no difference (Hennekens et al. 1996). And, in contrast to the findings of two epidemiologic studies in which smokers appeared to enjoy the greatest protection from β-carotene, trials with a higher percentage of smokers seemed somewhat more prone to adverse effects of supplementation. A preliminary, subgroup analysis from the Physicians Health Study suggested that β-carotene might be effective in preventing recurrent, as opposed to incident, coronary disease (Gaziano and Hennekens 1993). This finding was not replicated in the subset of ATBC participants who had a history of myocardial infarction at randomization (Rapola et al. 1997). Paradoxically, and despite the lack of effect of supplementary β-carotene, two of the trials found that prerandomization serum β-carotene levels were significantly inversely associated with cardiovascular disease occurrence consistent with findings from epidemiologic studies (Greenberg et al. 1996, Virtamo et al. 1998).

Why Don't the Trials and Epidemiologic Studies Agree? It is unlikely that the trials were either too short or used too low a dose of β-carotene to demonstrate a preventive effect. Trials of effective interventions for coronary heart disease typically begin to show results within 2 y of treatment. The intervention periods of all of the reviewed trials lasted at least 4 y. The mean serum β-carotene level (2.2 μmol/L) attained in even the trial with the lowest β-carotene dose is ~5–10 times that associated with increased cardiovascular disease risk (Greenberg et al. 1996, Hennekens et al. 1996, Virtamo et al. 1998). It is possible that there were unintended adverse effects at the high levels attained, but well supported explanations as to what they might be were not advanced.

A more likely explanation for the discrepancy between the trial results and the epidemiologic studies is that serum/adipose β-carotene levels are confounded by one or more unmeasured factors that may be correlated with reduced β-carotene levels and also predict coronary heart disease risk. For historical reasons, notably the interest in β-carotene as an anticancer agent, studies have focused predominantly on β-carotene. But, β-carotene is not the most prevalent circulating carotenoid, comprising only~15–30% of all carotenoids. Other carotenoids found in significant amounts are lycopene (20–40%), cryptoxanthin (13–20%), lutein (10–20%), α-carotene (5–10%), and zeaxanthin (1–5%) (Ascherio et al. 1992, Brady et al. 1996, Michaud et al. 1998, Yeum et al. 1996). Though lycopene and β-carotene predominate in the serum, lutein predominates in both red blood cells and peripheral blood mononuclear cells (Fotouhi et al. 1996). Carotenoid levels in white cell subsets may be particularly important because many important steps in atherosclerotic lesion development involve the actions of these cells (Steinberg 1995).

Relatively few epidemiologic studies have measured carotenoids other than β-carotene. Kohlmeier et al. (1997) found that adipose levels of lycopene, α- and β-carotene all were inversely associated with incident nonfatal myocardial infarction, but when modeled simultaneously, only lycopene remained an independent predictor of the outcome. Street et al. (1994) found that

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TABLE 2

Cohort studies of dietary carotenoid intake and coronary heart disease

Study	Outcome[1]	Dietary consituent	Adjusted relative risk[2]
Rimm et al. 1993	CHD	Provitamin A	↓[3,4]
		Carotenoids	↓ ↓ ↓[4,5]
Knekt et al. 1994	CHD death	Provitamin A	↔[6]
		Carotenoids	↓[7]
Gaziano et al. 1995	Fatal MI	Servings of high carotenoid foods	↓ ↓ ↓[4]
Pandey et al. 1995	CHD death	β-carotene	↔
Sahyoun et al. 1996	CHD death	Sum of five carotenoids	↓ ↓
Kushi et al. 1996	CHD death	Provitamin A carotenoids	↔

[1] MI is myocardial infarction, CHD is Coronary Heart Disease.
[2] Relative risk (RR) contrasting the highest carotenoid category to the lowest adjusting for confounders.
[3] ↓ denotes an RR <0.8 but >0.5, ↓ ↓ an RR between 0.5 and 0.33, ↓ ↓ ↓ an RR < 0.33, and ↔ an RR between 0.8 and 1.25.
[4] Significant, $P < 0.05$.
[5] Results for cigarette smokers only.
[6] Men only.
[7] Women only.

the serum levels of all four measured carotenoids (β-carotene, lycopene, lutein and zeaxanthin) were significantly inversely associated with incident myocardial infarction, but only in smokers. It was not determined which among them might have been an independent predictor of risk. Among α-carotene, β-carotene, β-cryptoxanthin, lutein + zeaxanthin (the analytic method did not distinguish between the two) and lycopene, Iribarren et al. (1997a) found lutein + zeaxanthin to be the carotenoid with the strongest inverse association with extreme carotid artery intima-medial thickening.

