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Dietary intake of carotenoids and retinol and the risk of acute myocardial infarction in Italy

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Abstract

Background: Carotenoids may reduce the risk of coronary heart disease through their antioxidant properties, but the results of epidemiological studies are controversial. We analysed the relation between the intake of selected carotenoids and retinol and risk of acute myocardial infarction (AMI).

Methods: A case-control study was conducted in Milan, Italy, in 1995–2003. Cases were 760 patients with nonfatal AMI, and controls 682 patients admitted to hospital.

Results: The risk of AMI decreased with increasing intake of α-carotene (odds ratios, OR = 0.71, 95% confidence intervals, CI 0.51–0.98, for the highest vs the lowest quartile of intake), β-carotene (OR = 0.71, 95% CI 0.50–1.01) and β-criptoxanthin (OR = 0.64, 95% CI 0.46–0.88). No associations emerged for total carotenoids, lycopene, lutein plus zeaxanthin and retinol.

Conclusions: Our study suggests a weak protective effect of α-carotene, β-carotene and β-criptoxanthin on the risk of AMI. It also indicates that total carotenoids, lycopene, lutein plus zeaxanthin and retinol were not related to the risk of the disease.

Keywords: *Antioxidants, carotenoids, lycopene, myocardial infarction, retinol, risk factors*

Introduction

It has been suggested that β-carotene, lycopene and other carotenoids may reduce the risk of coronary heart disease (CHD). This has been attributed to their antioxidant ability to inhibit the oxidation of low-density lipoproteins (LDL) [1,2], mainly in smokers [3,4], as oxidized LDL may be more atherogenic than native LDL [5]. However, the results of epidemiologic studies are controversial. Older observational studies, besides vitamin C and E, have investigated mostly β-carotene, a carotenoid with provitamin A activity, and have suggested that it was unrelated or inversely related to CHD [6]. However, randomized intervention trials in primary prevention of cardiovascular disease have shown no benefit from β-carotene supplementation [7–11], or a weak protection in men, but not in women, with a combination of ascorbic acid, vitamin E, β-carotene, selenium and zinc [12], or even a direct association with CHD in smokers after β-carotene supplementation during the 6-year post-trial follow-up of the ATBC study [13].

More recent observational studies, besides β-carotene, have considered also other carotenoids and antioxidants and overall evidence still suggests no relation or an inverse association [14]. Retinol, the pre-formed vitamin A, is generally not related to cardiovascular risk [15].

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We investigated the association between selected carotenoids and retinol and risk of nonfatal acute myocardial infarction (AMI) using data from a case-control study conducted in Milan, Italy, where dietary habits were collected by a food-frequency questionnaire tested for reproducibility [16] and validity [17].

Patients and methods

Data derive from a case-control study of nonfatal AMI, conducted in the greater Milan, Italy, between 1995 and 2003 [18,19]. Cases were 760 patients (580 men, 180 women; median age 61, range 19–79 years) with a first episode of nonfatal AMI, defined according to the World Health Organization criteria [20], admitted to a network of teaching and general hospitals in the area. Controls were 682 patients (439 men, 243 women; median age 59 years, range 18–79) from the same geographic area, admitted to the same hospitals for a wide spectrum of acute conditions, unrelated to known AMI risk factors. We excluded subjects with previous AMI or other major cardiovascular events. Among controls, 30% had traumas, 25% non-traumatic orthopedic disorders, 18% acute surgical conditions, 18% eye, nose, throat or teeth disorders and 9% miscellaneous other illnesses unrelated to diet. Less than 5% of the cases and controls approached refused to participate.

Interviews were conducted in hospital using a structured questionnaire, including information on socio-demographic factors, anthropometric variables, smoking, alcohol and coffee consumption, other lifestyle habits, physical activity, a problem-oriented medical history and history of AMI in first degree relatives. Cholesterol levels were obtained from clinical records.

The structured questionnaire included information on socio-demographic factors, anthropometric variables, general lifestyle habits, such as smoking, alcohol and coffee consumption, physical activity at work, family history of AMI and personal history of selected diseases.

