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Fruit, Vegetable, and Antioxidant Intake and All-Cause, Cancer, and Cardiovascular Disease Mortality in a Community-dwelling Population in Washington County, Maryland

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Higher intake of fruits, vegetables, and antioxidants may help protect against oxidative damage, thus lowering cancer and cardiovascular disease risk. This Washington County, Maryland, prospective study examined the association of fruit, vegetable, and antioxidant intake with all-cause, cancer, and cardiovascular disease death. CLUE participants who donated a blood sample in 1974 and 1989 and completed a food frequency questionnaire in 1989 ($N = 6,151$) were included in the analysis. Participants were followed to date of death or January 1, 2002. Compared with those in the bottom fifth, participants in the highest fifth of fruit and vegetable intake had a lower risk of all-cause (cases = 910; hazard ratio (HR) = 0.63, 95% confidence interval (CI): 0.51, 0.78; p-trend = 0.0004), cancer (cases = 307; HR = 0.65, 95% CI: 0.45, 0.93; p-trend = 0.08), and cardiovascular disease (cases = 225; HR = 0.76, 95% CI: 0.54, 1.06; p-trend = 0.15) mortality. Higher intake of cruciferous vegetables was associated with lower risk of all-cause mortality (HR = 0.74, 95% CI: 0.60, 0.91; p-trend = 0.04). No statistically significant associations were observed between dietary vitamin C, vitamin E, and beta-carotene intake and mortality. Overall, greater intake of fruits and vegetables was associated with lower risk of all-cause, cancer, and cardiovascular disease death. These findings support the general health recommendation to consume multiple servings of fruits and vegetables (5–9/day).

antioxidants; cardiovascular diseases; diet; fruit; mortality; neoplasms; vegetables

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio.

Because cardiovascular disease and cancer are the two leading causes of death in the United States (1), factors that can reduce their toll may lead to important improvements in both health and longevity. Both diseases have risk factors in common; important among them are cigarette smoking, obesity, and suboptimal diet (2).

Emphasis on the benefits of high intakes of fruits and vegetables is based on 1) the usually tacit assumption that such diets are very likely to be low in fatty foods, 2) the many observational studies reporting the association of high intakes with decreased incidence rates of cardiovascular disease and cancer (3–11), and 3) the presumptive protection afforded by the various antioxidants in many fruits and vegetables (6, 12–18). Increased intake of fruits and vegetables may thus provide a defense against oxidative stress, a potential target for preventing cancer and cardiovascular disease. Overall, the studies examining intakes of fruits and vegetables have observed lower rates of all-cause, cancer, and cardiovascular disease mortality (3–12, 19).

Whether particular antioxidants, such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), and beta-carotene, may underlie these associations has been examined. In cohort studies, higher intake of vitamin C has been associated with lower risk of all-cause mortality (6, 20–23), whereas the results have been either null (12, 20, 24) or lower (6, 21, 23, 25) regarding the risk of cancer or cardiovascular disease mortality associated with greater intake of vitamin C. In general, cohort studies have observed

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decreased risk of deaths from cancer or cardiovascular disease with higher intake of vitamin E (6, 12, 16–18, 23, 26–34). In cohort studies, high intake of beta-carotene has been associated with a lower incidence of and mortality from cancer and cardiovascular disease (27, 35). In contrast, randomized trials, such as the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), Beta-Carotene and Retinol Efficacy Trial (CARET), and Cambridge Heart Antioxidant Study (CHAOS) (33, 36, 37), have reported increases in cancer incidence (i.e., lung) and mortality (i.e., all-cause, lung cancer, cardiovascular deaths) in the supplement arms of these trials, suggesting potential harmful effects of supplementing with high-dose, single-antioxidant supplements. Hypotheses to explain this discrepancy include that high doses used during the trial may have resulted in pro-oxidant activity and residual confounding in cohort studies due to imperfect classification of factors such as smoking that may have biased the results (33, 37, 38).

Studies have been conducted in special populations (i.e., health-conscious, older adults) and in European countries to specifically assess the association of fruit and vegetable intake with all-cause, cancer, and cardiovascular disease mortality. Rarely have studies assessed all three mortality outcomes together, and few have been based on community populations in the United States (6). Because of the commonality of many of the risk factors for these diseases, assessment of these associations together is needed. We investigated the relation of intakes of fruits and vegetables and of dietary ascorbic acid, beta-carotene, and alpha-tocopherol with all-cause, cardiovascular disease, and cancer mortality in the community-based CLUE cohort studies in Washington County, Maryland. Since the effect of antioxidants on mortality may vary by oxidative burden, we also considered whether these associations differed by cigarette smoking and body mass index, both sources of oxidative stress.

MATERIALS AND METHODS

Population

This study was conducted within the Odyssey Cohort, which included men and women who volunteered for two cohort studies (CLUE I and CLUE II) established in 1974 and 1989 in Washington County, Maryland. The two CLUE studies drew their names from the campaign slogan, "Give Us a Clue to Cancer and Heart Disease." Forming the Odyssey Cohort are 8,394 residents who participated in both studies by donating a blood sample at both time points. In 1989, 7,217 Odyssey participants returned the food frequency questionnaire (FFQ), of whom 6,563 adequately completed the modified short Block FFQ (39). Inadequate completion was defined as reporting a total energy intake outside the range of 800–5,000 kcal per day for men and 500–3,500 kcal per day for women, leaving more than half of the items blank, or reporting eating fewer than three foods per day. In addition, for compatibility with a companion study of genetic factors in Odyssey, 412 participants were also excluded because a blood sample was no longer available, DNA amplification did not occur, or results of genotyping were ambiguous. These exclusions left 6,151 persons for this analysis.

