

Vitamin A Intake and Hip Fractures Among Postmenopausal Women

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INGESTION OF TOXIC AMOUNTS OF vitamin A has long been known to have adverse skeletal effects.^{1,2} In animals, retinoic acid suppresses osteoblast activity,³ stimulates osteoclast formation,⁴ and antagonizes the ability of vitamin D to maintain normal serum calcium levels,⁵ all of which may contribute to the accelerated bone resorption and fractures observed with hypervitaminosis A.⁶ In humans, long-term ingestion of high amounts of vitamin A can lead to hypercalcemia and bone abnormalities.⁷ In addition, lower bone mass⁸ and decreased biochemical markers for bone turnover⁹ have been observed in patients treated with retinoids for skin diseases.

These documented effects on bone from acute toxic exposure or chronic high-dose intake of vitamin A have led to speculation that long-term consumption of diets high in vitamin A may contribute to osteoporosis and hip fractures. In Sweden, where both vitamin A intake and hip fracture incidence are high, Melhus et al¹⁰ reported a 10% reduction in femoral bone mineral density and a doubling of the risk of hip fracture among women consuming more than 1500 µg/d of retinol compared with women who consumed less than 500 µg/d. However, in contrast with these findings, there was no evidence that vitamin A intake was associated with radial bone loss among post-

Context Ingestion of toxic amounts of vitamin A affects bone remodeling and can have adverse skeletal effects in animals. The possibility has been raised that long-term high vitamin A intake could contribute to fracture risk in humans.

Objective To assess the relationship between high vitamin A intake from foods and supplements and risk of hip fracture among postmenopausal women.

Design Prospective analysis begun in 1980 with 18 years of follow-up within the Nurses' Health Study.

Setting General community of registered nurses within 11 US states.

Participants A total of 72337 postmenopausal women aged 34 to 77 years.

Main Outcome Measures Incident hip fractures resulting from low or moderate trauma, analyzed by quintiles of vitamin A intake and by use of multivitamins and vitamin A supplements, assessed at baseline and updated during follow-up.

Results From 1980 to 1998, 603 incident hip fractures resulting from low or moderate trauma were identified. After controlling for confounding factors, women in the highest quintile of total vitamin A intake (≥ 3000 µg/d of retinol equivalents [RE]) had a significantly elevated relative risk (RR) of hip fracture (RR, 1.48; 95% confidence interval [CI], 1.05-2.07; *P* for trend = .003) compared with women in the lowest quintile of intake (<1250 µg/d of RE). This increased risk was attributable primarily to retinol (RR, 1.89; 95% CI, 1.33-2.68; *P* for trend < .001 comparing ≥ 2000 µg/d vs <500 µg/d). The association of high retinol intake with hip fracture was attenuated among women using postmenopausal estrogens. Beta carotene did not contribute significantly to fracture risk (RR, 1.22; 95% CI, 0.90-1.66; *P* for trend = .10 comparing ≥ 6300 µg/d vs <2550 µg/d). Women currently taking a specific vitamin A supplement had a nonsignificant 40% increased risk of hip fracture (RR, 1.40; 95% CI, 0.99-1.99) compared with those not taking that supplement, and, among women not taking supplemental vitamin A, retinol from food was significantly associated with fracture risk (RR, 1.69; 95% CI, 1.05-2.74; *P* for trend = .05 comparing ≥ 1000 µg/d vs <400 µg/d).

Conclusions Long-term intake of a diet high in retinol may promote the development of osteoporotic hip fractures in women. The amounts of retinol in fortified foods and vitamin supplements may need to be reassessed.

