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Circulating Carotenoid Concentrations and Incident Hypertension: The Coronary Artery Risk Development in Young Adults (CARDIA) study

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Abstract

Background—Several epidemiological studies have demonstrated that carotenoid concentrations relate inversely to cardiovascular disease incidence. Thus, we examined the association of circulating carotenoids with hypertension, a major macrovascular disease risk factor.

Methods—Black and white men and women in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, aged 18 to 30 years at recruitment (1985–1986) from 4 US cities, were investigated over 20 years. At years 0, 7, and 15, we determined the relationships of the sum of 4 serum carotenoids (α -carotene, β -carotene, lutein/zeaxanthin, cryptoxanthin) and of lycopene with incident hypertension using proportional hazards regression models.

Results—In 4412 participants, year 0 sum of 4 carotenoids was significantly inversely associated with 20 year hypertension incidence after adjustment for baseline systolic blood pressure and other confounding factors (relative hazard per SD increase of sum of 4 carotenoids: 0.91; 95% confidence interval: 0.84–0.99). The inverse relationship persisted in time-dependent models updating year 0 sum of 4 carotenoids with year 7 and year 15 values (relative hazard per SD increase of sum of 4 carotenoids: 0.84; 95% confidence interval: 0.77–0.92). Lycopene was unrelated to hypertension in any model.

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Disclosures

None

Conclusion—Those with higher concentrations of sum of carotenoids, not including lycopene, generally had lower risk for future hypertension.

Keywords

Antioxidant; Carotenoids; Epidemiology; Hypertension; Prospective studies

Hypertension strongly predicts cardiovascular diseases,¹ mortality, and disability. It is an important public-health challenge worldwide.² In the US, 26.4% of the adult population in 2000 had hypertension, and 29.2% are predicted to have hypertension by 2025.²

Oxidative stress might play a role in the pathophysiology of hypertension.^{3,4,5} Supporting this contention, gamma glutamyltransferase (γ -GGT), which may be a marker of oxidative stress,⁶ was shown to predict hypertension.^{7,8} Since antioxidants neutralize oxidative stress, high circulating antioxidant concentrations might relate inversely to hypertension. Some previous studies including a CARDIA report showed that antioxidant rich plant foods were inversely related to incidence of elevated blood pressure (BP).^{9,10} Furthermore, the Dietary Approaches to Stop Hypertension (DASH) trial showed that the fruit-and-vegetable diet, which is high in various carotenoids, reduced systolic BP by 2.8 mm Hg more ($P<0.001$) than the control diet,¹¹ similar to a Japanese study that increased fruit and vegetable intake and reduced sodium intake for 1 year.¹² An Israeli placebo controlled trial¹³ found reduced blood pressure in hypertensives after 4 weeks of consumption of a carotenoid-rich tomato extract. However, the SU.VI.MAX trial found no reduction in incident BP after 6.5 years of supplementation with a combination of purified antioxidant vitamins and minerals.¹⁴ Thus, it is plausible that serum carotenoids, which might play an antioxidant role or be a marker of a generally healthy diet and lifestyle, relate inversely to future BP increase. However, only a few cross-sectional studies^{4,15,16} and one prospective study¹⁴ have reported an inverse relation between serum carotenoids and hypertension. Therefore, we conducted longitudinal analyses to clarify whether serum carotenoid concentrations measured at 3 different examinations predict incident hypertension in the Coronary Artery Risk Development in Young Adults (CARDIA) study.

METHODS

The CARDIA and YALTA Studies

The CARDIA study, a biethnic, prospective, multicenter epidemiologic study of the evolution of cardiovascular disease risk factors in young adults, has been described in detail elsewhere.¹⁷ Briefly, from 1985 to 1986, 5115 African American and White individuals aged 18 to 30 years were examined in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. At the Birmingham, Minneapolis, and Chicago sites, participants were randomly selected from total communities or from specific census tracts. In Oakland, participants were randomly selected from members of the Kaiser Permanente Medical Care Program. Recruitment achieved nearly equal numbers at each site of race (African American, White), sex, education, and age (18–24 years, 25–30 years). Fifty percent of invited individuals contacted were examined (47% African Americans and 60% of Whites) and became the CARDIA cohort. Reexamination occurred after 2, 5, 7, 10, 15, and 20 years. The Young Adult Longitudinal Trends in Antioxidants (YALTA) study is ancillary to CARDIA and measured serum carotenoid concentrations in most CARDIA participants at years 0, 7, and 15.