Exposure assessment

Demographic characteristics (e.g., age, race, marital status, and education) and brief medical history information (e.g., smoking history, resting blood pressure) were collected during administration of the baseline questionnaires in 1974 and 1989. In addition, the 1989 questionnaire gathered information on current height and weight. Plasma cholesterol concentration was measured for all participants when blood was collected in 1989. In the 1996, 1998, and 2000 follow-up questionnaires, participants reported on any medical history of cancer, cardiovascular disease, and other major illnesses and the corresponding year in which the disease was diagnosed.

Usual frequency of consumption of total fruits, total vegetables, cruciferous vegetables, ascorbic acid, alpha-tocopherol, and beta-carotene over the past year was estimated from a 61-item, modified Block FFQ completed in 1989 (40). Use of multivitamins and single supplements, including vitamin C, vitamin E, and vitamin A, was also ascertained. For each particular food item, participants selected from categories of "never" to "2+ per day" for frequency of intake and "small," "medium," and "large" for portion size. Fruit questions referred to apples, applesauce, pears, cantaloupes, oranges, grapefruit, and any other fruit such as bananas and fruit cocktail. Tomatoes, broccoli, spinach, mustard greens, turnip greens, collards, cabbage, carrots, mixed vegetables, green salads, sweet potatoes, yams, and any other vegetables such as green beans, corn, and peas were captured as vegetables on this FFQ. Fruit and vegetable intake was calculated by summing the product of the portion size (age and gender specific) of all fruit and vegetable items and the daily frequency of intake. A second fruit and vegetable summary variable was created that additionally included juices such as orange and other fruits. Potatoes were excluded from both summary variables. The summary measure of cruciferous vegetables included broccoli, mustard greens, and turnip greens. Intake of vitamin E, vitamin C, and beta-carotene from the diet was calculated by multiplying the portion size, the daily frequency of intake, and the content of the antioxidant per serving using the Diet Nut version 3.0 program (40).

Outcome assessment

Participants were followed regarding vital status from date of blood collection in 1989 to January 1, 2002. Cancer deaths (*International Classification of Diseases*, Ninth Revision, codes 140–239) and cardiovascular disease deaths (*International Classification of Diseases*, Ninth Revision, codes 390–459) were ascertained from the underlying cause on Maryland State death certificates as coded by state nosologists. Of the 910 participants confirmed to be deceased, 307 (33.7 percent) deaths were due to cancer, 378 (41.5 percent) to cardiovascular disease, and 225 (24.7 percent) to other causes. The majority of cancer deaths were due to lung (25 percent), colorectal (11 percent), prostate (7 percent), and breast (7 percent) cancers. Myocardial infarction (35 percent) was the most common cause of cardiovascular disease mortality. Extensive searches were conducted to determine vital status on all participants, including credit tracing and a Social Security Administration search. Approximately 3 percent (n = 199) were lost to follow-up. Since these participants were not found during the mortality searches, they were included in the follow-up and were administratively censored on January 1, 2002.

Statistical analyses

Intakes of dietary antioxidant nutrients were analyzed, separately for males and females, by using two different estimates, one not energy adjusted by the residual method and one adjusted for energy intake by residual analysis (41). The distribution of intakes of fruits and vegetables, cruciferous vegetables, and antioxidant nutrients was divided into fifths, separately for males and females, and was then pooled over gender, such that the lowest fifth for males and the lowest fifth for females were combined. In addition, intakes of fruits and vegetables and of cruciferous vegetables were categorized into below and at or above 2.30 (overall median) servings per day and 0.17 (overall median) servings per day, respectively.

Directly age-standardized demographic and health characteristics were compared across fifths of the distribution of daily servings of fruits and vegetables. Cox proportional hazards regression analysis was used to estimate hazards ratios for all-cause, cancer, and cardiovascular disease death, adjusting for age. For antioxidant nutrients, three models were used. Two of the models (one age adjusted and one multivariate) included energy-adjusted antioxidant nutrient values from residual analysis in the model, while the other model included an antioxidant nutrient value that was not energy adjusted by using the residual method. Estimates were further adjusted for smoking status (never, former, current; never, former, current <10 cigarettes/day, 10–20 cigarettes/day, >20 cigarettes/day) and other potentially confounding factors (e.g., plasma cholesterol concentration, body mass index) in the multivariate analysis. Marital status and education did not significantly alter the risk estimates and thus were not included in the multivariate models. Indicator terms for fifths of the distribution of fruit and vegetable, cruciferous vegetable, and antioxidant nutrient intake were entered into the model. Ordinal terms for the fifths of distribution of fruit and vegetable, cruciferous vegetable, and antioxidant nutrient intake were included in the model to test for trend, the coefficients for which were evaluated by using the Wald test. Additionally, analyses were conducted to compare the bottom fifth with the top four fifths; median values included in Cox proportional hazards regression analysis were used to assess a threshold effect.

