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Serum α-Carotene Concentrations and Risk of Death Among US Adults

The Third National Health and Nutrition Examination Survey Follow-up Study

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Background: Much research has been conducted relating total carotenoids—and β-carotene in particular—to risk of cancer and cardiovascular disease (CVD). Limited data are emerging to implicate the important role of α-carotene in the development of CVD or cancer.

Methods: We assessed the direct relationship between α-carotene concentrations and risk of death among 15 318 US adults 20 years and older who participated in the Third National Health and Nutrition Examination Survey Follow-up Study. We used Cox proportional hazard regression analyses to estimate the relative risk for death from all causes and selected causes associated with serum α-carotene concentrations.

Results: Compared with participants with serum α-carotene concentrations of 0 to 1 μg/dL (to convert to micromoles per liter, multiply by 0.01863), those with higher serum levels had a lower risk of death from all causes ($P<.001$ for linear trend): the relative risk for death was 0.77 (95% confidence interval, 0.68-0.87) among those with α-carotene concentrations of 2 to 3 μg/dL, 0.73 (0.65-0.83) among those with concentrations of 4 to 5 μg/dL, 0.66 (0.55-0.79) among those with concentrations of 6 to 8 μg/dL, and 0.61 (0.51-0.73) among those with concentrations of 9 μg/dL or higher after adjustment for potential confounding variables. We also found significant associations between serum α-carotene concentrations and risk of death from CVD ($P=.007$), cancer ($P=.02$), and all other causes ($P<.001$). The association between serum α-carotene concentrations and risk of death from all causes was significant in most subgroups stratified by demographic characteristics, lifestyle habits, and health risk factors.

Conclusions: Serum α-carotene concentrations were inversely associated with risk of death from all causes, CVD, cancer, and all other causes. These findings support increasing fruit and vegetable consumption as a means of preventing premature death.

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OXIDATIVE DAMAGE TO DNA, proteins, and lipids may play an important role in the pathogenesis of some chronic diseases, including cardiovascular disease (CVD) and cancer.[1] In vitro study results have suggested that antioxidants directly scavenge reactive oxygen and nitrogen species and thus delay or prevent oxidative damage.[1] Carotenoids (α-carotene, β-carotene, lycopene, lutein, β-cryptoxanthin, zeaxanthin, and astaxanthin) are potent antioxidants that are synthesized by plants and microorganisms.[2] The circulating carotenoids in the human body are obtained mainly through consumption of fruits and vegetables that are rich in carotenoids or antioxidant supplements containing β-carotene.[3]

Results from many studies have shown that a high consumption of fruits and vegetables is associated with low risks for many chronic diseases, including cancer, coronary heart disease, stroke, and type 2 diabetes mellitus.[4-10] Prospective cohort study results have also linked higher intake of dietary carotene to a lower risk of cancer and CVD.[9] However, elements in fruits and vegetables that contribute to the health effects remain to be elucidated. Results from randomized trials have generally shown that the consumption of β-carotene supplements has no significant effect on supplement users' risk of cancer, CVD, or type 2 diabetes mellitus.[11-14]

Therefore, carotenoids other than β-carotene may contribute to the reduction in disease risk, and their effects on risk of disease merit investigation.[15]

Relatively few studies have directly examined the association between α-carotene concentrations and risk of cancer or CVD. Findings from limited number of studies on the association between serum or plasma α-carotene concentrations and risk of death have been inconsistent. In a recent study of Japanese adults aged 39 to 80 years who were followed up for as many as 12 years, those with higher levels of serum α-carotene were found to be at lower risk of death from CVD and cancer than those with lower levels.[16,17] In contrast, no significant association between serum α-carotene levels and risk of death from CVD was found in the Physicians' Health Study II, in which a study population of primarily white US men and women was followed up for 2 years,[18,19] or in a study of Dutch adults aged 65 to 85 years who were followed up for approximately 7 years.[20] This inconsistency in study findings may have been the result of demographic differences in study cohorts, small sample sizes, or short follow-up periods. To assess the association between serum α-carotene concentrations and risk of death from all causes, CVD, cancer, and all other causes in a larger, more diverse study cohort over a longer study period, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) of US adults 20 years and older and linked mortality follow-up data on NHANES III participants.

METHODS

STUDY POPULATION

The NHANES III (1988-1994) recruited study participants using a multistage, stratified sampling process designed to produce a survey sample that was representative of the civilian noninstitutionalized US population 20 years and older.[21] The NHANES III underwent institutional review board approval, and written informed consent was received from all participants. After being interviewed in their homes, participants were invited to a mobile examination center, where they had a clinical examination and provided a blood sample. Response rates were 86% for the household interviews and 78% for the medical examinations.[22] Of 16 573 survey adults who attended a medical examination center, 15 631 (94.3%) provided serum samples for α-carotene measurements. After the exclusion of participants who were ineligible for mortality follow-up because of insufficient identifying data (social security number, full name, sex, race, date of birth, state of birth, state of residence) for matching or length of follow-up of 1 month or less (n = 19), as well as those who had missing data on covariates (n = 294), our study cohort consisted of 15 318 NHANES III participants (92.4% of all participants who appeared at a medical examination center).

LABORATORY PROCEDURES USED TO ASSESS BASELINE BIOMARKERS OF NHANES III PARTICIPANTS

A detailed description of laboratory procedures has been published elsewhere.[23] In brief, serum samples were aliquoted, stored at −70°C, and shipped on dry ice to the NHANES laboratory at the Centers for Disease Control and Prevention, Atlanta, Georgia. Serum concentrations of α-carotene and β-carotene were quantified by isocratic high-performance liquid chromatography with detection at 3 different wavelengths (Waters HPLC system, Waters Chromatography Division, Milford, Massachusetts).

