



Original Contribution

Antioxidant Intake and Risk of Osteoporotic Hip Fracture in Utah: An Effect Modified by Smoking Status

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The role of antioxidant intake in osteoporotic hip fracture risk is uncertain and may be modified by smoking. In the Utah Study of Nutrition and Bone Health, a statewide, population-based case-control study, the authors investigated whether antioxidant intake was associated with risk of osteoporotic hip fracture and whether this association was modified by smoking status. The analyses included data on 1,215 male and female cases aged ≥ 50 years who incurred a hip fracture during 1997–2001 and 1,349 age- and sex-matched controls. Diet was assessed by food frequency questionnaire. Among ever smokers, participants in the highest quintile of vitamin E intake (vs. the lowest) had a lower risk of hip fracture after adjustment for confounders (odds ratio = 0.29, 95% confidence interval (CI): 0.16, 0.52; p -trend < 0.0001). The corresponding odds ratio for β -carotene intake was 0.39 (95% CI: 0.23, 0.68; p -trend = 0.0004), and for selenium intake it was 0.27 (95% CI: 0.12, 0.58; p -trend = 0.0003). Vitamin C intake did not have a significant graded association with hip fracture risk among ever smokers. Similar findings were obtained when an overall antioxidant intake score was used (odds ratio = 0.19, 95% CI: 0.10, 0.37; p -trend < 0.0001). No similar associations were found in never smokers. Antioxidant intake was associated with reduced risk of osteoporotic hip fracture in these elderly subjects, and the effect was strongly modified by smoking status.

aged; antioxidants; diet; dietary supplements; hip fractures; nutrition; osteoporosis; smoking

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; MMSE, Mini-Mental State Examination.

Osteoporotic hip fracture has emerged as a major public health problem in elderly populations worldwide (1, 2). In the last two decades, numerous studies have investigated the relation between vitamin C intake and bone mineral density (3–8). Many (3–6) but not all (7, 8) studies revealed that vitamin C intake was positively associated with bone mineral density at the sites of the femoral neck, radius, or ulna. Two intervention trials (9, 10) indicated that vitamin C supplementation increased bone mineral density in postmeno-

pausal women. Less is known about associations between intakes of other antioxidants (vitamin E, β -carotene, and selenium) and bone health, and scant research in this area has included men, who also have a substantial risk of osteoporotic hip fracture in many populations.

Tobacco smoke contains large amounts of oxidants and free radicals that induce excessive oxidative stress (11), a condition associated with reduced bone mineral density (12). A recent meta-analysis that examined data from 29

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cross-sectional studies and 19 cohort and case-control studies showed that, compared with nonsmokers, smokers had a reduced bone mineral density and an increased risk of osteoporotic hip fracture (13).

Data on the relation between antioxidant intake and hip fracture risk are scarce. A few studies that evaluated the effect of vitamin C intake on hip fracture risk produced conflicting results (14–16). Antioxidants are capable of scavenging free radicals generated by tobacco smoke and other sources in humans (14). It is biologically plausible that increased antioxidant intake may reduce the risk of hip fracture by counteracting the deleterious effect of smoking on bones. The objectives of the present study were to investigate whether antioxidant intake was inversely associated with the risk of osteoporotic hip fracture and whether this association was modified by smoking status.

MATERIALS AND METHODS

Study population

The Utah Study of Nutrition and Bone Health is a state-wide case-control study of risk factors for osteoporotic hip fracture in elderly Utah men and women. The Utah population is largely of northern European ancestry. Cases were persons aged 50 years or older who sustained a fracture of the proximal femur during the period 1997–2001. They were ascertained from 18 Utah hospitals that treat 98 percent of all hip fracture cases occurring in the state of Utah. Controls were recruited from Utah residents who had never had a hip fracture. They were frequency-matched to cases by age (within 5 years) and sex. Controls were randomly selected from two sources: the Utah driver's license database for persons less than 65 years of age and Health Care Financing Administration records of Medicare recipients for persons aged 65 years or older. These databases covered 87.4 percent and 92.8 percent of the general Utah population in the specified age groups, respectively.

All eligible cases and controls were invited to participate in the study. Similar proportions of cases (23.2 percent) and controls (24.0 percent) refused to complete an interview. Because of illness, frailty, dementia, or death, 37.2 percent of cases and 16.8 percent of controls were unable to participate. An additional 2.8 percent of cases and 3.4 percent of controls could not be located. This resulted in an overall participation rate of 36.9 percent among cases and 55.8 percent among controls.