Analyses were conducted to evaluate multiplicative interaction in which the association between the nutrient or food item and mortality was stratified by gender, cigarette smoking (ever, never smoking), and body mass index (<25 kg/m^2, ≥25 kg/m^2). When the analyses were stratified by smoking status and body mass index, thirds of fruit and vegetable and of nutrient intake were used because of smaller numbers in each cell. To test for multiplicative interaction, the main effect terms for fruit and vegetable and antioxidant intake and the stratification factor, along with the cross-product term, were included in the model. The coefficient for the cross-product term was evaluated by the Wald test. All statistical analyses were performed by using SAS software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

At the start of follow-up in 1989, participants ranged in age from 30 to 93 years, 63 percent were female, and 13 percent were current smokers. Reflecting the demographics of Washington County in terms of race, 99 percent were White. Table 1 reports the age-standardized characteristics of the population according to intake of fruits and vegetables. Participants who consumed higher amounts of fruits and vegetables were older, had completed more years of education, and were less likely to have ever smoked. Those who consumed the lowest amounts of fruits and vegetables were less likely to be treated for hypercholesterolemia. Overall, mean intakes of fruits, vegetables, and cruciferous vegetables were 1.15 servings per day, 1.53 servings per day, and 0.25 servings per day, respectively. Mean intakes of dietary vitamin C, vitamin E, and beta-carotene for the cohort were 102.6 mg per day, 8.4 mg per day, and 2,096 μg per day, while total (diet and supplement) means were 225.2 mg per day, 20.8 mg per day, and 2,444 μg per day, respectively.

Table 2 presents the hazard ratios for all-cause mortality according to fifths of the distribution of intake of fruits and vegetables, cruciferous vegetables, vitamin C, vitamin E, and beta-carotene. Compared with those in the bottom fifth, participants in the top fifth of fruit and vegetable intake had a lower risk of all-cause mortality (hazard ratio (HR) = 0.58, 95 percent confidence interval (CI): 0.47, 0.71; p-trend < 0.0001). This association was slightly attenuated after multivariate adjustment (HR = 0.63, 95 percent CI: 0.51, 0.78; p-trend = 0.0004). Throughout the Results section, multivariate-adjusted results are presented. Because there seemed to be a threshold effect, the combined top four fifths were compared with the lowest fifth of intake (HR = 0.82, 95 percent CI: 0.75, 0.90). Analogous to the results for total fruits and vegetables, a lower risk of all-cause mortality was also seen when we compared the highest with the lowest fifths of cruciferous vegetables (HR = 0.78, 95 percent CI: 0.64, 0.96; p-trend = 0.13) and of energy-adjusted beta-carotene (HR = 0.81, 95 percent CI: 0.66, 1.00; p-trend = 0.19) in the multivariate models. A protective association was observed when we compared the top four fifths with the bottom fifth of intake of cruciferous vegetables (HR = 0.32, 95 percent CI: 0.13, 0.80), but not for individual nutrients, vitamin C, and vitamin E (not shown). Only slight differences in results were observed with and without adjustment for energy for the analyses of antioxidants. Throughout the Results section, energy-adjusted antioxidant results are presented. Similar estimates were observed when juice intake was included in the summation of fruits and vegetables, when supplement information was included in the anti-

TABLE 1. Age-standardized baseline characteristics of the study cohort according to fifths of fruit and vegetable intake, Washington County, Maryland, 1989*

Characteristic	Fifth of intake				
	1	2	3	4	5
No. of participants	1,229	1,231	1,230	1,231	1,230
Mean age in years (SD†)	52.2 (13.4)	54.7 (12.9)	56.6 (12.5)	58.6 (12.4)	59.4 (11.8)
Female (%)	61.9	62.7	63.1	62.7	62.7
Married (%)	74.0	79.9	78.9	78.3	77.3
Mean no. of years of education	11.7	12.1	12.6	12.6	12.7
Smoking status (%)					
Never	43.5	47.4	50.2	53.9	51.8
Former	36.0	36.7	36.8	36.2	41.0
Current	20.5	15.9	13.0	9.9	7.2
Ever diagnosed with cancer (%)‡	13.81	20.97	22.51	23.53	19.18
Ever diagnosed with diabetes (%)‡	12.45	19.78	19.41	21.98	26.37
Ever had a myocardial infarction (%)‡	17.96	19.42	16.99	20.39	20.39
Ever had a stroke (%)‡	20.69	25.86	10.34	18.97	24.14
Mean systolic blood pressure (mmHg)	128.8	129.3	129.1	128.9	129.1
Mean diastolic blood pressure (mmHg)	79.3	79.6	79.8	79.6	79.5
Treatment for hypertension					
Yes (%)	25.2	28.1	28.7	26.6	28.2
Mean cholesterol concentration (mg/dl)	211.3	213.7	211.2	209.7	209.5
Treatment for elevated cholesterol					
Yes (%)	5.0	5.4	4.5	6.4	8.0
Body mass index in kg/m^2 (%)					
25.0–29.9	37.2	41.6	38.6	41.7	38.2
≥30.0	18.3	18.2	17.8	17.7	18.6
Multivitamin use (%)	23.5	26.1	26.1	26.9	31.2
Vitamin A use (%)	10.0	11.0	12.3	15.1	19.0
Vitamin C use (%)	39.1	41.3	45.7	51.5	54.5
Vitamin E use (%)	27.7	32.9	35.6	39.0	40.3
Mean fat intake (g/day)	63.9	60.9	58.3	56.6	52.4
Mean saturated fat intake (g/day)	22.3	20.9	19.6	18.8	16.8
Mean cholesterol intake (mg/day)	210.5	196.2	195.0	186.0	171.8
Mean alcohol intake (g/day)	4.3	3.7	4.4	3.8	3.3
Meat (servings/day)§	0.25	0.26	0.27	0.27	0.25