Total serum cholesterol concentrations were measured enzymatically in a series of coupled reactions that hydrolyze cholesterol esters and oxidize the 3-OH cholesterol group. High-density lipoprotein cholesterol (HDL-C) concentrations were measured after the precipitation of the other lipoproteins with a polyanion/divalent cation mixture. Total cholesterol and HDL-C analyses were performed with an automated chemistry analyzer (Hitachi 704 Analyzer; Boehringer Mannheim Diagnostics, Indianapolis, Indiana). Non–HDL-C concentrations were calculated by subtracting HDL-C concentrations from total cholesterol concentrations.

DEMOGRAPHIC CHARACTERISTICS AND PHYSICAL EXAMINATION MEASURES AT BASELINE

Participants' age (in years), race/ethnicity (white, non-Hispanic black, Mexican American, or other), education level (less than high school, high school, or beyond high school) smoking status (current smoker, former smoker, or never smoker), and alcohol consumption (times in the previous month) were based on self-reports of participants. Physical activity level was determined by participants' self-reported frequency of engaging in specific types of leisure-time exercise or activities during the previous month multiplied by the rate of energy expenditure (intensity rating) for those activities according to a standardized coding method.[24] Participants' body mass index was calculated from their measured weight and height. The mean blood pressure was calculated as the average of the second and third readings for those who had 3 measurements, as the second reading for those who had 2 measurements, and as the only reading for those who had 1 measurement.[25]

LINKED MORTALITY DATA THROUGH DECEMBER 31, 2006

The NHANES III participants with sufficient identifying data were matched to the National Death Index (NDI) to determine their survival status through December 31, 2006.[26] The National Center for Health Statistics performed linkage with probabilistic matching between NHANES III and NDI data and reviewed death certificates to ensure that deaths reported in the NDI were matched to the correct NHANES III participants.

We used a standardized list of 113 causes based on the *International Classification of Diseases, Ninth Revision*, and the *International Statistical Classification of Diseases, 10th Revision*, codes to determine decedents' underlying cause of death[27] and divided the causes of death into 3 major categories: CVD, cancer, and all other causes. We divided CVD into the subcategories of ischemic heart disease, stroke, and other CVD. We divided cancer into cancer of the aerodigestive system (ie, cancers of lip, oral cavity, pharynx, esophagus, stomach, colon, rectum, anus, liver, intrahepatic bile ducts, pancreas, and larynx); cancer of the lung, trachea, or bronchus; and all other cancers according to their frequencies and their possible relations to α-carotene concentrations. Also, we divided all other causes into the subcategories of diabetes mellitus, chronic lower respiratory disease, and all other diseases.

STATISTICAL ANALYSIS

We first estimated the population distribution of serum α-carotene concentrations by sex and age. Because the distribution of serum α-carotene concentrations was skewed to

Table 1. Major Causes of Deaths and Number of Deaths Among Adults 20 Years and Older in the United States: Third National Health and Nutrition Examination Survey Follow-up Study, 1988-2006

Cause of Death	List No. From 113 Underlying Causes of Death[a]	Total Cohort	Serum α-Carotene Concentration, μg/dL				
			0-1	2-3	4-5	6-8	≥9
All causes	1-135	3810	888	895	1035	596	396
CVD	53-74	1671	345	381	469	289	187
Ischemic heart disease	58-63	958	199	209	268	166	116
Stroke	70	293	45	70	95	51	32
Other CVD	53-57, 64-69, 71-74	420	101	102	106	72	39
Cancer	19-43	834	230	208	221	107	68
Cancer of aerodigestive track	20-26	221	63	57	56	26	19
Cancer of lung, trachea, bronchus	27	248	90	57	60	23	18
All other cancers	19, 28-43	365	77	94	105	58	31
All other causes	1-18, 44-52, 75-135	1305	313	306	345	200	141
Diabetes mellitus	46	126	28	35	33	16	14
Chronic lower respiratory disease	82-86	157	44	40	43	18	12
All other diseases	1-18, 44-45, 47-52, 75-81, 87-135	1022	241	231	269	166	115

Abbreviation: CVD, cardiovascular disease.
SI conversion factor: To convert α-carotene concentration to micromoles per liter, multiply by 0.01863.
[a] Based on Anderson et al.[27]

the right, we used square root transformation to improve the distribution. We also divided the continuum of serum α-carotene concentrations into 5 categories (ie, 0-1, 2-3, 4-5, 6-8, and ≥9 μg/dL [to convert to micromoles per liter, multiply by 0.01863]) according to its approximate quintile cutoff values and compared baseline characteristics of participants according to these 5 levels using 2-sample *t* tests. A total of 12 variables, including participants' demographic characteristics, lifestyle and behavioral risk factors, and biomarkers, were used to control for individual characteristics that might confound or modify the association between α-carotene concentrations and risk of death.

We conducted Cox proportional hazard regression analysis to estimate hazard ratios (relative risks) for death from all causes and major specific causes in which we treated serum α-carotene concentrations as either a categorical variable (5 levels) or a continuous variable. We used age in months as the time scale in survival analyses with left truncation (ie, participants entered into the cohort at different ages) and determined the participants' age in months at the end of follow-up by adding their age in months at baseline examination to the number of months they were followed up. We provided unadjusted and adjusted risk estimates for these potential confounders. We used *t* tests with orthogonal polynomial coefficients to test for linear trends in relative risks.