For this report, we excluded participants who did not report their smoking status ($N=20$) or were missing year 0 serum carotenoid data ($N=302$), and 81 participants for missing information on confounding factors, leaving 4712 for the cross-sectional analyses.

Furthermore, we excluded 136 participants who had prevalent hypertension at the year 0 exam and 164 who did not attend any follow-up examination, leaving 4412 participants for prospective analysis.

Self-report and anthropometric measurements

Sex, race, education, date of birth, and weekly alcohol consumption were determined at baseline and each follow-up survey by structured interview or by self-administered questionnaire (at each examination unless otherwise specified). Smoking status was ascertained using an interviewer-administered questionnaire supplemented at year 0 only by serum cotinine measurements. Participants were classified as self-reported never, former, or current smokers as of year 0; the 186 self-reported year 0 nonsmokers whose serum cotinine concentration was ≥ 14 ng/mL at year 0 were reclassified as current smokers. A physical activity score was derived from the CARDIA Physical Activity History, a simplified version of the Minnesota Leisure Time Physical Activity Questionnaire.¹⁸ Alcohol intake (mL/day) was computed from the self-reported frequency of beer, wine, and liquor consumed per week. Body weight with light clothing was measured to the nearest 0.09 kg, and height without shoes was measured to the nearest 0.5 cm. Body mass index (BMI) was computed as weight divided by height squared (kg/m^2).

Biochemical variables

All participants were asked to avoid smoking and heavy physical activity for at least 2h before each examination. After plasma or serum separation, aliquots were stored at -70°C until shipped on dry ice to a central laboratory. Sera obtained at CARDIA year 0, 7, and 15 were used in the YALTA study to assay the carotenoids α - and β -carotene, lycopene, zeaxanthin plus lutein, and β -cryptoxanthin (Molecular Epidemiology and Biomarker Research Laboratory, University of Minnesota). The HPLC-based assay of carotenoids was a modification of the method of Bieri et al.¹⁹ to optimize detection of carotenoids with calibration as described by Craft et al.²⁰ and sample handling as described by Gross et al.²¹ Calibration was performed with pure compounds (Hoffmann-La Roche; Sigma Chemical Co.). Quality-control procedures included routine analysis of plasma and serum control pools containing high and low concentrations of each analyte. In addition, the laboratory routinely analyzed National Institute of Standards (NIST) reference sera and was a participant in the NIST Fat-Soluble Vitamin Quality Assurance Group. The CV were $<10\%$ for all analytes and control pools. The intraclass correlation coefficients (ratio of between-person variance to between- plus within-person variance) were 0.93 for α -carotene, 0.98 for β -carotene, 0.73 for lutein plus zeaxanthin, 0.97 for β -cryptoxanthin, 0.73 for lycopene.²²

At each examination, plasma lipids were measured by the University of Washington Northwest Lipid Research Clinic Laboratory. Total triglycerides and total HDL-cholesterol were measured by enzymatic procedures. HDL-cholesterol was measured after dextran sulfate–magnesium precipitation. LDL-cholesterol was calculated using the Friedewald equation.

Incidence of hypertension

Systolic and diastolic BPs were measured at every examination after a 5 minute rest in a quiet room using the means of the second and third random zero sphygmomanometer measurements, except that the measurement was made with an Omron oscillometer (HEM907XL) at year 20, calibrated to random zero sphygmomanometer values based on dual readings in 903 participants. The recalibrated year 20 systolic BP was 3.74 ± 0.96 times the observed Omron systolic BP, while the recalibrated year 20 diastolic BP was 1.30 ± 0.97 times the observed Omron diastolic BP. We used year 2, year 5, year 7, year 10, year 15, and year 20 data to assess the incidence of hypertension, excluding those with hypertension

at baseline. We also collected information on antihypertensive medication at every examination. The definition of hypertension at each examination was systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or taking antihypertensive medication.¹