* Directly standardized to the age distribution of the analytic cohort.
† SD, standard deviation.
‡ Positive response to any or all on the 1996, 1998, or 2000 follow-up questionnaires for ever having or being diagnosed with cancer, diabetes, myocardial infarction, or stroke prior to 1989.
§ A summary measure of beef and hamburger consumption.

oxidant nutrient measure, or when results were stratified by gender and body mass index (data not shown).

In table 3, hazard ratios for cancer mortality are presented according to fifths of the distribution of fruit and vegetable, cruciferous vegetable, and nutrient intake. Compared with participants in the lowest fifth, those in the highest fifth of fruit and vegetable intake had a lower risk of cancer death (HR = 0.65, 95 percent CI: 0.45, 0.93; p-trend = 0.08). All other associations for cancer mortality examining fifths of intake of cruciferous vegetables, vitamin C, vitamin E, and

TABLE 2. Multivariate hazard ratios for all-cause mortality by fifths of intake of fruits and vegetables and of dietary antioxidant nutrients, Washington County, Maryland, 1989

	Fifth of intake					*p* trend
	1	2	3	4	5	
Fruits/vegetables						
Median servings/day	0.87	1.61	2.31	3.21	4.89	
No. of deaths	187	149	184	197	193	
No. of person-years	14,968	15,149	15,055	14,955	15,015	
HR* (95% CI*)†	1.00	0.66 (0.53, 0.81)	0.70 (0.57, 0.86)	0.65 (0.53, 0.79)	0.58 (0.47, 0.71)	<0.0001
HR (95% CI)‡	1.00	0.68 (0.55, 0.84)	0.74 (0.60, 0.90)	0.71 (0.58, 0.87)	0.63 (0.51, 0.78)	0.0004
Cruciferous vegetables						
Median servings/day	0.03	0.12	0.17	0.27	0.53	
No. of deaths	175	140	188	197	210	
No. of person-years	13,446	13,155	17,466	15,541	15,534	
HR (95% CI)†	1.00	0.75 (0.60, 0.94)	0.77 (0.62, 0.94)	0.84 (0.68, 1.03)	0.74 (0.60, 0.91)	0.04
HR (95% CI)‡	1.00	0.76 (0.61, 0.96)	0.82 (0.67, 1.01)	0.88 (0.71, 1.08)	0.78 (0.64, 0.96)	0.13
Vitamin C§						
Median mg/day	39.4	66.1	94.2	124.1	175.6	
No. of deaths	165	143	175	195	232	
No. of person-years	15,173	15,163	15,074	15,021	14,711	
HR (95% CI)†	1.00	0.76 (0.61, 0.95)	0.78 (0.63, 0.97)	0.75 (0.61, 0.92)	0.88 (0.72, 1.07)	0.38
HR (95% CI)‡	1.00	0.92 (0.75, 1.15)	0.78 (0.63, 0.97)	0.88 (0.71, 1.09)	0.95 (0.77, 1.17)	0.61
HR (95% CI)¶	1.00	0.78 (0.62, 0.98)	0.80 (0.65, 0.99)	0.79 (0.64, 0.97)	0.95 (0.77, 1.17)	0.92
Vitamin E§						
Median mg/day	5.1	6.2	7.0	8.2	12.4	
No. of deaths	186	171	156	178	219	
No. of person-years	14,966	15,127	15,150	15,142	14,756	
HR (95% CI)†	1.00	0.92 (0.75, 1.13)	0.79 (0.64, 0.97)	0.86 (0.70, 1.06)	0.94 (0.77, 1.14)	0.47
HR (95% CI)‡	1.00	0.96 (0.78, 1.19)	1.04 (0.84, 1.28)	1.00 (0.79, 1.26)	0.99 (0.78, 1.27)	0.95
HR (95% CI)¶	1.00	0.95 (0.77, 1.17)	0.80 (0.64, 0.99)	0.89 (0.72, 1.09)	0.98 (0.80, 1.19)	0.74
Beta-carotene§						
Median µg/day	679.2	1,198.9	1,697.0	2,412.1	3,884.8	
No. of deaths	159	155	189	200	207	
No. of person-years	15,119	15,204	14,947	14,937	14,935	
HR (95% CI)†	1.00	0.80 (0.64, 1.00)	0.88 (0.72, 1.09)	0.84 (0.68, 1.04)	0.81 (0.66, 1.00)	0.13
HR (95% CI)‡	1.00	0.87 (0.70, 1.07)	0.91 (0.73, 1.12)	0.79 (0.63, 0.98)	0.86 (0.69, 1.06)	0.11
HR (95% CI)¶	1.00	0.80 (0.64, 1.00)	0.89 (0.72, 1.11)	0.87 (0.71, 1.08)	0.81 (0.66, 1.00)	0.19

* HR, hazard ratio; CI, confidence interval.