To further examine whether the association between serum α-carotene concentrations and risk of death from all causes might be consistent in subpopulations, we conducted subgroup analyses stratified by each level of demographic characteristics, lifestyle and behavioral risk factors, and biomarkers. We used Wald χ^2 tests to assess the interactions between serum α-carotene concentrations and all stratification variables on the outcome variables. To account for the possible nonlinear association between serum α-carotene concentrations and risk of death, we also estimated relative risks by performing Cox proportional hazard regression analyses with a 3-knot spline and treating serum α-carotene concentrations as a continuous variable.[28]

We analyzed all data using the SAS system for Windows (Release 9.2; SAS Institute Inc, Cary, North Carolina) and SUDAAN software (Release 10; Research Triangle Institute, Research Triangle Park, North Carolina). In all analyses, sample weights were used to account for the varying probabilities of complex sampling design and nonresponse and to produce nationally representative estimates. We considered results of 2-tailed *t* tests used in 2 groups or χ^2 tests used in 2-way comparisons to be statistically significant if *P* values were <.05, results of 2-tailed *t* tests used in multiple comparisons to be statistically significant if *P* values were <.005 (equivalent to *P* values <.05 after Bonferroni correction), and estimates of relative risks to be significantly different from 1 if the 95% confidence interval did not include 1.

RESULTS

The mean (SE) concentration of serum α-carotene was 4.79 (0.09) μg/dL for the entire cohort, including 4.22 (0.10) μg/dL among men and 5.31 (0.11) μg/dL among women (*P*<.001 for difference by sex). Of the 15 318 eligible NHANES III participants in our study, 3810 were found to have died over a mean follow-up period of 13.9 years through 2006 (**Table 1**). We found significant differences by serum α-carotene concentration in the following characteristics: mean age, alcohol consumption, leisure-time physical activity, body mass index, serum HDL-C concentration, and serum non–HDL-C concentration, as well as in the distribution of study participants by sex, race/ethnicity, education level, and smoking status (all *P*<.001) (**Table 2**).

We found that serum α-carotene concentration was inversely associated with unadjusted risk of death from all causes, CVD, cancer, and all other causes (all *P*<.001 for linear trend) (**Table 3**). After adjusting for the demographic characteristics, lifestyle habits, and health risk factors presented in Table 2, we found that serum α-carotene concentration was inversely associated with adjusted risk of death from all causes (*P*<.001 for linear trend), CVD (*P*=.007 for linear trend), cancer (*P*=.02 for linear trend), and all other causes (*P*<.001 for linear trend) (Table 3). In the various subcategories for cause of death, we found a significant inverse association between serum α-carotene con-

Table 2. Characteristics of Participants in the Third National Health and Nutrition Examination Survey Follow-up Study, 1988-2006, by Serum α-Carotene Concentration at Baseline (1988-1994)[a]

Variable	Total Cohort	Serum α-Carotene Concentration, μg/dL					*P* Value[b]
		0-1	2-3	4-5	6-8	≥9	
Unweighted sample size	15 318	3615	3814	3950	2349	1590	
Weighted, %	100	21.93 (0.75)	23.66 (0.63)	25.84 (0.56)	16.62 (0.47)	11.95 (0.63)	
Serum α-carotene concentration, μg/dL	4.79 (0.09)	0.93 (0.01)	2.59 (0.02)	4.43 (0.01)	6.79 (0.03)	14.18 (0.25)	<.001
Demographic variables							
Age, y	44.82 (0.46)	39.32 (0.33)	43.31 (0.50)	46.42 (0.65)	48.00 (0.75)	50.00 (0.82)	<.001
Male sex, %	47.88 (0.43)	57.16 (1.03)	51.54 (1.21)	47.18 (1.31)	40.92 (1.52)	34.79 (1.93)	<.001
Race/ethnicity, %							
Non-Hispanic white	76.94 (1.27)	74.78 (1.34)	77.04 (1.40)	78.23 (1.55)	79.28 (1.85)	74.69 (2.69)	.75
Non-Hispanic black	10.37 (0.61)	18.22 (1.14)	12.01 (0.88)	7.21 (0.52)	5.46 (0.40)	6.38 (0.96)	<.001
Mexican American	5.07 (0.41)	3.57 (0.33)	5.74 (0.51)	6.29 (0.59)	5.26 (0.56)	3.61 (0.43)	.76
Other race/ethnicity	7.61 (0.81)	3.43 (0.55)	5.21 (0.82)	8.27 (1.09)	10.00 (1.50)	15.33 (2.48)	<.001
Education, %							
Less than high school	24.81 (1.03)	32.23 (1.48)	25.99 (1.50)	23.01 (1.31)	20.51 (1.50)	18.76 (1.73)	<.001
High school	33.59 (0.76)	41.48 (1.30)	36.94 (1.23)	31.56 (1.34)	28.40 (1.42)	24.07 (1.45)	<.001
Beyond high school	41.60 (1.26)	26.29 (1.62)	37.08 (1.36)	45.43 (1.70)	51.09 (2.09)	57.17 (2.19)	<.001
Lifestyle habits and health risk factors							
Smoking status, %							
Current smoker	28.14 (0.79)	50.12 (1.54)	33.70 (1.37)	22.60 (1.20)	13.81 (1.07)	8.70 (1.09)	<.001
Former smoker	26.11 (0.60)	17.88 (1.04)	25.97 (1.41)	29.49 (0.93	29.24 (1.48)	29.82 (1.70)	<.001
Never smoker	45.75 (0.76)	32.01 (1.51)	40.33 (1.12)	47.91 (1.24)	56.95 (1.39)	61.48 (2.21)	<.001
Alcohol consumption (times in previous month)	8.73 (0.36)	11.98 (0.81)	8.77 (0.52)	7.71 (0.44)	7.52 (0.50)	6.61 (0.62)	<.001
Leisure-time physical activity (METs)	110.27 (3.17)	97.88 (4.29)	95.75 (4.03)	111.44 (4.70)	129.35 (6.82)	132.73 (5.25)	<.001
BMI	26.52 (0.11)	27.65 (0.22)	27.01 (0.20)	26.50 (0.14)	25.59 (0.13)	24.80 (0.18)	<.001
Systolic blood pressure, mm Hg	120.40 (0.40)	120.70 (0.41)	120.18 (0.51)	120.49 (0.61)	120.15 (0.79)	120.48 (0.84)	.82
Serum HDL-C, mg/dL	50.72 (0.34)	47.77 (0.52)	49.15 (0.52)	50.73 (0.52)	53.47 (0.49)	55.40 (0.78)	<.001
Serum non–HDL-C cholesterol, mg/dL	153.46 (0.87)	144.20 (1.18)	151.89 (1.26)	157.06 (1.68)	158.61 (1.60)	158.59 (1.70)	<.001
Serum β-carotene, μg/dL	20.18 (0.31)	8.10 (0.14)	13.06 (0.23)	19.30 (0.46)	29.04 (0.73)	46.02 (1.05)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; METs, metabolic equivalents.