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menopausal women participating in a 4-year calcium supplementation trial,¹¹ and neither serum retinol level nor vitamin A supplement use was related to either radial bone mass or fracture history among a sample of postmenopausal women in Iowa.¹²

To further investigate this issue, we conducted an 18-year prospective analysis of vitamin A intake and hip fractures among postmenopausal women in the Nurses' Health Study. We anticipated an increased risk of hip fracture among the women with the high-

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est retinol consumption from foods or supplements, but no significant increase with higher carotenoid intakes since long-term supplementation with beta carotene does not increase serum retinol concentrations.¹³

METHODS

The Nurses' Health Study (NHS) began in 1976 when 121 700 female registered nurses aged 30 to 55 years and living in 1 of 11 US states responded to the initial mailed questionnaire. A medical history and information on behaviors and lifestyle were collected at that time. Subsequent follow-up questionnaires have been mailed every 2 years to update data, collect information on new risk factors of interest, and identify incident diseases. Dietary data were first collected in 1980. At least 90% of the cohort has responded in each 2-year follow-up cycle. Deaths are confirmed through the National Death Index. Approximately 98% of the cohort is white.

Only postmenopausal women (via natural or surgical menopause) who responded to the dietary questionnaire in 1980 were included in this analysis. Women entered analysis in 1980 or in the follow-up cycle in which they first reported being postmenopausal. We excluded women at baseline with a previous hip fracture or a diagnosis of cancer, heart disease, stroke, or osteoporosis because these conditions could have caused a change in usual dietary habits. A total of 72 337 women ranging in age from 34 to 77 years contributed to this analysis.

Hip Fractures

On the 1982 questionnaire, participants were asked to report all previous hip fractures along with the circumstances and the date of fracture. Incident fractures were similarly reported on subsequent questionnaires. Only fractures due to low or moderate trauma (eg, tripping, slipping, falling from the height of a chair) were considered cases for this study. About 15% of the reported hip fractures occurred with high-trauma events (eg, motor ve-

hicle accidents, skiing, horseback riding) and were therefore excluded. We anticipated a high degree of accuracy for self-reported hip fractures in a cohort of registered nurses. Indeed, in a small validation study of 30 reported hip fractures, medical records confirmed all reports.¹⁴

Dietary Assessment

Dietary intake was assessed in 1980, 1984, 1986, 1990, and 1994 with a semi-quantitative food frequency questionnaire (FFQ), which consisted of a list of foods with a selection of 9 responses ranging from "never" to "6 or more times per day" for reporting the frequency of consumption of the specified standard portion size. The FFQ food list began with 61 items in 1980 and increased to 116 items in 1984 and to more than 130 items on the later FFQs. Nutrient contents of foods were derived primarily from US Department of Agriculture sources and supplemented with data from food manufacturers and published research. Carotenoid contents were obtained from a US Department of Agriculture and National Cancer Institute database.^{15,16} Use of brand-specific multivitamins and single vitamin or mineral supplements also was reported and added to total nutrient intakes (assessment of beta carotene supplement use did not begin until 1984, at which time it was used by less than 1% of the cohort). The FFQ also requested specification of the type of fat or oil and brand of margarine used in cooking and baking, and this information was used to calculate nutrients in fried and baked foods.

Exposure data were derived for total vitamin A, retinol, and provitamin A carotenoids, including beta carotene, alpha carotene, and beta cryptoxanthin. All measures were adjusted for total energy intake using regression analysis.¹⁷ In these analyses, the vitamin A, retinol, and carotenoid intakes were cumulatively updated during follow-up. That is, at the beginning of each 2-year follow-up cycle, the nutrient intake was calculated as the mean of all reported intakes up to that time. For example, at the beginning of analysis in 1980, vi-

tamin A intake was simply the value from the 1980 FFQ; in the 2-year cycle beginning in 1994, vitamin A intake was calculated as the mean of the values from the 1980, 1984, 1986, 1990, and 1994 FFQs.

Statistical models also included the following dietary variables that are potential confounders of the association between vitamin A and hip fractures: calcium, vitamin D, vitamin K, protein, alcohol, and caffeine. As was done for the vitamin A and carotenoid measures, the covariate nutrient intakes that are correlated with total energy intake (all except alcohol and caffeine) were adjusted for total energy, and all were cumulatively updated during follow-up.