† Estimated from Cox proportional hazards regression analysis, adjusting for age and energy. Nutrients were energy adjusted by using the residual method.

‡ Estimated from Cox proportional hazards regression analysis, adjusting for age, smoking status, body mass index, cholesterol concentration, and energy. Nutrients were not energy adjusted by using the residual method.

§ The median values for the lowest and highest fifths of total (dietary and supplemental) intakes of vitamin C, vitamin E, and beta-carotene were 47.2 and 218.3 mg/day, 6.8 and 18.6 mg/day, and 775.2 and 4,316.0 µg/day, respectively.

¶ Estimated from Cox proportional hazards regression analysis, adjusting for age, smoking status, body mass index, cholesterol concentration, and energy. Nutrients were energy adjusted by using the residual method.

beta-carotene were not statistically significant, and no trends across fifths of intake were observed. When we compared the highest four fifths of intake with the bottom fifth of fruit and vegetable (HR = 0.85, 95 percent CI: 0.73, 0.99) and cruciferous vegetable (HR = 0.25, 95 percent CI: 0.05, 1.14) intake, the risk of cancer mortality was lower. When stratified by gender and body mass index, results were similar to the overall findings (data not shown).

TABLE 3. Multivariate hazard ratios for cancer mortality by fifths of intake of fruits and vegetables and of dietary antioxidant nutrients, Washington County, Maryland, 1989

	Fifth of intake					*p* trend
	1	2	3	4	5	
Fruits/vegetables						
No. of deaths	63	53	60	70	61	
No. of person-years	14,968	15,149	15,055	14,955	15,015	
HR* (95% CI*)†	1.00	0.71 (0.49, 1.02)	0.71 (0.50, 1.01)	0.73 (0.52, 1.03)	0.58 (0.40, 0.83)	0.01
HR (95% CI)‡	1.00	0.73 (0.50, 1.05)	0.75 (0.52, 1.06)	0.82 (0.58, 1.15)	0.65 (0.45, 0.93)	0.08
Cruciferous vegetables						
No. of deaths	62	47	58	70	70	
No. of person-years	13,446	13,155	17,466	15,541	15,534	
HR (95% CI)†	1.00	0.72 (0.49, 1.05)	0.67 (0.47, 0.96)	0.84 (0.60, 1.19)	0.73 (0.52, 1.03)	0.26
HR (95% CI)‡	1.00	0.73 (0.50, 1.07)	0.71 (0.50, 1.02)	0.89 (0.63, 1.25)	0.77 (0.55, 1.10)	0.43
Vitamin C						
No. of deaths	64	46	56	66	75	
No. of person-years	15,173	15,163	15,074	15,021	14,711	
HR (95% CI)†	1.00	0.65 (0.44, 0.95)	0.69 (0.48, 0.98)	0.72 (0.51, 1.02)	0.82 (0.58, 1.15)	0.52
HR (95% CI)‡	1.00	0.96 (0.67, 1.37)	0.73 (0.51, 1.06)	0.85 (0.59, 1.22)	0.91 (0.64, 1.31)	0.50
HR (95% CI)§	1.00	0.67 (0.46, 0.98)	0.71 (0.49, 1.02)	0.77 (0.54, 1.09)	0.91 (0.64, 1.28)	0.93
Vitamin E						
No. of deaths	67	56	47	64	73	
No. of person-years	14,966	15,127	15,150	15,142	14,756	
HR (95% CI)†	1.00	0.83 (0.58, 1.18)	0.66 (0.45, 0.96)	0.85 (0.60, 1.20)	0.91 (0.65, 1.27)	0.71
HR (95% CI)‡	1.00	0.94 (0.66, 1.35)	0.95 (0.65, 1.38)	1.02 (0.69, 1.52)	1.07 (0.71, 1.63)	0.66
HR (95% CI)§	1.00	0.86 (0.60, 1.22)	0.68 (0.47, 0.99)	0.89 (0.63, 1.26)	0.96 (0.69, 1.34)	0.95
Beta-carotene						
No. of deaths	66	48	64	57	72	
No. of person-years	15,119	15,204	14,947	14,937	14,935	
HR (95% CI)†	1.00	0.62 (0.43, 0.91)	0.76 (0.54, 1.08)	0.63 (0.44, 0.90)	0.75 (0.53, 1.05)	0.17
HR (95% CI)‡	1.00	0.94 (0.66, 1.34)	0.67 (0.46, 0.99)	0.88 (0.61, 1.25)	0.83 (0.58, 1.20)	0.31
HR (95% CI)§	1.00	0.62 (0.43, 0.91)	0.78 (0.55, 1.10)	0.66 (0.46, 0.94)	0.77 (0.55, 1.08)	0.26

* HR, hazard ratio; CI, confidence interval.

† Estimated from Cox proportional hazards regression analysis, adjusting for age and energy. Nutrients were energy adjusted by using the residual method.

‡ Estimated from Cox proportional hazards regression analysis, adjusting for age, smoking status, body mass index, cholesterol concentration, and energy. Nutrients were not energy adjusted by using the residual method.

§ Estimated from Cox proportional hazards regression analysis, adjusting for age, smoking status, body mass index, cholesterol concentration, and energy. Nutrients were energy adjusted by using the residual method.