Studies of Dietary Carotenoid Intake. Epidemiologic studies of diet have not been very helpful in identifying the contributions of individual carotenoids to disease risk. Most studies have examined dietary total provitamin A carotenoid intake (predominantly β-carotene) because food values for individual carotenoids were previously unavailable. Among the six prospective studies of dietary carotenoids (see **Table 2**) and coronary heart disease, four measured provitamin A carotenoid consumption, one the consumption of fruits and vegetables high in carotenoids and one the total of five carotenoids (α- and β-carotene, lutein, lycopene and cryptoxanthin). Five found the relative risk of coronary events to be lower in those consuming greater amounts of carotenoids (Gaziano et al. 1995, Knekt et al. 1994, Pandey et al. 1995, Rimm et al. 1993, Sahyoun et al. 1996), but only two could rule out the role of chance (Gaziano et al. 1995, Rimm et al. 1993). Gaziano et al. (1995) examined the combined servings of six food categories high in carotenoids in a cohort of 1,299 elderly Massachusetts residents and found that those in the upper 25th percentile of consumption had significantly lower risk of fatal myocardial infarction (RR = 0.27). The authors also compared those consuming ≥1 serving per day of each of the six food categories to those consuming less than 1 serving per day. The categories with statistically significant inverse associations with risk of cardiovascular disease death were carrots and/or squash (RR = 0.40) and salads and/or green leafy vegetables (RR=0.49). Rimm et al. (1993) found a significant inverse relationship between provitamin A carotenoid intake and incident coronary heart disease in a population of 39,910 male health professionals 45–75 y of age, but the relationship was seen only in former and current smokers (RR comparing extreme quintiles of intake for smokers: 0.30; ex-smokers: 0.60; never smokers: 1.09).

Two studies of dietary intake are consistent with the idea that relationships between β-carotene and coronary disease may be confounded by other dietary constituents (Knekt et al. 1994, Sahyoun et al. 1996). In these studies, there were stronger inverse associations with the consumption of foods high in carotenoids than with calculated carotenoid intake. In a cohort of 5,133 Finnish men and women, Knekt et al. (1994) found the relative risk of coronary mortality to be 34% lower in those in the highest tertile of vegetable consumption compared to the lowest tertile of consumption in both genders. In men, however, those in the highest tertile of provitamin A carotenoid consumption were at no lower risk of death. There was little difference in the findings for women. Sahyoun et al. (1996) studied dietary carotenoid intake in a cohort of 747 Massachusetts residents aged 60 y and over. The sum of dietary intake of α-carotene, β-carotene, lutein + zeaxanthin, lycopene and β-cryptoxanthin was related to heart disease mortality over the 12 y of follow-up. Those in the highest 20% of intake had an adjusted relative risk of death of 0.64 ($P > 0.05$) compared to those with the lowest 20% of intake. The relative risk for high intake of dark green/orange vegetables was 0.61 ($P < 0.05$), and the relative risk for high intake of all vegetables was 0.49 ($P < 0.05$). Other carotenoids are not the only dietary constituents that may confound the β-carotene–coronary heart disease relationship. Folate is also found in many high carotenoid foods, and there is increasing interest in folate in the prevention of cardiovascular disease through its role in homocysteine metabolism (Pahor et al. 1999).

Physiologic Factors That May Confound Epidemiologic Studies. In addition to dietary factors, physiologic differences may explain in part the inverse associations between serum β-carotene and coronary heart disease risk. Smoking and body mass index–both consistent predictors of disease risk–are also associated with lower serum β-carotene levels (Brady et al. 1996, Iribarren et al. 1997b). However, they are unlikely to explain discrepancies between trial and epidemiologic study results because epidemiologic analyses have generally accounted for these factors. Recent observations suggest that two other physiologic factors yet to be addressed in epidemiologic research may be potential confounders. Goulinet and Chapman (1997) have reported that the carotenoid content of LDL decreases with increasing LDL density. Small dense LDL is more readily oxidizable than less dense LDL and is thought to have greater atherogenic potential (Pahor et al. 1999) Thus, lower carotenoid levels may reflect differences in the lipoprotein density profiles that themselves may predict coronary heart disease risk. Markers of inflammation are emerging as important independent predictors of risk of acute coronary events. Several epidemiologic studies have shown that increased levels of inflammatory markers, such as C-reactive protein, fibrinogen and white blood cell count, are associated with increased coronary heart disease rates (Danesh et al. 1998). The role of inflammatory markers has not been explored in the context of the β-carotene-coronary heart disease relationship, but studies do show a link between inflammation and reduced β-carotene levels. Iribarren et al. (1997b) found serum sialic acid, a marker of inflammation, to be strongly associated with lower serum β-carotene levels in Atherosclerosis Risk in Communities Study participants. Inflammatory

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markers seem to affect other carotenoids as well. Boosalis et al (1996) found that elderly Catholic nuns with elevated C-reactive protein levels had significantly lower plasma levels of β-carotene, α-carotene and lycopene, but not lutein/zeaxanthin or cryptoxanthin. Among 22 patients with nonsmall cell carcinoma of the lung, Talwar et al. (1997) found lutein to be inversely association with C-reactive protein levels. Lycopene, α- and β-carotene levels were too low to measure in many patients. These studies are cross-sectional in design and, therefore, do not rule out an anti-inflammatory role for the carotenoids. A link between carotenoid levels and inflammation might explain the stronger inverse associations found among cigarette smokers. Smoking is an inflammatory stress and leads to increased levels of C-reactive protein. It may be that among smokers, a higher serum carotenoid level is indicative of an individual experiencing less of an inflammatory response to smoking. If so, such individuals might be at lower risk for some adverse consequences of smoking. Conversely, one of the carotenoids might have an anti-inflammatory action in smokers. β-carotene does reduce breath-pentane output, a measure of lipid peroxidation in smokers but not nonsmokers (Allard et al. 1994).

In summary, the clinical trial evidence shows that supplemental β-carotene does not prevent coronary heart disease, though the benefits of other carotenoids has not been ruled out. The epidemiologic evidence is generally supportive of the notion that a diet rich in high carotenoid foods is associated with a reduced risk of heart disease. Whether this risk reduction is due to the action of one or several carotenoids, other plant-based substances or is secondary to unappreciated confounding factors is at this point unclear.

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