Data were available from 1,371 cases and 1,369 controls. Cases with hip fractures caused by high-impact trauma (for example, automobile accidents or a fall from above chair height) were excluded ($n = 117$). Also excluded were subjects with missing data on smoking status ($n = 2$) or dietary intake ($n = 6$) and subjects with outlying values ($n = 55$), including 41 for energy intake (<600 kcal/day or $>5,000$ kcal/day), three for calcium intake ($>15,000$ mg/day), seven for vitamin D intake ($>3,000$ IU/day), and four for physical activity level (>100 hours/week). After these exclusions, complete data from 1,215 cases (340 men and 875 women; 97.7 percent Caucasian) and 1,349 controls (452 men and 897 women; 96.7 percent Caucasian) were available for analysis.

Data collection

The study protocols were approved by the institutional review boards of all participating hospitals and Utah State University. Written, informed consent was obtained from each participant before interview. Cases and controls were interviewed at their place of residence. The interview for cases was conducted, on average, 4.2 months after the occurrence of their hip fracture. Data were collected on demographic characteristics, physical activity, cognitive function, cigarette smoking, alcohol drinking, dietary intake, use of vitamin and mineral supplements and estrogen preparations, and medical history during the year before hip fracture (for cases) or during the past year (for controls). Physical activity was evaluated in terms of categories of walking, housework, gardening or yard work, and 11 kinds of recreational activities. The time spent on all kinds of physical activity was summed and expressed in hours per week. Cognitive function was assessed by means of the Mini-Mental State Examination (MMSE) (17), and the MMSE scores used in the analyses were adjusted for sensory impairment. The frequencies of use and dosages of vitamin and mineral supplements taken were recorded during the interview. Total intakes of each vitamin and mineral from supplements were thus obtained.

The diet of all participants was assessed by means of a 137-item picture-sort food frequency questionnaire (FFQ). A detailed description of the Utah picture-sort FFQ and data on its validation have been published elsewhere (18). Energy-adjusted Spearman rank correlation coefficients for correlation between the Utah picture-sort FFQ and the mean of three 24-hour dietary recalls for major nutrients and vitamins (all ages) ranged from 0.24 to 0.65 in men and from 0.25 to 0.59 in women (18). In the dietary survey, subjects were asked to recall the average frequency of consumption of each food item included in the FFQ during the year before hip fracture (for cases) or during the past year (for controls). Usual daily nutrient intake was calculated by multiplying the amount in a standard portion size of each food item by the reported frequency of consumption and summing over all food items. Nutrient intake from food sources was added to estimated intake from supplement sources to obtain an estimate of total nutrient intake.

Statistical analyses

Risks of hip fracture in relation to antioxidant intakes were estimated as odds ratios and 95 percent confidence intervals by unconditional logistic regression analysis. Intakes of each of four antioxidants—vitamins C and E, β -carotene, and selenium—were divided into quintiles. The risk of hip fracture in progressively higher quintiles of intake was compared with that in the lowest quintile. Potentially confounding factors included in the initial multivariate models were as follows: age; sex; body mass index (weight (kg)/height (m)²); total hours of physical activity per week (in quartiles), daily dietary intakes of energy, calcium, vitamin D, and protein; and use of cigarettes (never and ever), alcohol (never, former, and current), and caffeine (never, former, and current). Because only a small proportion of

participants were current smokers (8.6 percent in men and 4.7 percent in women), former smokers and current smokers were combined into the group "ever smokers." The initial models included interaction terms between age, sex, and smoking status and intakes of each of the four antioxidants (classified in quintiles). The statistical significance of each interaction was examined using the likelihood ratio test. Terms for interactions between age and sex and each of the four antioxidants were not significant and were thus removed from the initial models. For the interactions of smoking status with vitamins C and E, β -carotene, and selenium, p values were 0.10, 0.09, 0.24, and 0.72, respectively. In view of the borderline-significant interactions between smoking and vitamins C and E, the biologic plausibility of interactions between smoking and antioxidants, and the insignificant interaction between sex and antioxidants in hip fracture risk, subsequent analyses for each of the four antioxidants were performed for never and ever smokers separately in men and women combined.