Table 4 shows hazard ratios for cardiovascular disease mortality according to fifths of the distribution of intake of fruits and vegetables, cruciferous vegetables, and the dietary nutrients vitamin C, vitamin E, and beta-carotene. When we examined the fifths of distribution, risk of cardiovascular disease mortality was slightly lower for participants in the top fifth of fruit and vegetable (HR = 0.76, 95 percent CI: 0.54, 1.06) and cruciferous vegetable (HR = 0.89, 95 percent CI: 0.64, 1.25) intake compared with the bottom fifth. In contrast, we found no association of vitamin C, vitamin E, or beta-carotene with cardiovascular disease mortality. No associations were present when comparing the top four fifths of intake of fruits and vegetables, cruciferous vegetables, vitamin C, vitamin E, and beta-carotene with the bottom fifth of intake (not shown). When stratified by gender and body mass index, results were similar to the overall findings (data not shown).

A further analysis was conducted to evaluate the association of mortality with the recommended daily consumption of five or more servings per day of fruits and vegetables for good health. In this cohort, only 9 percent reported five or more servings per day of fruits and vegetables. The risks of all-cause (HR = 0.80, 95 percent CI: 0.64, 1.00) and cancer (HR = 0.77, 95 percent CI: 0.51, 1.15) mortality were lower

TABLE 4. Multivariate hazard ratios for cardiovascular disease mortality by fifths of intake of fruits and vegetables and of dietary antioxidant nutrients, Washington County, Maryland, 1989

	Fifth of intake					*p* trend
	1	2	3	4	5	
Fruits/vegetables						
No. of deaths	67	62	80	82	87	
No. of person-years	14,968	15,149	15,055	14,955	15,015	
HR* (95% CI*)†	1.00	0.76 (0.54, 1.08)	0.83 (0.60, 1.15)	0.74 (0.53, 1.02)	0.71 (0.51, 0.98)	0.07
HR (95% CI)‡	1.00	0.80 (0.56, 1.12)	0.86 (0.62, 1.20)	0.79 (0.56, 1.09)	0.76 (0.54, 1.06)	0.15
Cruciferous vegetables						
No. of deaths	62	62	91	78	85	
No. of person-years	13,446	13,155	17,466	15,541	15,534	
HR (95% CI)†	1.00	0.95 (0.67, 1.35)	1.06 (0.77, 1.46)	0.94 (0.67, 1.32)	0.83 (0.60, 1.16)	0.27
HR (95% CI)‡	1.00	0.99 (0.70, 1.43)	1.17 (0.84, 1.62)	1.03 (0.74, 1.45)	0.89 (0.64, 1.25)	0.51
Vitamin C						
No. of deaths	59	61	70	82	106	
No. of person-years	15,173	15,163	15,074	15,021	14,711	
HR (95% CI)†	1.00	0.90 (0.63, 1.29)	0.84 (0.60, 1.20)	0.83 (0.60, 1.17)	1.05 (0.76, 1.50)	0.73
HR (95% CI)‡	1.00	1.03 (0.74, 1.44)	0.74 (0.52, 1.05)	0.98 (0.70, 1.36)	1.04 (0.74, 1.45)	0.87
HR (95% CI)§	1.00	0.92 (0.64, 1.31)	0.85 (0.60, 1.21)	0.84 (0.60, 1.19)	1.10 (0.79, 1.52)	0.57
Vitamin E						
No. of deaths	73	69	66	75	95	
No. of person-years	14,966	15,127	15,150	15,142	14,756	
HR (95% CI)†	1.00	0.95 (0.69, 1.32)	0.86 (0.62, 1.20)	0.95(0.68, 1.31)	1.01 (0.74, 1.37)	0.91
HR (95% CI)‡	1.00	1.08 (0.79, 1.49)	1.12 (0.80, 1.55)	1.08 (0.75, 1.55)	1.04 (0.71, 1.54)	0.84
HR (95% CI)§	1.00	1.03 (0.74, 1.44)	0.91 (0.65, 1.28)	1.02 (0.74, 1.42)	1.07 (0.79, 1.46)	0.69
Beta-carotene						
No. of deaths	51	64	80	96	87	
No. of person-years	15,119	15,204	14,947	14,937	14,935	
HR (95% CI)†	1.00	1.00 (0.69, 1.44)	1.12 (0.79, 1.59)	1.19 (0.84, 1.67)	0.99 (0.70, 1.41)	0.75
HR (95% CI)‡	1.00	0.81 (0.57, 1.14)	1.11 (0.80, 1.54)	0.88 (0.63, 1.24)	0.93 (0.66, 1.30)	0.88
HR (95% CI)§	1.00	0.97 (0.67, 1.41)	1.13 (0.79, 1.61)	1.23 (0.88, 1.74)	0.97 (0.68, 1.38)	0.75

* HR, hazard ratio; CI, confidence interval.

† Estimated from Cox proportional hazards regression analysis, adjusting for age and energy. Nutrients were energy adjusted by using the residual method.

‡ Estimated from Cox proportional hazards regression analysis, adjusting for age, smoking status, body mass index, cholesterol concentration, and energy. Nutrients were not energy adjusted by using the residual method.