The food and nutrient assessments from the FFQ have been validated in several substudies within the NHS cohort. In a comparison of the 1986 FFQ with two 1-week diet records among 191 women, correlation coefficients were 0.79 for total vitamin A from food only and 0.59 for retinol from food only.¹⁸ In another substudy,¹⁹ the correlation between beta carotene intake from the 1986 FFQ and plasma beta carotene levels among 186 women was 0.31 ($P < .05$).

Other Covariates

Smoking status, number of cigarettes smoked per day, use of postmenopausal hormones, and body weight were requested on all biennial questionnaires. Body mass index was calculated at each 2-year cycle from the current weight and the height reported on the 1976 questionnaire. The number of hours of physical activity per week spent in leisure-time activities was reported in 1980, 1982, 1986, 1988, 1992, 1994, and 1996, and values were cumulatively updated in analysis. Use of thiazide diuretics was assessed in 1980, 1982, 1988, 1994, and 1996.

Statistical Analysis

Person-time was accrued for each participant from the return date of the 1980 questionnaire or the questionnaire on

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which she first reported being postmenopausal until the occurrence of a hip fracture, death, or the end of follow-up on June 1, 1998. The 72337 women in this analysis contributed a total of 860355 person-years. For analyses of vitamin A, retinol, and beta carotene from food sources only, women were excluded when they reported taking a multivitamin or a specific vitamin A or beta carotene supplement. These analyses included 34386 women and 313138 person-years. Current exposure and covariate information was used to allocate person-time to the appropriate category for each variable at the beginning of each 2-year follow-up cycle. In the main analyses, women were categorized into quintiles of vitamin A, retinol, and carotenoid intakes, and age-adjusted incidence rates were calculated for each quintile. Relative risks (RRs) were then calculated as the ratio of risk in each quintile compared with the risk in the first, or referent, quintile. We used proportional hazards models to calculate multivariate RRs, adjusting simultaneously for the potential confounding variables. To examine linear trend, the vitamin A, retinol, and carotenoid exposure variables were entered into the models as continuous values. All analyses were carried out using SAS, version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

TABLE 1 outlines the changes in vitamin A, retinol, and beta carotene intakes and in consumption patterns of supplements and foods that were major contributors to vitamin A intake in the NHS cohort during follow-up. Between 1980 and 1994, mean total retinol intake decreased from 1378 to 1114 $\mu\text{g}/\text{d}$ and mean total beta carotene intake increased from 4278 to 5908 $\mu\text{g}/\text{d}$. Multivitamins were the primary contributors to total retinol (35%-43% of intake), and carrots contributed the most to total beta carotene intake (30%-41% of intake). Liver was the primary food source of retinol, although its contribution declined between 1980 and 1994 while the percentages from milk and breakfast cereals increased.

In 1994, mean retinol intake limited to food sources was 546 $\mu\text{g}/\text{d}$, similar to the 527 $\mu\text{g}/\text{d}$ reported for women aged 51 to 70 years in the 1988-1994 Third National Health and Nutrition Examination Survey (NHANES III).²⁰ Beta carotene intake from food in the NHS cohort remained fairly stable during follow-up at about 4500 $\mu\text{g}/\text{d}$, much higher than the mean intake of 2665 $\mu\text{g}/\text{d}$ reported from NHANES III.

Multivitamins were used by 34% of the cohort in 1980; this increased to 53% by 1996. Vitamin A supplement use remained between 3% and 5% dur-

ing the follow-up period. No more than 3% of the cohort used beta carotene supplements between 1984 and 1992. This increased to 10% in 1994.

The recommended dietary allowance for vitamin A has recently been set at 700 $\mu\text{g}/\text{d}$ for women, with a tolerable upper limit of 3000 $\mu\text{g}/\text{d}$.²⁰ During follow-up, about 14% of NHS women had intakes below the recommended dietary allowance while 21% consumed more than the tolerable upper limit.