For observation of the independent effect of each of the four antioxidants on hip fracture risk, the aforementioned multivariate model fitted for each single antioxidant was further adjusted for the other three antioxidants. Since decline in cognitive function may affect the validity of dietary data, all analyses were repeated after exclusion of subjects whose adjusted MMSE scores were 17 or less (an indicator of severe cognitive impairment (19)). Linear trends across quintiles of antioxidant intake were tested by weighting each quintile by its median value.

To investigate the relation between overall antioxidant intake and risk of hip fracture, a composite variable, antioxidant intake score, was created. For each of the four antioxidants examined (vitamins C and E, β -carotene, and selenium), persons in quintiles 1–5 (ranging from low intake to high intake) were assigned a corresponding score of 1–5. The total antioxidant intake score for a given participant was obtained by summing the scores over all four antioxidants, producing a range of scores from 4 to 20. In the multivariate models, antioxidant intake score was divided into quintiles, with the lowest quintile used as the reference category. Multivariate analyses with covariates similar to those used in the models for individual antioxidant intake were performed. Statistical significance was set at $p < 0.05$ (two-sided), and all analyses were conducted using SAS software (version 8; SAS Institute, Inc., Cary, North Carolina).

RESULTS

Characteristics of cases and controls according to smoking status are shown in table 1. In both never smokers and ever smokers, cases were leaner and less physically active than controls and had lower total intakes of vitamins C and E and β -carotene. In both cases and controls, ever smokers had lower total intakes of vitamin C and β -carotene than never smokers. There were no marked differences in total selenium intake between cases and controls or between never smokers and ever smokers. Dietary intake, as compared with supplement intake, was a minor source of total intakes of vitamin C (31.6–36.8 percent) and vitamin E

(7.1–10.3 percent), whereas it was a major source of total intakes of β -carotene (72.4–78.4 percent) and selenium (87.4–96.1 percent). A high proportion of participants used supplements of vitamins C (61.5–69.6 percent) and E (59.6–66.9 percent). Cigarette smoking was more common in cases (former smokers, 23.8 percent; current smokers, 7.5 percent) than in controls (former smokers, 22.1 percent; current smokers, 4.5 percent).

Apparent interactions were found between intakes of vitamin E, β -carotene, and selenium and smoking in the risk of hip fracture (table 2). A significant linear trend toward a lower risk of hip fracture with successively higher quintiles of vitamin E, β -carotene, and selenium intake was observed in ever smokers but not in never smokers. After adjustment for age, sex, body mass index, physical activity, dietary intakes of energy, calcium, vitamin D, and protein, and use of caffeine and alcohol, odds ratios in progressively higher quintiles of vitamin E intake (as compared with the lowest) in ever smokers were 0.90 (95 percent confidence interval (CI): 0.54, 1.50), 0.71 (95 percent CI: 0.41, 1.22), 0.56 (95 percent CI: 0.32, 0.98), and 0.29 (95 percent CI: 0.16, 0.52) (p -trend < 0.0001). The corresponding odds ratios among ever smokers were 0.65 (95 percent CI: 0.41, 1.02), 0.65 (95 percent CI: 0.40, 1.04), 0.36 (95 percent CI: 0.21, 0.61), and 0.39 (95 percent CI: 0.23, 0.68) (p -trend = 0.0004) for β -carotene and 0.71 (95 percent CI: 0.42, 1.19), 0.55 (95 percent CI: 0.32, 0.94), 0.36 (95 percent CI: 0.19, 0.65), and 0.27 (95 percent CI: 0.12, 0.58) (p -trend = 0.0003) for selenium. Unlike vitamin E, β -carotene, and selenium, vitamin C did not have an inverse graded association with the risk of hip fracture in ever smokers but instead showed a threshold effect. Further adjustment for intakes of the other three antioxidants in the multivariate models only slightly attenuated the observed associations between a single antioxidant and hip fracture risk. After exclusion of participants whose adjusted MMSE scores were 17 or less, the results remained essentially unchanged.

A similar interaction between antioxidant intake score and smoking status in the risk of hip fracture was detected (table 3). An inverse dose-response relation between antioxidant intake score and hip fracture risk was found in ever smokers. After adjustment for the same confounding factors as those noted above, odds ratios in progressively higher quintiles (as compared with the lowest) were 0.51 (95 percent CI: 0.30, 0.89), 0.39 (95 percent CI: 0.22, 0.67), 0.28 (95 percent CI: 0.15, 0.53), and 0.19 (95 percent CI: 0.10, 0.37) (p -trend < 0.0001). Like individual antioxidant intakes, antioxidant intake score was not inversely associated with the risk of hip fracture in never smokers.