Statistical analysis

Given earlier analyses in these data in which findings were similar for 4 carotenoids (α -carotene, β -carotene, lutein/zeaxanthin, and β -cryptoxanthin) and quite different for lycopene,^{23–26} the primary focus in the present analyses was on the sum of the 4 carotenoid concentrations, with secondary focus on individual carotenoids, including lycopene. Cross-sectional data in Table 1 were adjusted for year 0 age, sex, race, center and education using linear regression. We calculated relative hazards for hypertension incidence using Cox proportional hazard models. Thus, the adjusting variables for hypertension incidence analyses were: Model 1: year 0 values of age (years), study center, race, sex, education; Model 2: Model 1 plus total energy intake, alcohol consumption (mL/day), smoking status, BMI (kg/m²), physical activity (continuous), total-cholesterol (continuous), HDL-cholesterol (continuous), triglycerides (continuous), and use of vitamin supplement (A, C, or E); and Model 3: Model 2 plus baseline systolic BP. We also performed time-dependent Cox proportional models. We used year 0 carotenoid concentrations for the follow-up period between year 0 and year 7, replaced them at year 7 through year 15 with year 7 carotenoid concentrations and at year 15 with year 15 carotenoid concentrations through year 20. For purposes of the time-dependent models only, we imputed missing year 7 and 15 carotenoid levels by multiplying their baseline concentration by the ratio of the mean carotenoid concentration in all available participants at the followup examination to the corresponding mean at baseline, i.e., $1.18 \times$ (year 0 sum of 4 carotenoids) was imputed at year 7 and $1.38 \times$ (year 7 sum of 4 carotenoids) was imputed at year 15, or $1.53 \times$ (year 0 sum of 4 carotenoids) if year 7 and year 15 carotenoids were both missing. A similar operation was conducted for each individual carotenoid.

Finally, repeated measures regression analysis was used to relate time dependent carotenoid concentrations to the pattern of BP values across all 7 examinations. Rather than truncating many high BP values by excluding those taking BP lowering medication, we included them and used their measured BP. Such people tend to have higher BP than nonmedicated people, even though their medicated BP generally decreases relative to their own values at earlier examinations when they were not medicated. Covariates were as in the analyses with hypertension as the dependent variable, updated to their current or most recent value for each repeat.

We combined former and never smokers as nonsmokers under the assumption that oxidative stress is lower in former smokers than in current smokers. Interaction p-values were analyzed using a product term.

RESULTS

Baseline characteristics

The 4712 participants eligible for year 0 baseline cross-sectional analyses comprised 54.9% women, 48.7% whites, and 60.3% with education beyond high school. Proportions of current smoker, former smoker and never smoker at year 0 were 34.6%, 11.5% and 54.0%, respectively. Mean age (standard deviation) was 24.8 (3.6) years at year 0. The mean values of the sum of 4 serum carotenoid and lycopene concentrations were 44.5 (23.9) $\mu\text{g/L}$ and 29.9 (14.5) $\mu\text{g/L}$, respectively. At year 0, 136 (2.9%) participants had hypertension. Cross-sectional correlates of carotenoids have been reported extensively elsewhere.^{23–26}

Cross sectional findings

Adjusted year 0 sum of 4 carotenoid concentrations was higher in lower BP categories (Table 1). Adjusted mean year 0 sum of 4 carotenoid concentrations was the lowest in the participants who were hypertensive at year 0. Findings for each carotenoid alone, except for lycopene, were similar to results for the sum of 4 carotenoids. These tendencies were unchanged even when further adjusted for total energy intake, alcohol consumption (mL/day), smoking, BMI (kg/m²), physical activity (continuous), total-cholesterol (continuous), HDL-cholesterol (continuous), triglycerides (continuous), and use of vitamin supplements (A, C, or E). (data not shown) Similarly, adjusted year 7 and 15 carotenoid concentrations were mostly inversely associated with BP levels at year 7 and 15, respectively, except that lycopene was unrelated to BP (Table 1).