SI conversion factors: To convert α- and β-carotene values to micromoles per liter, multiply by 0.01863; to convert cholesterol values to millimoles per liter, multiply by 0.0259.

[a] All data are weighted mean (SE) for continuous variables and weighted percentage (SE) for categorical variables.

[b] *P* values were obtained from *t* tests for linear trends in the proportions or means across the 5 α-carotene levels.

centration and risk of death from cancer of the aerodigestive track ($P<.001$ for linear trend), diabetes ($P=.002$ for linear trend), and chronic lower respiratory disease ($P<.001$ for linear trend).

We also found a significant linear trend in the association between serum α-carotene concentrations and risk of death from all causes in all subgroups (all $P<.05$) stratified by demographic characteristics, lifestyle habits, and health risk factors (**Table 4**) except in participants aged 20 to 44 years, Mexican Americans, those who engaged in no leisure-time physical activity, those with a body mass index between 25.0 and 29.9 (calculated as weight in kilograms divided by height in meters squared), those with a low HDL-C concentration, and those with a low β-carotene concentration. There were significant interactions between serum α-carotene concentrations and age, race/ethnicity, smoking status, and systolic blood pressure on risk of death from all causes ($P=.03$-$.003$).

We found an inverse dose-response relationship between continuous serum α-carotene concentrations and risk of death from all causes (**Figure**, A), from CVD (Figure, B), and from all other causes (Figure, D). Increased serum α-carotene concentrations were strongly associated with decreased risk of death from cancer at its lower concentrations (Figure, C); however, the association appeared to be attenuated at serum α-carotene concentrations of 16 μg/dL and above.

COMMENT

In this prospective study of a nationally representative sample of US adults over a mean follow-up period of 13.9 years, we found that serum α-carotene concentrations were inversely associated with risk of death from all causes, CVD, cancer, and all causes other than CVD and cancer. The negative association between serum α-carotene concentrations and overall risk of death was also significant in most subgroups stratified by demographic characteristics, lifestyle habits, and health risk factors.

The strengths of our study include its large sample size and relatively long follow-up period. Our results showed inverse associations of serum α-carotene concentrations with the risk of death from all causes, CVD, cancer, and all other causes. Similar results were reported in a study of 3061 Japanese adults, among whom serum concentrations of α-carotene were inversely associated

Table 3. Estimated Relative Risk (RR) of Death From All Causes and Major Specific Causes Among 15 318 US Adults 20 Years and Older by Serum α-Carotene Concentration: Third National Health and Nutrition Examination Survey Follow-up Study, 1988-2006