The subjects' usual diet during the 2 years prior to AMI or hospital admission (for controls) was investigated through an interviewer-administered food frequency questionnaire, including 78 foods, recipes and beverages. Subjects were asked to indicate the average weekly frequency of consumption of several dietary items; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. To estimate total energy and nutrient intake, an Italian food composition database was used [21,22]. The intake of β-carotene equivalent was defined as the sum of the intake of β-carotene, and the half intake of α-carotene, α-and β-cryptoxanthin [23]. However, its value does not correspond to the exact sum, as it derived from different sources [21,22]. Total carotenoid intake was obtained adding up the intake of α-carotene, β-carotene, cis-β-carotene, γ-carotene, ζ-carotene, α-cryptoxanthin, β-cryptoxanthin, lycopene and lutein plus zeaxanthin. All major sources of carotenoids and retinol were analyzed as our food frequency questionnaire included information on the consumption of many common Italian foods and recipes. The food frequency questionnaire was satisfactorily reproducible [16] and valid [17]: the correlation coefficients for reproducibility ranged from 0.48 to 0.69 [16], and for validity from 0.34 to 0.56 [17].

Data analysis

Odds ratios (OR) of AMI, and the corresponding 95% confidence intervals (CI), for subsequent quartiles of intake of various carotenoids and retinol were derived using unconditional multiple logistic regression

Table I. Distribution of 760 cases of AMI and 682 controls according to age and other selected variables. Milan, Italy, 1995–2003.

	AMI		Controls	
	No.	%	No.	%
Age (years)				
< 50	140	18.4	168	24.6
50–59	198	26.1	187	27.4
60–69	293	38.6	224	32.8
≥ 70	129	17.0	103	15.1
Sex				
Men	580	76.3	439	64.4
Women	180	23.7	243	35.6
Education (years)*				
< 7	321	42.9	308	45.8
7–11	239	31.9	222	33.0
≥ 12	189	25.2	142	21.1
Smoking habit				
Non smokers	425	55.9	476	69.8
Current smokers	335	44.1	206	30.2
< 15 (cigarettes/day)	77	10.1	76	11.1
≥ 15 (cigarettes/day)	258	34.0	130	19.1
Coffee consumption (cups/day)*				
≤ 3	402	53.0	422	61.9
> 3	357	47.0	260	38.1
Alcohol consumption (drinks/day)				
< 1	365	48.0	317	46.5
1– < 2	104	13.7	94	13.8
≥ 2	291	38.3	271	39.7
Body mass index (kg/m^2)*				
< 24	199	26.3	204	30.2
24– < 27	261	34.4	224	33.1
≥ 27	298	39.3	248	36.7
History of hypertension				
No	519	68.3	513	75.2
Yes	241	31.7	169	24.8
History of diabetes				
No	650	85.5	644	94.4
Yes	110	14.5	38	5.6
Family history of AMI				
No	511	67.2	557	81.7
Yes	249	32.8	125	18.3

* The sum does not add up to the total because of missing values.

models [24], including terms for age, sex, study, education, tobacco smoking, alcohol and coffee drinking, non-alcohol total calorie intake, body mass index, physical activity, cholesterol level, history of diabetes, hyperlipidemia and hypertension, and family history of AMI in first degree relatives. Tests for trend were based on the likelihood ratio test between models with and without a linear term for each micronutrient.

Results

Table I shows the distribution of cases with AMI and controls according to age, sex and other selected covariates. Cases were more often smokers of 15 or more cigarettes/day and drinkers of more than 3 cups of coffee/day, and reported more often a history of hypertension and diabetes, and a family history of AMI in first degree relatives.

Table II gives the mean daily intake among controls of retinol and selected carotenoids, and the OR of AMI according to quartiles of intake. The OR decreased with increasing intake of α-carotene (OR = 0.71 for the highest vs the lowest quartile of intake) and β-crptoxanthin (OR = 0.64) and tended to decrease with the intake of β-carotene (OR = 0.71) and β-carotene equivalents (OR = 0.76). No meaningful associations emerged for lycopene, lutein plus zeaxanthin, retinol and total carotenoids.