DISCUSSION

An inverse dose-response association between intakes of vitamin E, β -carotene, and selenium and the risk of hip fracture was observed among ever smokers in this elderly Utah population. Ever smokers in the highest quintile of intakes of vitamin E, β -carotene, and selenium had 71 percent, 61 percent, and 73 percent lower risks of hip fracture than those in the lowest quintile, respectively. Vitamin C

TABLE 1. Characteristics of cases and controls by smoking status, Utah Study of Nutrition and Bone Health, 1997–2001*

Characteristic	Never smokers				Ever smokers			
	Cases (n = 835)		Controls (n = 991)		Cases (n = 380)		Controls (n = 358)	
	Mean or %	SD†	Mean or %	SD	Mean or %	SD	Mean or %	SD
Mean age (years)	77.6	8.8	76.1	9.6	73.7	9.5	73.3	10.4
Female sex (%)	81.6		75.8		51.1		40.8	
Mean body mass index‡	24.5	4.8	26.4	4.9	24.2	4.9	26.4	4.9
Mean amount of physical activity (hours/week)	11.9	13.4	12.5	12.9	11.6	15.2	13.2	14.8
Mean nutrient intake								
Energy (kcal/day)	2,249	743	2,168	720	2,426	820	2,308	704
Vitamin C from food (mg/day)	155	80	149	70	144	85	136	71
Total vitamin C§ (mg/day)	434	505	471	534	391	494	404	438
Vitamin E from food (mg α -TE†/day)	10	6	10	5	10	6	11	6
Total vitamin E§ (mg α -TE/day)	127	194	140	204	97	168	146	195
β -Carotene from food (mg/day)	4.8	3.4	5.0	3.5	4.0	3.4	4.2	2.8
Total β -carotene§ (mg/day)	6.6	5.6	6.9	6.5	5.1	4.8	5.8	5.6
Selenium from food (μ g/day)	95	38	90	35	99	41	97	35
Total selenium§ (μ g/day)	106	44	103	44	108	47	110	51
Calcium from food (mg/day)	1,086	487	1,054	454	1,082	509	1,015	427
Total calcium§ (mg/day)	1,566	762	1,534	781	1,461	799	1,406	733
Vitamin D from food (IU/day)	288	158	274	150	288	165	270	145
Total vitamin D§ (IU/day)	550	335	542	341	541	362	512	339
Protein (g/day)	88	33	86	32	94	37	91	31
Caffeine (mg/day)	81	153	74	133	262	308	261	322
Supplement use (%)								
Vitamin C	67.1		69.6		61.5		65.6	
Vitamin E	65.6		66.9		59.6		65.0	
β -Carotene	45.9		45.0		36.7		44.3	
Selenium	38.8		41.5		31.1		41.7	
Calcium	67.9		67.3		55.7		61.3	
Vitamin D	58.7		61.4		56.5		53.8	
Alcohol drinking (%)								
Never drinker	83.3		85.4		24.3		25.6	
Former drinker	9.6		7.3		43.3		37.9	
Current drinker	7.1		7.4		32.5		36.5	

* Owing to missing data, sample sizes for body mass index, β -carotene intake, and categorical variables were slightly different from those shown.

† SD, standard deviation; α -TE, α -tocopherol equivalents.

‡ Weight (kg)/height (m)².

§ Total from food and supplements combined.

intake was also inversely associated with hip fracture risk in ever smokers, but this association did not show a dose-response effect. No significant associations were found between any of the four antioxidants examined and hip fracture risk in never smokers. Similar findings were obtained when antioxidant intake score was used in the analysis.