Cause of Death	Serum α-Carotene Concentration, μg/dL[a]					*P* Value[b]
	0-1	2-3	4-5	6-8	≥9	
Unadjusted risk estimates						
All causes	1 [Ref]	0.67 (0.58-0.78)	0.56 (0.49-0.64)	0.47 (0.39-0.56)	0.39 (0.33-0.46)	<.001
CVD	1 [Ref]	0.74 (0.60-0.92)	0.65 (0.53-0.79)	0.60 (0.48-0.74)	0.47 (0.37-0.60)	<.001
Ischemic heart disease	1 [Ref]	0.68 (0.53-0.88)	0.64 (0.48-0.84)	0.59 (0.43-0.81)	0.47 (0.33-0.66)	<.001
Stroke	1 [Ref]	1.40 (0.79-2.49)	1.55 (0.88-2.73)	1.06 (0.59-1.88)	0.87 (0.43-1.78)	.48
Other CVD	1 [Ref]	0.68 (0.45-1.03)	0.42 (0.29-0.60)	0.49 (0.32-0.74)	0.38 (0.23-0.61)	<.001
Cancer	1 [Ref]	0.58 (0.44-0.75)	0.51 (0.41-0.63)	0.34 (0.25-0.45)	0.34 (0.22-0.50)	<.001
Cancer of aerodigestive track	1 [Ref]	0.52 (0.29-0.94)	0.42 (0.26-0.68)	0.18 (0.10-0.34)	0.22 (0.11-0.45)	<.001
Lung cancer	1 [Ref]	0.49 (0.31-0.79)	0.45 (0.29-0.69)	0.28 (0.16-0.49)	0.32 (0.16-0.66)	.002
All other cancers	1 [Ref]	0.71 (0.44-1.14)	0.64 (0.41-0.99)	0.51 (0.31-0.84)	0.44 (0.23-0.83)	.009
All other causes	1 [Ref]	0.68 (0.55-0.84)	0.52 (0.42-0.65)	0.43 (0.32-0.59)	0.34 (0.26-0.46)	<.001
Diabetes	1 [Ref]	0.61 (0.35-1.07)	0.17 (0.09-0.33)	0.16 (0.07-0.37)	0.14 (0.06-0.30)	<.001
Chronic lower respiratory disease	1 [Ref]	0.57 (0.36-0.91)	0.42 (0.26-0.67)	0.24 (0.11-0.55)	0.12 (0.05-0.27)	<.001
All other diseases	1 [Ref]	0.72 (0.56-0.92)	0.61 (0.47-0.78)	0.54 (0.38-0.75)	0.45 (0.32-0.62)	<.001
Adjusted risk estimates[c]						
All causes	1 [Ref]	0.77 (0.68-0.87)	0.73 (0.65-0.83)	0.66 (0.55-0.79)	0.61 (0.51-0.73)	<.001
CVD	1 [Ref]	0.82 (0.66-1.02)	0.82 (0.66-1.00)	0.78 (0.63-0.98)	0.71 (0.55-0.91)	.007
Ischemic heart disease	1 [Ref]	0.75 (0.58-0.98)	0.82 (0.61-1.11)	0.81 (0.57-1.14)	0.74 (0.52-1.07)	.21
Stroke	1 [Ref]	1.51 (0.82-2.79)	1.78 (0.94-3.34)	1.17 (0.60-2.29)	1.02 (0.40-2.61)	.84
Other CVD	1 [Ref]	0.77 (0.51-1.15)	0.53 (0.36-0.78)	0.65 (0.42-1.00)	0.57 (0.31-1.07)	.06
Cancer	1 [Ref]	0.67 (0.51-0.88)	0.69 (0.54-0.88)	0.51 (0.37-0.72)	0.57 (0.34-0.96)	.02
Cancer of aerodigestive track	1 [Ref]	0.60 (0.32-1.10)	0.51 (0.28-0.92)	0.23 (0.11-0.46)	0.26 (0.14-0.50)	<.001
Lung cancer	1 [Ref]	0.62 (0.39-0.98)	0.78 (0.49-1.24)	0.64 (0.37-1.11)	0.96 (0.34-2.72)	.98
All other cancers	1 [Ref]	0.78 (0.46-1.32)	0.76 (0.45-1.28)	0.66 (0.36-1.21)	0.60 (0.29-1.26)	.17
All other causes	1 [Ref]	0.80 (0.66-0.97)	0.69 (0.56-0.86)	0.64 (0.45-0.89)	0.55 (0.39-0.78)	<.001
Diabetes	1 [Ref]	0.79 (0.44-1.41)	0.26 (0.14-0.50)	0.29 (0.12-0.72)	0.33 (0.13-0.82)	.002
Chronic lower respiratory disease	1 [Ref]	0.62 (0.39-0.98)	0.57 (0.35-0.92)	0.33 (0.15-0.72)	0.14 (0.06-0.36)	<.001
All other diseases	1 [Ref]	0.85 (0.67-1.08)	0.81 (0.62-1.04)	0.80 (0.55-1.15)	0.76 (0.49-1.16)	.18

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; Ref, reference value.
SI conversion factor: To convert α-carotene values to micromoles per liter, multiply by 0.01863.
[a] Data are given as RR (95% CI). Age was the time scale in the Cox proportional hazard regression analyses.
[b] Linear trends were examined with *t* tests.
[c] Relative risks (hazard ratios) and their 95% CIs were adjusted for demographic characteristics, lifestyle habits, and health risk factors presented in Table 2.

with the risk of CVD,[17] and in a recent study of 559 elderly Dutch men, among whom dietary intake of α-carotene was inversely associated with risk of death from CVD.[29] However, no inverse association was found between α-carotene levels and overall risk for death in a study of 638 elderly Dutch persons[20] or between α-carotene levels and risk for CVD events in a case-control study of 499 American men who experienced CVD events and 499 who did not experience CVD events during a mean follow-up period of 2.1 years.[18] These studies, however, had relatively small sample sizes and short follow-up periods and thus less statistical power to detect associations. In contrast, our analyses were based on data from a much larger, population-based cohort, which was followed up for nearly 4 times as long; therefore, our findings should be more reliable and generalizable to the general population than those of previous studies of the relationship between α-carotene levels and risk of various adverse health outcomes.

Consistent with findings from previous studies,[30-33] our results showed an especially strong association between serum α-carotene concentrations and risk for death from some specific causes, including cancers of the aerodigestive track, diabetes, and chronic lower respiratory disease. Specifically, our results were consistent with those from a 1997 nested case-control study among Japanese American men in Hawaii,[30] which showed that (1) low serum α-carotene concentrations were associated with increased risk of cancers of the upper aerodigestive track, including esophageal cancer, laryngeal cancer, and oral-pharyngeal cancer; (2) consumption of fruits and vegetables and serum α-carotene concentrations were inversely associated with the incidence of type 2 diabetes mellitus[31,33]; and (3) serum α-carotene concentrations were directly associated with lung function,[32] which in turn may protect against chronic lower respiratory disease and its progression in persons who already have the disease.