Longitudinal prediction of systolic BP

In repeated measures regression prediction with adjustment for year 0 age, sex, race, center, and education, and systolic BP, as well as alcohol intake, total cholesterol, HDL cholesterol, triglycerides, energy intake, body mass index, smoking, and physical activity concurrent with each BP repeat, average systolic BP (year 0 through 20) was lower by -0.09 (standard error, se: 0.10) mmHg per $25 \mu\text{g/l}$ of the baseline sum of 4 carotenoids ($p=0.33$), while systolic BP was predicted to change by -0.5 (se: 0.08) mmHg per $25 \mu\text{g/l}$ of concurrent change in the sum of 4 carotenoids ($p<0.001$), whenever during the study that change occurred. Excluding participants who reported current smoking at any examination, average systolic BP was lower by -0.23 (standard error, se: 0.11) mmHg per $25 \mu\text{g/l}$ of the baseline sum of 4 carotenoids ($p=0.03$), and systolic BP was again predicted to change by -0.5 (se: 0.09) mmHg per $25 \mu\text{g/l}$ of change in the sum of 4 carotenoids ($p<0.001$).

Year 0 carotenoids and hypertension incidence

During 20 years of follow-up, 971 cases of hypertension were observed with incidence inversely related to year 0 serum carotenoids; incidence rates across sum of 4 carotenoid concentration quartiles were 16.2, 14.9, 13.7, and 10.4 per 1000 person-years, respectively (Table 2). The HR for incident hypertension decreased gradually as the quartile of sum of 4 carotenoids increased, such that p for trend analyzing the sum of 4 carotenoids as a continuous variable indicated a significant inverse association with hypertension incidence (Table 2). In models using only baseline predictors, most carotenoids were inversely related to hypertension incidence (Table 3), although only the relation of β -cryptoxanthin at year 0 with hypertension incidence was statistically significant after adjustment for baseline BP values. In the model using time dependent carotenoids and covariates, sum of 4 carotenoids, α -carotene, β -carotene, lutein/zeaxanthin, and β -cryptoxanthin were all significantly inverse to incident hypertension, and lycopene was positively though not significantly related to incident hypertension (Table 3).

We did not find any significant interaction for year 0 carotenoids predicting hypertension incidence with age, sex, race or smoking as the modifying factor (range of p for interaction: 0.23 – 0.81).

DISCUSSION

The sum of 4 serum carotenoid concentrations, excluding lycopene, was generally inversely associated with incident hypertension and systolic blood pressure. These relations were observed irrespective of smoking status.

Only 3 cross-sectional studies reported the relation between serum carotenoids and hypertension.^{4,15,16} Our cross-sectional finding that the sum of 4 carotenoids (α -carotene,

β -carotene, lutein/zeaxanthin, and β -cryptoxanthin) was significantly inversely related to the systolic BP levels was consistent with those previous studies. Our prospective findings that serum carotenoid concentrations predicted future hypertension risk and systolic BP were also consistent with the result observed in placebo arms of the SU.VI.MAX trial.¹⁴ They showed that after 6.5 years follow-up, an inverse association of serum β -carotene at baseline with hypertension was observed in the 498 normotensive men allocated to the placebo control group. The odds ratios for incident hypertension in the highest tertiles of serum β -carotene concentration compared with the lowest tertile were 0.53 (0.33–0.86) and P for trend was 0.03 in multivariate analyses. These findings were also consistent with prospective studies that have shown an inverse relation of fruit or vegetable intake, which supply carotenoids, with hypertension incidence including our study,⁹ the Chicago Western Electric Study,¹⁰ the DASH 8 week feeding trial of people with high normal BP or hypertension,¹¹ a 1 year high fruit and vegetable dietary trial in Japan,¹² and a 4 week trial of a carotenoid-rich tomato extract in Israel.¹³ It might be seen as inconsistent with 6.5 year findings in the SU.VI.MAX study, which found no relation of vitamin supplementation with future hypertension.¹⁴ However, we consider it likely that other food constituents besides carotenoids play a role in the association of serum carotenoids and BP, and that the null findings in SU.VI.MAX relate to use of purified compounds, rather than foods. Thus, although it is still unknown whether carotenoids themselves reduce the risk of hypertension (for example through their antioxidant properties), serum carotenoids can at least be considered as favorable health markers for future hypertension. Further, in our data baseline serum carotenoids and change of carotenoids related to reduced average (year 0 through 20) and change in systolic BP, which suggests that change in BP level was determined not only by baseline lifestyle but also lifestyle change during the follow-up period.