In the present study, we produced a new parameter, antioxidant intake score, to investigate the association of overall antioxidant intake with hip fracture risk. Several biochem-

ical indices—for example, plasma total antioxidant capacity and plasma total peroxyl-trapping potential—have been used to estimate overall antioxidant activity in the human body (20, 21). The principle behind these indicators lies in biochemical measurements of the ability of human plasma or other tissues to counteract oxidants and scavenge free radicals (20, 21). Recently, in a Belgian cohort study (22), a dietary oxidative balance score was computed from dietary intakes of antioxidants (vitamin C and β -carotene) and a prooxidant (iron) and was related to all-cause and

TABLE 2. Risk of osteoporotic hip fracture according to quintile of selected antioxidant intakes in men and women aged ≥ 50 years, Utah Study of Nutrition and Bone Health, 1997–2001

Antioxidant group	Quintile of antioxidant intake*					<i>p</i> -trend†
	First	Second	Third	Fourth	Fifth	
Vitamin C						
Median vitamin C intake (mg/day)	93	159	239	488	1,095	
Never smokers						
No. of cases	154	167	181	172	161	
No. of controls	181	192	200	187	231	
Odds ratio‡	1.00§	0.98	0.95	0.99	0.71	0.021
95% confidence interval		0.71, 1.35	0.68, 1.32	0.71, 1.38	0.51, 1.00	
Ever smokers						
No. of cases	104	74	73	65	64	
No. of controls	73	80	59	88	58	
Odds ratio‡	1.00§	0.59	0.67	0.43	0.65	0.38
95% confidence interval		0.36, 0.94	0.40, 1.13	0.26, 0.72	0.38, 1.13	
Vitamin E						
Median vitamin E intake (mg of α -tocopherol equivalents/day)	7	13	30	152	315	
Never smokers						
No. of cases	153	171	184	169	158	
No. of controls	205	186	171	208	221	
Odds ratio‡	1.00§	1.07	1.27	1.03	0.92	0.13
95% confidence interval		0.77, 1.48	0.90, 1.79	0.74, 1.42	0.65, 1.30	
Ever smokers						
No. of cases	83	90	91	67	49	
No. of controls	72	65	67	68	86	
Odds ratio‡	1.00§	0.90	0.71	0.56	0.29	<0.0001
95% confidence interval		0.54, 1.50	0.41, 1.22	0.32, 0.98	0.16, 0.52	
β-Carotene						
Median β -carotene intake (mg/day)	1.8	3.4	4.9	7.0	12.2	
Never smokers						
No. of cases	145	151	175	185	179	
No. of controls	168	193	196	215	219	
Odds ratio‡	1.00§	0.84	0.92	0.84	0.79	0.27
95% confidence interval		0.60, 1.16	0.66, 1.27	0.61, 1.17	0.56, 1.17	
Ever smokers						
No. of cases	123	84	73	44	56	
No. of controls	80	84	69	67	58	
Odds ratio‡	1.00§	0.65	0.65	0.36	0.39	0.0004
95% confidence interval		0.41, 1.02	0.40, 1.04	0.21, 0.61	0.23, 0.68	
Selenium						
Median selenium intake (μ g/day)	58	79	99	121	162	
Never smokers						
No. of cases	162	156	175	172	170	
No. of controls	215	211	192	193	180	
Odds ratio‡	1.00§	0.91	1.14	1.15	1.17	0.30
95% confidence interval		0.66, 1.25	0.82, 1.60	0.79, 1.67	0.75, 1.83	
Ever smokers						
No. of cases	64	71	63	65	70	
No. of controls	51	61	71	75	72	
Odds ratio‡	1.00§	0.71	0.55	0.36	0.27	0.0003
95% confidence interval		0.42, 1.19	0.32, 0.94	0.19, 0.65	0.12, 0.58	

* Includes both food and supplement sources.

† Linear trend across quintiles of antioxidant intake.

‡ Adjusted for age, sex, body mass index, physical activity, dietary intakes of energy, calcium, vitamin D, and protein, and use of caffeine and alcohol. Calcium and vitamin D intakes included both food and supplement sources.

§ Reference category.

TABLE 3. Risk of osteoporotic hip fracture according to quintile of antioxidant intake score in men and women aged ≥ 50 years, by smoking status, Utah Study of Nutrition and Bone Health, 1997–2001

Quintile of antioxidant intake score	Never smokers				Ever smokers			
	No. of cases	No. of controls	OR*,†	95% CI*	No. of cases	No. of controls	OR†	95% CI
Quintile 1 (6)‡	86	116	1.00§		73	41	1.00§	
Quintile 2 (9)	148	177	0.94	0.65, 1.37	73	65	0.51	0.30, 0.89
Quintile 3 (12)	202	210	1.08	0.75, 1.58	91	85	0.39	0.22, 0.67
Quintile 4 (14)	157	176	0.98	0.65, 1.46	60	64	0.28	0.15, 0.53
Quintile 5 (17)	242	312	0.80	0.53, 1.19	83	103	0.19	0.10, 0.37
<i>p</i> -trend¶			0.22				<0.0001	

* OR, odds ratio; CI, confidence interval.