In the past several decades, β-carotene has received attention for its possible role in the prevention of several chronic diseases, including cancer and CVD. However, randomized clinical trials have failed to link β-carotene supplements to reduced incidence and mortality of cancer or CVD or to reduced incidence of adverse effects among smokers and workers exposed to asbestos.[11-13] Although α-carotene is recognized as a major component of carotenoids, its protective effects against cancer and CVD have been investigated less than those of β-carotene.

Table 4. Estimated Relative Risk (RR) of Death Among 15 318 US Adults 20 Years and Older by Serum α-Carotene Concentration and Stratification Variables: Third National Health and Nutrition Examination Survey Follow-up Study, 1988-2006

Stratification Variable	Mean (SE)[b]	Serum α-Carotene Concentration, μg/dL[a]					*P* Value[c]
		0-1	2-3	4-5	6-8	≥9	
Sex							.97
Male	4.2 (0.1)*	1 [Ref]	0.77 (0.63-0.93)	0.74 (0.63-0.88)	0.69 (0.53-0.88)	0.61 (0.42-0.88)	(.007)
Female	5.3 (0.1)	1 [Ref]	0.77 (0.61-0.97)	0.73 (0.60-0.89)	0.63 (0.48-0.83)	0.61 (0.47-0.79)	(<.001)
Age, y							.02
20-44	4.2 (0.1)*	1 [Ref]	0.69 (0.44-1.08)	0.57 (0.34-0.96)	0.86 (0.49-1.54)	0.52 (0.20-1.34)	(.27)
45-64	5.4 (0.2)	1 [Ref]	0.73 (0.54-0.98)	0.72 (0.57-0.91)	0.55 (0.39-0.78)	0.41 (0.22-0.76)	(.002)
≥65	5.6 (0.1)	1 [Ref]	0.88 (0.71-1.10)	0.82 (0.67-1.01)	0.75 (0.61-0.92)	0.75 (0.61-0.92)	(.003)
Race/ethnicity							.03
Non-Hispanic white	4.7 (0.1)	1 [Ref]	0.78 (0.66-0.91)	0.75 (0.64-0.87)	0.65 (0.52-0.81)	0.58 (0.47-0.72)	(<.001)
Non-Hispanic black	3.8 (0.2)*	1 [Ref]	0.78 (0.64-0.94)	0.77 (0.64-0.92)	0.49 (0.38-0.63)	0.75 (0.56-1.01)	(.002)
Mexican American	4.5 (0.1)	1 [Ref]	0.80 (0.54-1.17)	0.72 (0.54-0.94)	0.80 (0.50-1.28)	0.79 (0.50-1.24)	(.40)
Education							.23
Less than high school	4.2 (0.1)	1 [Ref]	0.84 (0.72-0.98)	0.80 (0.68-0.93)	0.74 (0.59-0.94)	0.74 (0.57-0.97)	(.02)
High school	4.1 (0.1)	1 [Ref]	0.86 (0.68-1.08)	0.76 (0.58-1.00)	0.61 (0.47-0.81)	0.50 (0.37-0.70)	(<.001)
Beyond high school	5.7 (0.1)*	1 [Ref]	0.52 (0.40-0.69)	0.56 (0.39-0.82)	0.53 (0.35-0.80)	0.44 (0.30-0.65)	(.001)
Smoking status							.003
Current smoker	3.0 (0.1)*	1 [Ref]	0.56 (0.43-0.73)	0.63 (0.48-0.83)	0.38 (0.23-0.61)	0.55 (0.35-0.86)	(.004)
Former smoker	5.2 (0.1)	1 [Ref]	1.05 (0.81-1.36)	0.85 (0.64-1.12)	0.82 (0.63-1.06)	0.79 (0.57-1.08)	(.035)
Never smoker	5.7 (0.1)	1 [Ref]	0.87 (0.69-1.10)	0.87 (0.72-1.05)	0.82 (0.64-1.07)	0.68 (0.54-0.87)	(.006)
Alcohol consumption							.81
Consumed alcohol	4.5 (0.1)*	1 [Ref]	0.89 (0.71-1.11)	0.83 (0.65-1.06)	0.73 (0.52-1.01)	0.68 (0.47-0.96)	(.03)
Did not consume alcohol	5.1 (0.1)	1 [Ref]	0.70 (0.60-0.82)	0.70 (0.60-0.80)	0.63 (0.52-0.77)	0.58 (0.48-0.70)	(<.001)
Leisure-time physical activity							.85
Any	4.9 (0.1)*	1 [Ref]	0.76 (0.66-0.88)	0.71 (0.62-0.82)	0.65 (0.52-0.81)	0.60 (0.48-0.74)	(<.001)
None	4.4 (0.1)	1 [Ref]	0.79 (0.61-1.02)	0.83 (0.65-1.06)	0.72 (0.55-0.95)	0.73 (0.52-1.02)	(.06)
BMI							.81
<25.0	5.3 (0.1)*	1 [Ref]	0.73 (0.61-0.88)	0.63 (0.48-0.83)	0.62 (0.44-0.86)	0.54 (0.41-0.71)	(<.001)
25.0-29.9	4.8 (0.1)**	1 [Ref]	0.88 (0.68-1.13)	0.87 (0.66-1.13)	0.71 (0.52-0.97)	0.78 (0.54-1.14)	(<.001)
≥30.0	3.7 (0.1)	1 [Ref]	0.75 (0.58-0.97)	0.76 (0.58-0.98)	0.70 (0.52-0.94)	0.52 (0.36-0.75)	(<.001)
Systolic blood pressure, mm Hg							.008
≥130	4.8 (0.1)	1 [Ref]	0.84 (0.72-0.98)	0.89 (0.76-1.05)	0.76 (0.62-0.93)	0.74 (0.59-0.92)	(.009)
<130	4.8 (0.1)	1 [Ref]	0.68 (0.56-0.82)	0.57 (0.46-0.70)	0.55 (0.41-0.74)	0.47 (0.35-0.64)	(<.001)
HDL-C							.54
Low[d]	4.2 (0.1)*	1 [Ref]	0.89 (0.72-1.10)	0.82 (0.66-1.02)	0.73 (0.55-0.97)	0.78 (0.52-1.15)	(.11)
Normal	5.1 (0.1)	1 [Ref]	0.71 (0.59-0.87)	0.72 (0.59-0.87)	0.63 (0.50-0.78)	0.55 (0.43-0.69)	(<.001)
Non–HDL-C, mg/dL							.23
≥160	5.1 (0.1)*	1 [Ref]	0.69 (0.58-0.82)	0.74 (0.62-0.89)	0.65 (0.52-0.82)	0.60 (0.47-0.77)	(<.001)
<160	4.6 (0.1)	1 [Ref]	0.85 (0.71-1.03)	0.71 (0.60-0.83)	0.67 (0.53-0.84)	0.62 (0.47-0.81)	(<.001)
Serum β-carotene concentration, μg/dL							.50
≥20	8.2 (0.1)*	1 [Ref]	0.74 (0.53-1.04)	0.83 (0.60-1.16)	0.73 (0.54-0.98)	0.64 (0.47-0.88)	(.006)
<20	2.9 (0.1)	1 [Ref]	0.80 (0.69-0.92)	0.72 (0.62-0.85)	0.62 (0.47-0.81)	0.68 (0.32-1.44)	(.18)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; Ref, reference value.