Serum carotenoids are also known to be affected by cigarette smoking, which reduces carotenoid concentrations. Therefore, it is important that the inverse relation of carotenoids with hypertension was not explained by cigarette smoking. Furthermore, we previously reported that relations of carotenoids with several cardiovascular disease risk factors differed by smoking status.^{23–26} Relations of carotenoids with oxidative stress (F_2 -isoprostanes, γ -glutamyltransferase), markers of inflammation (white blood cell, CRP) and a marker of endothelial dysfunction (soluble intercellular adhesion molecule-1) were stronger in current smokers than non-smokers.^{17,18} Conversely, inverse relations of carotenoids with diabetes incidence and insulin resistance were observed only in nonsmokers.²³ These results suggest that the role of carotenoids or metabolism of carotenoids differ in nonsmokers vs. smokers. In this study, we did not find interaction between smoking status and sum of 4 carotenoids for hypertension incidence, i.e., the beneficial effect of carotenoids on BP was similarly observed for current smokers and nonsmokers. Thus, we concluded that the beneficial effect of carotenoids on BP was not explained only by nonsmoking but also by other healthy behaviors, such as consuming fruit or vegetables.

In this study, the association of lycopene with cross sectional BP level or that with future hypertension was weaker than other carotenoids, a finding consistent with our previous finding that inverse associations of lycopene with markers of inflammation, oxidative stress, and endothelial dysfunction were weaker than those of other carotenoids.²³ Thus, although lycopene itself is an antioxidant, lycopene concentration might mark a less healthy lifestyle in this cohort. We previously showed that lycopene concentration was positively related to mean intakes of meat and alcohol; and that concentrations of triglycerides were higher across lycopene quartiles, whereas intake of fruit and use of vitamin supplements were lower.²³ The distinct epidemiologic features of lycopene compared to other carotenoids in the CARDIA study does cast some doubt of the theory that any benefit of carotenoids on health is solely related to their antioxidant function.

Limitations of all observational epidemiologic studies apply to the findings presented here. Nevertheless, our data add to the tightly controlled findings of the 8-week long DASH intervention¹¹, providing a strong, 20-year epidemiologic base for an association of carotenoids and therefore diet in a complex setting where many different plant chemicals may be eaten. The study is supportive in a general way of the DASH and similar plant-centered, nutrient rich diets for long term health. The study adds support for research focus on phytochemicals in the blood and the diet in relation to hypertension. It also adds support for a recommendation for the general population to enhance consumption of nutrient-rich plant foods. Besides fruits and vegetables generally and avoidance of high sodium products, we note that phytochemicals including folic acid, catechins, flavonoids and polyphenolic compounds found in berries, nuts, whole grains, coffee, tea, and chocolate could have influenced the carotenoid levels in our study. However, we did not have sufficient data to identify which specific dietary components might be most influential in the association between circulating carotenoids and hypertension. Our epidemiologic approach is not likely to uncover specific biochemical pathways related to hypertension. Further, more specific studies are needed to elucidate biological pathways.

In conclusion, serum carotenoid concentrations except for lycopene were generally inversely associated with baseline BP level, independent of smoking status. Furthermore, those with higher concentrations of sum of carotenoids, not including lycopene, generally had lower risk for future hypertension. Therefore, the concentrations of the 4 serum carotenoids might play a role in the beneficial association of several foods with elevated BP, which we previously reported in this cohort.⁹

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Table 1

Cross-sectional relations of year 0, 7, and 15 systolic/diastolic blood pressure (BP) level with serum carotenoid concentrations (mg/l) at the corresponding examination, the CARDIA/YALTA study 1985–86, 1992–93, and 2005–06.