† Adjusted for age, sex, body mass index, physical activity, dietary intakes of energy, calcium, vitamin D, and protein, and use of caffeine and alcohol. Calcium and vitamin D intakes included both food and supplement sources.

‡ Numbers in parentheses, median value per quintile; see text for definition.

§ Reference category.

¶ Linear trend across quintiles of antioxidant intake score.

cause-specific mortality. Because vitamins C and E, β -carotene, and selenium have different food sources (23), the antioxidant intake score created in the present study reflects not only overall antioxidant intake but also the degree of dietary diversity in the study population. No significant interactions were found between the four antioxidants (all p 's > 0.27), which indirectly justifies the approach of computing a summary score. The inverse association between antioxidant intake score and risk of hip fracture in ever smokers strengthens the findings obtained for individual antioxidants. However, the validity and suitability of this new index needs to be confirmed in future studies.

A few studies have examined the relation between antioxidant intake and risk of hip fracture, and the results are controversial (14–16, 24). In a case-control study nested in the Swedish Mammography Cohort (14), evidence was found that among women with a low intake of vitamin C or vitamin E, current smokers had an approximately three-fold increased risk of hip fracture compared with never smokers. However, this promoting effect of cigarette smoking was not seen among women with a high intake of vitamin C or vitamin E. Unlike vitamins C and E, intakes of β -carotene and selenium did not show effect modification of the association between smoking and hip fracture risk. A limitation of this Swedish study is that only history of multivitamin supplement use, not the actual doses taken, was considered in the analyses. In the Uppsala Longitudinal Study of Adult Men (24), neither dietary intake nor serum level of β -carotene was associated with fracture risk. A case-control study of 161 cases and 168 controls performed in Caucasian-American women (16) reported no significant association between vitamin C intake and the risk of hip fracture; however, the findings of this small study should be considered with caution, because only about half the foods that contribute to vitamin C intake were covered in the questionnaire. In the Third National Health and Nutrition Examination Survey (15), dietary vitamin C intake did not have a significant relation with self-reported fracture risk in women, but it had a U-shaped relation with fracture

risk in men. A higher serum vitamin C level was associated with a decreased risk of fracture among postmenopausal women with a history of smoking and estrogen use. The limitations of the Third National Health and Nutrition Examination Survey, a cross-sectional study, include the facts that use of vitamin C supplements was not taken into account and that some fractures might have been caused by high-impact trauma but not eliminated from the analysis.

One reason for the discrepant findings of the above studies may be that data on the history and amounts of use of multivitamin supplements were lacking or not considered. Failure to include supplemental intakes of vitamins in analyses may produce errors in nutrient estimates and misclassification of subjects with regard to their total intake (25). In the present study, low intakes of vitamins C and E from both dietary and supplemental sources were associated with an increased risk of hip fracture in ever smokers, a finding consistent with some previous studies (14, 15). However, the present study differed from those studies in that intakes of all antioxidants examined were inversely associated with hip fracture risk in ever smokers, and intakes of vitamin E, β -carotene, and selenium appeared to reduce the risk of hip fracture in a dose-response manner.

Several strengths of the present study are worthy of mention. A large sample comprising persons of both sexes was drawn from the entire state of Utah; thus, these findings are representative of a broad range of social and economic levels in a large geographic area. Unlike the case in many other studies, the availability of data on amounts of use of antioxidant supplements allowed estimates of total antioxidant intake. The results of the present study were obtained after exclusion of hip fractures that were due to automobile accidents and other high-impact traumas. The associations between antioxidant intake and hip fracture risk were investigated not only by examining individual antioxidants separately but also by treating them as a whole with the antioxidant intake score.