SI conversion factors: To convert α- and β-carotene values to micromoles per liter, multiply by 0.01863; to convert cholesterol values to millimoles per liter, multiply by 0.0259.

[a] Data are given as RR (95% CI). Age was the time scale in the Cox proportional hazard regression analyses. Estimates of RRs (hazard ratios) and their 95% CIs were adjusted for demographic characteristics, lifestyle habits, and health risk factors presented in Table 2.

[b] Within each level of the stratification variables, the mean value with an asterisk or a double asterisk is significantly different from the mean value(s) of other level(s), $P = .01$ (equivalent to $P < .05$ after Bonferroni correction for multiple comparisons); *t* tests were used to test for equality.

[c] For each stratification variable, *P* values were based on results of Wald χ^2 tests for the interaction between the serum α-carotene concentration and each stratification variable. *P* values in parentheses were based on results of *t* tests for the linear trend in RRs within each level of stratification variable.

[d] Defined as less than 40 mg/dL among men and less than 50 mg/dL among women.

Although α-carotene is chemically similar to β-carotene, in vivo study results suggest that α-carotene is about 10 times more effective than β-carotene in inhibiting the proliferation of human neuroblastoma cells[34]; that α-carotene, but not β-carotene, has a potent inhibitory effect against liver carcinogenesis[35]; and that α-carotene is more effective than β-carotene in inhibiting the tumor-promoting action of glycerol in lung carcinogenesis and skin tumor promotion.[35] Moreover, results from a population-based case-control study of the association between the consumption of fruits and vegetables and risk of lung cancer suggest that consumption of yellow-orange (carrots, sweet potatoes or pumpkin, and winter squash) and dark-green (broccoli, green beans, green peas, spinach, turnip greens, collards, and leaf lettuce) vegetables, which have a high α-carotene content, was more strongly associated with a decreased