§ Estimated from Cox proportional hazards regression analysis, adjusting for age, smoking status, body mass index, cholesterol concentration, and energy. Nutrients were energy adjusted by using the residual method.

for those who consumed at least five fruit and vegetable servings per day compared with those who ate fewer. No association was present for cardiovascular disease mortality (HR = 1.04, 95 percent CI: 0.76, 1.42).

Because cigarette smoking results in a greater oxidative burden, we evaluated the association of fruit and vegetable intake separately among ever smokers and never smokers (table 5). When we compared the highest with the lowest third of fruit and vegetable intake, the risk of all-cause mortality was equally lower among ever smokers (HR = 0.77, 95 percent CI: 0.63, 0.95) and never smokers (HR = 0.72, 95 percent CI: 0.55, 0.95) (*p*-interaction = 0.92). Cancer mortality risk was lower with increasing fruit and vegetable intake for both never smokers (HR = 0.69, 95 percent CI: 0.41, 1.17) and ever smokers (HR = 0.85, 95 percent CI: 0.60, 1.20), although these associations were not statistically significant and effect modification was not present (*p*-interaction = 0.47). No statistically significant associations were observed between fruit and vegetable intake and cardiovascular disease mortality for either ever

TABLE 5. Multivariate hazard ratios for all-cause, cancer, and cardiovascular disease mortality by thirds of fruit and vegetable intake and smoking status, Washington County, Maryland, 1989

	Ever smokers: third of intake			Never smokers: third of intake		
	1	2	3	1	2	3
No. of person-years	13,538	12,487	11,580	11,499	12,686	13,353
All causes						
No. of deaths	189	177	201	97	117	129
Age-adjusted HR* (95% CI*)†	1.00	0.76 (0.62, 0.94)	0.77 (0.63, 0.95)	1.0	0.93 (0.71, 1.22)	0.73 (0.55, 0.96)
Adjusted HR‡	1.00	0.76 (0.62, 0.93)	0.77 (0.63, 0.95)	1.0	0.94 (0.71, 1.23)	0.72 (0.55, 0.95)
Cancer						
No. of deaths	68	64	75	29	37	34
Age-adjusted HR (95% CI)†	1.00	0.80 (0.56, 1.12)	0.85 (0.60, 1.19)	1.0	1.01 (0.62, 1.64)	0.70 (0.42, 1.18)
Adjusted HR§	1.00	0.80 (0.56, 1.12)	0.85 (0.60, 1.20)	1.0	1.01 (0.62, 1.64)	0.69 (0.41, 1.17)
Cardiovascular disease						
No. of deaths	65	77	81	43	48	64
Age-adjusted HR (95% CI)†	1.00	0.94 (0.68, 1.31)	0.89 (0.64, 1.25)	1.0	0.86 (0.57, 1.30)	0.79 (0.53, 1.19)
Adjusted HR¶	1.00	0.95 (0.68, 1.32)	0.87 (0.62, 1.23)	1.0	0.84 (0.55, 1.27)	0.78 (0.51, 1.18)

* HR, hazard ratio; CI, confidence interval.
† Estimated from Cox proportional hazards regression analysis, adjusting for age.
‡ Estimated from Cox proportional hazards regression analysis, adjusting for age, body mass index, and cholesterol concentration.
§ Estimated from Cox proportional hazards regression analysis, adjusting for age and body mass index.
¶ Estimated from Cox proportional hazards regression analysis, adjusting for age, body mass index, cholesterol concentration, and hypertension.

smokers or never smokers (p-interaction = 0.96). Similar estimates were observed when results were stratified by gender and body mass index (data not shown).

In addition, deaths that occurred close in time to 1989 (completion of the FFQ) may have represented participants who altered their diet because of a recent disease diagnosis. To assess this possibility, analyses were conducted to determine whether the estimates were affected by early deaths. Deaths that occurred in the first, up to the second, and up to the fifth year of follow-up were excluded. A further analysis was conducted by stratifying person-time at risk into the first 5 years of follow-up and the last 7 years of follow-up. Finally, participants who self-reported any cancer, myocardial infarction, stroke, or diabetes prior to 1989 were excluded from the analyses. Estimates from all three methods were comparable to the overall estimates (not shown). Finally, since the analyses were adjusted for smoking status categorized as never, former, and current, potential residual confounding may have occurred. To account for this possibility, diet-disease analyses were also conducted that included the number of cigarettes smoked; the estimates were similar to the estimates presented in the tables (not shown).

DISCUSSION

Higher intakes of fruits and vegetables, cruciferous vegetables, and antioxidant nutrients were hypothesized to decrease risk of all-cause, cancer, and cardiovascular disease mortality. In this study, higher intakes of fruits and vegetables and cruciferous vegetables were associated with lower risk of all-cause, cancer, and cardiovascular disease mortality. The association appeared to be a threshold effect, such that persons who consume at least one fruit and vegetable a day (the top four fifths of the cohort's distribution) may receive some benefit. There may be differences in dietary intake and health characteristics besides fruit and vegetable intake between the lowest fifth and the highest four fifths of the distribution. In our models, we adjusted for cholesterol concentration, hypertension, and body mass index, and the estimates did not change significantly from the crude estimates. Further analyses that included saturated fat intake were conducted; the results were similar to those from the overall models. Thus, this threshold may relate to a deficiency-versus-sufficiency association of fruits and vegetables with all-cause, cancer, and cardiovascular disease mortality. Persons may need to consume a sufficient amount to receive the health benefits associated with fruits and vegetables. When we examined particular antioxidant nutrients, higher intakes of vitamin C and vitamin E were not associated with all-cause, cancer, and cardiovascular disease mortality. Beta-carotene was associated with a lower risk of all-cause mortality and a nonstatistically significant lower risk of cancer mortality but was not associated with cardiovascular disease mortality.