The use of multivitamin and mineral supplements is common in the United States (26, 27). The National Health

Interview Survey, conducted in 1992 (26), showed that 24 percent of 12,005 US men and women took these supplements. In the Women Physicians' Health Study (27), 35.5 percent of the participants were regular users of multivitamin and mineral supplements. In the present study, the use of vitamin C and vitamin E supplements ranged from 59.6 percent to 69.6 percent and was the predominant source of these two vitamins. It remains unclear whether the use of multivitamin supplements regularly and in large doses is beneficial to bone health. This is an important question. The Recommended Dietary Allowance published recently by the Institute of Medicine was 75–90 mg/day for vitamin C and 15 mg of α -tocopherol equivalents/day for vitamin E (23). The present study revealed that among ever smokers, persons in the highest quintile of vitamin E intake (median, 316 mg of α -tocopherol equivalents/day) had a 73 percent reduction in hip fracture risk compared with those in the lowest quintile (7 mg of α -tocopherol equivalents/day). The corresponding risk reduction for vitamin C was 32 percent, while the median intakes of vitamin C were 95 mg/day and 1,098 mg/day for persons in the lowest and highest quintiles, respectively. In the present study, intakes of vitamins C and E went far beyond the Recommended Dietary Allowances and were primarily derived from multivitamin supplements, yet they still appeared to confer protection against the risk of osteoporotic hip fracture.

The mechanisms by which higher intakes of antioxidants were associated with a lower risk of hip fracture in ever smokers remain unclear. Several studies showed that smoking accelerated bone loss and increased fracture risk (13, 28–31). The adverse effects of smoking on bone health have been postulated to be partly attributable to increased oxidative stress (12). Oxygen-derived free radicals were found to be involved in the formation of new osteoclasts and enhanced bone absorption in cultured rodent bone (32). In a cross-sectional study (12), 8-iso-prostaglandin $F_2\alpha$, a biomarker of oxidative stress, was inversely correlated with bone mineral density at the sites of the femoral neck, lumbar spine, and distal forearm. Antioxidant vitamins and minerals may exert their favorable effects on bone mineral density and osteoporotic fracture risk by scavenging free radicals and in turn reducing oxidative stress in humans and animals. This may explain, in part, why intakes of different antioxidants and the antioxidant intake score were consistently associated with a low risk of hip fracture among ever smokers in the present study. Since cigarette smoking is not the only source of oxidative stress, it is largely unknown why antioxidant intake did not protect against hip fracture risk among nonsmokers. Some of the other sources of oxidative stress include excessive alcohol consumption and exposure to ionizing radiation. Alcohol consumption was low among participants in the present study, and nonsmokers are more likely to be nondrinkers. In modern society, exposure to high levels of ionizing radiation is uncommon in the general population.

Several limitations of the present study should be considered. Special attention should be paid to recall bias in a case-control study. Exclusion of persons with poor cognitive function did not substantially alter our results, which suggests that recall bias related to cognitive function, if any,

would not have influenced the findings to a great extent. Dietary assessment errors may have resulted in misclassification of participants with regard to their antioxidant intake. However, such errors would have tended to attenuate the observed associations (33, 34). Dietary assessment errors may be more pronounced for selenium, because the selenium content of foods varies markedly among countries or regions and depends primarily on the selenium content of the soil where the plants were grown or the animals were raised (23). However, the degree of this kind of measurement error should have been approximately the same for cases and controls and thus should not have considerably distorted risk estimates. A high antioxidant intake may be a proxy for a healthy lifestyle. Although we adjusted for cigarette smoking, alcohol drinking, coffee consumption, physical activity, and various nutrients in our analyses, the possibility that our results were confounded to some extent by other lifestyle factors not covered could not be entirely excluded. Although refusal rates were similar for cases and controls, low response rates (especially for cases) and exclusion of subjects who were unable to participate in the study because of illness, frailty, dementia, or death suggest that extrapolation of these findings to the frail elderly population should be made with caution.

The present study revealed that intakes of vitamin E, β -carotene, and selenium and overall antioxidant intake were associated with reduced risk of osteoporotic hip fracture in a dose-response manner among ever smokers in this elderly Utah population. An inverse relation was also observed between vitamin C intake and hip fracture risk in ever smokers, but this relation appeared to have a threshold effect. Intakes of the antioxidants examined did not reduce the risk of hip fracture in never smokers. Smoking has remarkably deleterious effects on bone health; thus, both active and passive exposure to tobacco smoke should be avoided. For persons who cannot easily avoid tobacco smoke because of personal addiction to tobacco or are unable to alter their passive exposure to tobacco smoke or other causes of oxidative stress, increased antioxidant intake may be beneficial. Use of supplemental β -carotene was associated with increased risk of lung cancer in two randomized intervention trials (35, 36); thus, caution should be exercised, and use of supplements deserves further study. However, increased antioxidant intake via dietary changes would also provide the other health benefits of a diverse, plant-based diet.

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