Year 0	<119/<79 mmHg	120–129/80–84 mmHg	130–139/85–89 mmHg	140+/90+ or treatment	P for trend
N	3591	742	243	136	
Sum of 4 carotenoids	45.5	41.9	41.6	39.6	<0.01
α -carotene	2.8	2.3	2.5	2.2	<0.01
β -carotene	15.7	13.6	13.4	12.7	<0.01
Lutein/zeaxanthin	18.5	17.9	17.7	17.6	0.03
β -cryptoxanthin	8.5	8.1	8.0	7.2	<0.01
Lycopene	29.7	30.2	32.0	28.4	0.31
Year 7					
N	2741	397	125	289	
Sum of 4 carotenoids	51.1	45.0	47.2	42.6	<0.01
α -carotene	3.8	3.3	3.3	3.0	<0.01
β -carotene	19.0	15.6	16.9	14.4	<0.01
Lutein/zeaxanthin	19.5	18.2	19.0	18.0	<0.01
β -cryptoxanthin	8.8	7.9	8.0	7.4	<0.01
Lycopene	32.4	33.0	33.9	32.6	0.49
Year 15					
N	1759	402	200	549	
Sum of 4 carotenoids	68.6	61.1	55.6	56.8	<0.01
α -carotene	6.2	5.1	4.3	4.6	<0.01
β -carotene	23.7	20.0	16.5	17.8	<0.01
Lutein/zeaxanthin	26.2	24.4	23.6	24.2	<0.01
β -cryptoxanthin	12.5	11.6	11.2	10.2	<0.01
Lycopene	39.5	40.3	39.6	39.8	0.87

Notes:

Sum of 4 carotenoids: sum of α -carotene, β -carotene, lutein/zeaxanthin, β -cryptoxanthin
Adjusted for age, race, sex, center, and education

Table 2

Relative hazards (RH) for hypertension incidence according to quartile of year 0 sum of 4 serum carotenoids: the CARDIA/YALTA study 1985–86 to 2005–06.

	year 0 sum of 4 carotenoids (mg/l)			
	Quartiles			
	Q1	Q2	Q3	Q4
Sum of 4 carotenoids	5.5–28.92	28.93–40.05	40.06–54.87	54.91–313.22
N	1103	1103	1103	1103
Cases	270	261	247	193
Model 1: RH (95%CI)	1.00	0.86 (0.73–1.03)	0.83 (0.70–0.99)	0.65 (0.54–0.78)
Model 2: RH (95%CI)	1.00	0.95 (0.80–1.10)	0.92 (0.76–1.10)	0.78 (0.63–0.96)
Model 3: RH (95%CI)	1.00	0.98 (0.82–1.16)	0.92 (0.77–1.11)	0.86 (0.70–1.06)

Model 1 adjusted for age, sex, race, center, and education

Model 2 adjusted for RH1+ year 0 levels of alcohol consumption, total cholesterol, HDL cholesterol, triglycerides, energy intake, body mass index, smoking, physical activity, and use of vitamin supplement

Model 3 adjusted for RH2+ year 0 systolic blood pressure

Table 3

Relative hazards (RH) for hypertension incidence per standard deviation of sum of 4 and individual carotenoid concentrations, the CARDIA/YALTA study 1985–86 to 2005–06.

	Sum of 4 carotenoids	α -carotene	β -carotene	Lutein/zeaxanthin	β -cryptoxanthin	Lycopene
Year 0 predictors (971/4412)						
Model 2: RH (95% CI)	0.89 (0.81–0.97)	0.92 (0.83–1.02)	0.90 (0.83–0.98)	0.94 (0.87–1.01)	0.92 (0.85–0.99)	0.98 (0.92–1.05)
Time dependent model (971/4412)*						
Model 2: RH (95% CI)	0.83 (0.76–0.90)	0.89 (0.55–0.87)	0.83 (0.76–0.92)	0.93 (0.86–1.00)	0.88 (0.81–0.95)	1.04 (0.97–1.11)

Model 2 adjusted for year 0 age, sex, race, center, education, alcohol consumption, total cholesterol, HDL cholesterol, triglycerides, energy intake, body mass index, smoking, physical activity, and use of vitamin supplement.

* We used year 7 carotenoids for the follow-up period between year 7 to year 10 and year 15 carotenoids for the period between year 15 to year 20. Missing followup carotenoid values were imputed; see Methods.