The OR for the highest quartile of intake compared to the lowest one in strata of age, sex, education and tobacco smoking are reported in Table III. There was no significant heterogeneity across strata of these covariates.

Discussion

This study found a weak inverse association of the intake of α-carotene, β-carotene and β-cryptoxanthin with the risk of nonfatal AMI. Other carotenoids not related to provitamin A, such as lutein plus zeaxanthin and retinol, were not related with risk.

Our results of a moderate protection on AMI risk of provitamin A carotenoids are in agreement with most epidemiologic evidence [6,14]. Serum carotenoids have been found inversely associated with CHD risk [25], while α-carotene has been found either inversely related to coronary artery disease [26] or not related to AMI [15,27] and cardiovascular disease risk [28]. Also β-carotene was reported either inversely associated with AMI [29,30] or coronary artery disease [26], or not associated with AMI [15,27] or cardiovascular disease risk [28], while β-cryptoxanthin [15] and

Table II. Mean intake of retinol and selected carotenoids, and distribution of AMI cases and controls, and corresponding odds ratios (OR) with 95% confidence intervals (CI) according to the intake of retinol and selected carotenoids. Milan, Italy, 1995–2003.

		OR (95% CI)* for quartile of intake				
Nutrient	Mean intake (μg) (sd)†	1	2	3	4	χ^2_{trend} (*p* value)
Retinol						
Cases/controls	785.6 (922.5)	191/171	183/170	190/170	196/171	
OR (95% CI)		1‡	1.00 (0.71–1.41)	1.16 (0.82–1.65)	1.00 (0.70–1.42)	0.06 (0.809)
Total carotenoids						
Cases/controls	18211.4 (17591.7)	215/170	194/171	172/171	179/170	
OR (95% CI)		1‡	0.91 (0.65–1.26)	0.82 (0.58–1.16)	0.84 (0.58–1.21)	1.09 (0.295)
β-carotene equivalents						
Cases/controls	3746.7 (1654.0)	219/171	222/170	165/170	154/171	
OR (95% CI)		1‡	1.05 (0.77–1.45)	0.85 (0.60–1.19)	0.76 (0.53–1.09)	3.19 (0.074)
α-carotene						
Cases/controls	684.4 (547.7)	253/170	171/171	171/171	165/170	
OR (95% CI)		1‡	0.70 (0.51–0.96)	0.71 (0.51–0.98)	0.71 (0.51–0.98)	4.17 (0.041)
β-carotene						
Cases/controls	4185.7 (1839.8)	241/171	199/170	167/171	153/170	
OR (95% CI)		1‡	0.85 (0.62–1.18)	0.74 (0.53–1.04)	0.71 (0.50–1.01)	4.36 (0.037)
β-cryptoxanthin						
Cases/controls	340.4 (368.3)	271/170	174/172	141/169	174/171	
OR (95% CI)		1‡	0.59 (0.43–0.81)	0.55 (0.40–0.77)	0.64 (0.46–0.88)	7.70 (0.006)
Lycopene						
Cases/controls	7189.5 (3722.5)	161/170	215/171	186/171	198/170	
OR (95% CI)		1‡	1.35 (0.97–1.88)	1.08 (0.76–1.54)	1.19 (0.82–1.70)	0.18 (0.667)
Lutein plus zeaxanthin						
Cases/controls	4015.2 (2027.5)	230/169	190/172	189/170	151/171	
OR (95% CI)		1‡	0.84 (0.61–1.16)	0.92 (0.66–1.28)	0.71 (0.50–1.01)	2.56 (0.110)

* Estimates from unconditional multiple logistic regression models including terms for age, sex, study, education, smoking, alcohol, coffee, non-alcohol total calorie intake, booly mass index, physical activity, cholesterol level, diabetes, hyperlipidemia, hypertension, and family history of AMI in first degree relatives.

† Average intake (and standard deviation) among controls.

‡ Reference category.

Table III. Odds ratios (OR) of AMI for the highest quartile of intake compared to the lowest one and corresponding 95% confidence intervals (CI) according to the intake of selected carotenoids in strata of age, sex, education and smoking status. Milan, Italy, 1995–2003.