The results for fruits and vegetables and for cruciferous vegetables were consistent in direction and magnitude with those from other cohort studies (3–12, 19). Some studies conducted in the United States, such as the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, the Nurses' Health Study, and Health Professionals Follow-up Study, and in older adults showed a strong linear trend, unlike in our study. These studies controlled for exercise (3) and included health-conscious persons whose intakes of fruits and vegetables were greater (9) than in our study. Although similar rates of obesity and a higher educational level were seen across the cohorts, other factors related to health, such as exercise, may vary. Differences in the associations among studies may also be due to less variability in antioxidant nutrient intake in the Odyssey Cohort.

In our study population, median intake of fruits and vegetables was 2.3 servings per day, which is lower than the national average of 3.6 servings per day as ascertained by the Behavioral Risk Factor Surveillance Study (42) and other studies, such as the Health Professionals Follow-up Study (5.1 servings/day) (5) and the Nurses' Health Study (6.1 servings/day) (5). In 1989, only 9.4 percent of the Odyssey population consumed at least five servings of fruits and vegetables per day, in contrast to the national estimate of 23.1 percent (43, 44). Our analysis of five fruits and vegetables per day showed that higher intake was associated with lower risk of all-cause and cancer mortality but not of cardiovascular disease mortality. In this study, the FFQ was used to rank study participants from low to high. The contrast across fifths (the lowest and highest median fifth was 0.87 serving/day and 4.89 servings/day) was narrower than in other studies. Although this difference may represent the distribution of a community-based population, this contrast may not have been adequate to detect associations.

Fruits and vegetables contain a wide array of nutrients and phytochemicals that may act together to produce a benefit; considering nutrients individually might not provide the answer. Additionally, other nutrients besides vitamin C and beta-carotene in fruits and vegetables may be driving the association of fruits and vegetables with mortality. This possibility may explain why the inverse association with fruits and vegetables was stronger and more consistent with mortality, whereas an association with particular nutrients was not present.

Other factors also may have attenuated these associations of fruits, vegetables, and antioxidant nutrients with mortality. Participants reported their usual intake of fruits and vegetables over the past year. Validation studies of FFQs have determined that persons tend to overreport their intake of fruits and vegetables, which also would overestimate vitamin C and beta-carotene intake, and underreport fat and oil intake, which would underestimate vitamin E intake (41, 45). Inaccurate reporting regarding fruits and vegetables should not have varied by outcome (i.e., mortality) in this prospective study and, as such, may have resulted in nondifferential misclassification. The effect of nondifferential misclassification would have tended to attenuate the relation between intakes of fruits and vegetables, cruciferous vegetables, and antioxidant nutrients with all-cause, cancer, and cardiovascular disease mortality.

The FFQ was collected only once during the study, which did not enable us to measure change in intake over time. However, we think that misclassification of fruit and vegetable intake over time by using baseline intake is limited. A brief measure of fruit and vegetable intake was obtained on a 1998 follow-up questionnaire. When we compared the two time points regarding intake of fruits and vegetables, the weighted kappa was good (0.51, 95 percent CI: 0.49, 0.54), showing that participants would have been ranked similarly at the two time points. Unfortunately, the 1998 questionnaire did not ask about dietary supplement use, and we were unable to assess any changes in supplement use over time.

Influence of recent disease on dietary intake at baseline was possible. Sensitivity analyses were restricted to those persons who died after the first, second, and fifth years of follow-up. Estimates were similar across all analyses, suggesting that the relation between diet and disease was consistent when both or either recent or older deaths were included.

The FFQ may not measure the biologically important component of antioxidants, such as the bioavailable levels or the biologically active levels. The FFQ measures only intake of particular items and does not take into account a person's level of oxidative stress, which can greatly deplete exogenous antioxidant stores and may confound or modify the associations (46).

Other factors have been known to cluster with or to affect intake of fruits and vegetables (47). Persons who consume higher amounts of fruits and vegetables are more likely to be more highly educated, less likely to be overweight/obese, and less likely to smoke cigarettes. These other factors, as well as multivitamin supplement use, were examined and controlled for in the analysis, although residual confounding cannot be excluded.

Persons in the Odyssey Cohort compared with the Washington County population as a whole were more likely to be female, more educated, and older, demographic characteristics similar to those of the participants in the two separate CLUE campaigns. In this community, outmigration was low (<3 percent) and is representative of a rural/suburban Caucasian community. Understanding typical intake of these foods and components and their relation to all-cause, cancer, and cardiovascular disease mortality would provide insight into areas for public health interventions, such as improving dietary patterns and increasing fruit and vegetable intake.

In summary, this study suggests that higher intakes of fruits and vegetables delay the risk of death, including cancer and cardiovascular disease, and it provides further support for the public health message to increase fruit and vegetable intake. Whether the benefit associated with greater consumption of fruits and vegetables is due to antioxidant content remains to be determined.

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