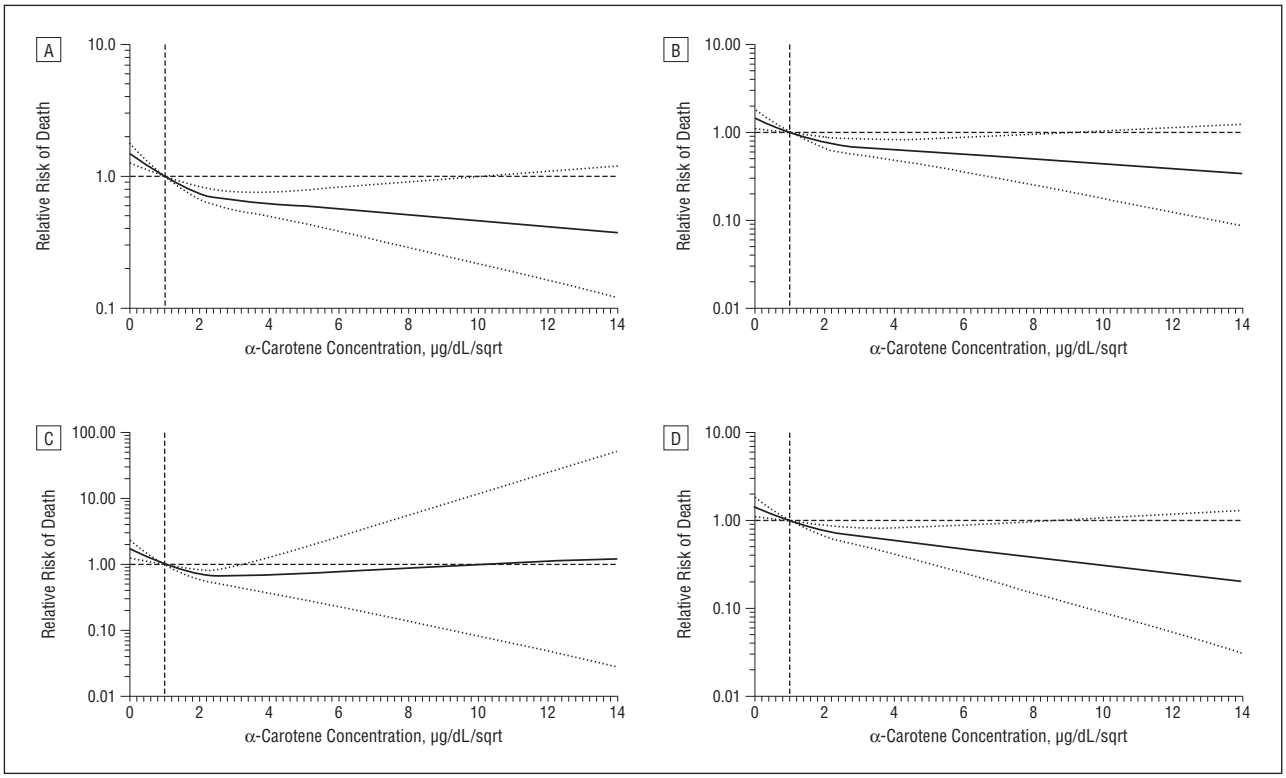

Figure. Estimated relative risk of death from all causes (A), cardiovascular disease (B), cancer (C), and all other causes (D) among US adults 20 years and older by level of serum α-carotene concentration compared with risk among those with a serum α-carotene concentration of 1 μg/dL (to convert to micromoles per liter, multiply by 0.01863) (approximately 22nd percentile, vertical line): Third National Health and Nutrition Examination Survey Follow-up Study, 1988-2006. The solid line indicates the fitted relationship between the relative risk for death and the serum α-carotene concentrations with a 3-knot spline; dashed lines, the 95% confidence intervals surrounding the estimates; sqrt, square root transformation.

risk of lung cancer than was consumption of all other types of vegetables.[36] In our population-based cohort study, serum α-carotene concentrations were more strongly associated with risk of death from cancer of aerodigestive track than risk of death from lung cancer. Also, the association between serum α-carotene concentrations and lung cancer appeared to be confounded and/or modified by smoking status. Future research is warranted to elucidate the mechanisms underlying the differential effects of α-carotene and β-carotene against cancer and CVD.

Because current antioxidant supplements or food additives contain little if any α-carotene,[37,38] we assumed that members of our study cohort obtained α-carotene primarily from consumption of fruits and vegetables. Studies have shown that plasma α-carotene is highly correlated with total consumption of fruits and vegetables, especially carrots and other root vegetables,[39,40] and that α-carotene coexists with β-carotene in fruits and vegetables, particularly in carrots.[41] Results from the Framingham Heart Study showed that participants obtained more than 75% of their dietary α-carotene from carrots.[42] Taken together, the results of these studies indicate that serum α-carotene concentrations can serve as a reliable and useful biomarker for fruit and vegetable consumption. The inverse relationship that we found between serum α-carotene concentrations and risk of death from various causes adds further support to previous findings that fruit and vegetable consumption is beneficial to people's health.[4-10]

We also found that although high serum concentrations of α-carotene may be needed to protect against death from CVD, a very high concentration of α-carotene may be less effective than lower concentrations against death from cancer. Previous study findings have similarly suggested that β-carotene seems to lose its antioxidant effects at very high levels.[43] This possible loss of protective effect at extremely high serum concentrations indicates a need for studies to determine the threshold serum concentration at which α-carotene produces positive health effects in the general population and the fruit and vegetable consumption necessary to reach this threshold concentration. Currently, the US Department of Agriculture's food pyramid recommends the consumption of 2 to 4 servings of fruits and 3 to 5 servings of vegetables daily.[43]

Our results are subject to 3 potential limitations. First, because only a single measurement of serum α-carotene concentration at baseline was available, bias from regression toward the mean may have led us to underestimate the strength for the association between serum α-carotene concentrations and risk of death. Second, possible misclassifications in the underlying cause of death of deceased study participants, particularly the misclassification of diabetes,[44] may also have biased our estimates for the association between α-carotene concentrations and risk of death toward null. Finally, our results may be subject to residual confounding owing to unmeasured biomarkers or health behaviors. It is possible that serum α-carotene concentrations may act as an in-

dicator of multiple interactive forces that are more proximal to the mortality outcomes of interest in our study, providing insights linking intake of vegetables and fruits to lower mortality risk.

In conclusion, our findings, based on data from a large representative sample of US adults, showed that serum α-carotene concentrations were inversely associated with the risk of death from all causes and death from CVD, cancer, and all causes other than CVD and cancer. They also showed that the inverse association was independent of demographic characteristics, lifestyle habits, and traditional health risk factors. Our results, if replicated in other studies and populations, suggest a need for clinical research into the health benefits of serum α-carotene.

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