	OR (95% CI)* for the highest quartile of intake compared to the lowest one							
	Age (years)		Sex		Education (years)		Tobacco smoking	
Nutrient	<65	≥65	Men	Women	<7	≥7	Non smokers	Current smokers
β-carotene equivalents	0.74 (0.46–1.17)	0.72 (0.39–1.34)	0.78 (0.51–1.20)	0.74 (0.35–1.56)	0.65 (0.37–1.15)	0.83 (0.51–1.34)	0.90 (0.56–1.43)	0.55 (0.30–1.03)
α-carotene	0.64 (0.42–0.96)	0.78 (0.44–1.40)	0.64 (0.43–0.94)	1.00 (0.50–2.00)	0.58 (0.35–0.97)	0.77 (0.49–1.21)	0.74 (0.48–1.13)	0.58 (0.33–1.01)
β-carotene	0.68 (0.43–1.06)	0.72 (0.39–1.33)	0.75 (0.49–1.14)	0.61 (0.29–1.28)	0.65 (0.37–1.15)	0.72 (0.45–1.15)	0.81 (0.51–1.27)	0.52 (0.28–0.98)
β-cryptoxanthin	0.69 (0.45–1.03)	0.62 (0.34–1.11)	0.77 (0.52–1.13)	0.46 (0.23–0.92)	0.53 (0.32–0.89)	0.69 (0.44–1.07)	0.62 (0.41–0.95)	0.67 (0.38–1.18)

* Estimates from unconditional multiple logistic regression models including terms for age, sex, study, education, smoking, alcohol, coffee, non-alcohol total calorie intake, body mass index, physical activity, cholesterol level, diabetes, hyperlipidemia, hypertension and family history of AMI, as appropriate.

zeaxanthin [29] were not associated with AMI and cardiovascular disease risk [28]. Lutein was found inversely related [29] or not associated with AMI [15] and cardiovascular disease risk [28], and lycopene was inversely related with risk of AMI [27], cardiovascular disease [31] and CHD [32], or not related to AMI [15,29] and cardiovascular disease risk [28]. Conversely, randomized clinical trials failed to confirm a role of antioxidants in the prevention of cardiovascular disease [7–13]. Reasons for this discrepancy include the relatively short period of treatment and observation in clinical trials compared to observational studies, and that in observational studies antioxidants may be simply indicators of a generally more favourable diet. Another reason may be that a combination of various antioxidants rather than a single one may exert the favourable effect on cardiovascular disease.

As α-carotene, β-carotene and β-cryptoxanthin derive essentially from plant foods, their protective effect on AMI may be due to a general beneficial role of vegetables and fruit [1] or to the combination or interaction of several components of vegetables and fruit. However, we found no association for other carotenoids mainly contained in vegetables and fruit, including lutein plus zeaxanthin and particularly lycopene, whose consumption in Italy is relatively high [33]. Thus, other mechanisms than the antioxidant effect may be responsible for the favourable effect of provitamin A on AMI risk. Other possibilities are that various carotenoids are contained in different amounts in various vegetables and fruit or that their dietary correlates are different. For example, the lack of association of lycopene (mainly deriving from tomato and tomato sauce in the Italian diet) might partly depend on the fact that most consumers of high amount of tomato sauce in the Italian diet also have a high intake of pasta, which may be an aspecific indicator of a poor diet in Italy [34]. Other reasons for inconsistent results in various studies include differences in characteristics and dietary patterns among populations.

A potential weakness of this study is that dietary habits of hospital controls may differ from those of the general population [24]. However, all diagnoses that might have involved long-term modifications of diet were excluded from the control group. Other possible sources of bias should be limited, since cases and controls were drawn from the same catchment areas, participation was almost complete, and allowance for several confounding factors did not notably modify the risk estimates. The results were consistent when comparison was made with different diagnostic categories of controls. Among the strengths of the study, there is the use of a validated [17] and reproducible [16] food frequency questionnaire, which allowed a comprehensive assessment of major nutrient sources in the Italian diet [33]. Further, total calorie intake and major potential confounding factors have been accounted for in the analysis.

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