TABLE 2 shows the age-standardized characteristics of the study population by quintiles of vitamin A intake. Women with higher vitamin A intakes, whether from food only or from food plus supplements, were less likely to smoke and were more physically active. Those who consumed more vitamin A from food had diets higher in calcium, protein, vitamin D, and vitamin K and somewhat lower in alcohol. They were also more likely to take a multivitamin, vitamin A, or beta carotene supplement. In the highest quintile of vitamin A intake from food plus supplements, 67% of the women were taking a multivitamin, compared with only 17% in the lowest quintile.

Among the postmenopausal women in the study population from 1980 to 1998, we identified 603 cases of non-traumatic hip fractures. The mean age at fracture was 64 years.

Table 1. Intakes of Vitamin A, Retinol, and Beta Carotene From Supplements and Foods, Nurses' Health Study, 1980-1998

	Year Assessed														
	Vitamin A					Retinol					Beta Carotene				
	1980	1984	1986	1990	1994	1980	1984	1986	1990	1994	1980	1984	1986	1990	1994
Daily intake, μg^*															
Mean	2178	2586	2134	2054	2373	1378	1266	1219	1085	1114	4278	4162	4290	4499	5908
Lowest	410	446	492	495	505	103	117	137	116	92	467	710	842	789	895
Highest	9869	9185	8649	7716	8959	8771	7838	7296	6034	6527	17903	14072	13313	14456	24278
Total intake, %†															
Multivitamin	24	23	25	21	22	37	38	43	35	41
Vitamin A supplement	6	7	6	4	5	9	11	10	7	10
Beta carotene supplement	1	1	6	1	2	3	14
Liver	14	13	8	10	7	22	21	14	19	15
Milk	5	5	5	6	5	7	7	9	11	11
Breakfast cereal	4	5	5	6	4	2	7	9	11	8
Carrots	20	19	20	23	23	41	39	33	37	30

*Vitamin A, retinol, and beta carotene values include intakes from food plus supplements. Vitamin A is measured in micrograms of retinol equivalents.
†Percentage contribution of individual foods and supplements toward total intake in the cohort. Ellipses indicate less than 1% of total intake.

VITAMIN A INTAKE AND HIP FRACTURES

Associations between hip fractures and cumulatively updated intakes of vitamin A, retinol, and beta carotene are shown in TABLE 3. Because of a lower prevalence of other risk factors among women with higher vitamin A intake, associations between vitamin A and risk of hip fracture were substantially stronger after controlling for these in multivariate analyses. For women in the highest quintile of vitamin A intake from food plus supplements compared with those in the lowest quintile, the multivariate RR of hip fracture was 1.48 (95% confidence interval [CI], 1.05-2.07) and the linear trend was significant ($P = .003$). For retinol from food plus supplements, the increase in risk was even greater (RR, 1.89; 95% CI, 1.33-2.68; P for trend $< .001$). For beta carotene, we observed

only a weak and nonsignificant increase in risk of hip fracture (RR, 1.22; 95% CI, 0.90-1.66; P for trend = .10). To compare our results with those from Melhus et al,¹⁰ we reanalyzed our data comparing women with retinol intakes of more than 1500 $\mu\text{g}/\text{d}$ with women consuming less than 500 $\mu\text{g}/\text{d}$. We found an RR of 1.64 (95% CI, 1.14-2.35) in the high-intake category, similar to the odds ratio of 1.54 (95% CI, 1.06-2.24) reported by Melhus et al from their model, which, like ours, controlled for calcium intake.

To assess risk of fracture from food sources only, we excluded women from further follow-up when they reported taking a multivitamin or a specific vitamin A or beta carotene supplement. These intakes from food do, however,

include vitamin A fortification of milk, margarine, and breakfast cereals. Relative risks were elevated in the highest quintiles of vitamin A intake from food (RR, 1.82; 95% CI, 0.97-3.40; P for trend = .24) and retinol from food (RR, 1.69; 95% CI, 1.05-2.74; P for trend = .05), similar to the results we observed for intakes from food plus supplements, despite the fact that the cut points for the highest quintiles in the food analyses were lower than those used in the analyses that included supplements. Beta carotene from food showed a weak and nonsignificant positive association with fracture risk. Although beta carotene is the primary dietary carotenoid with provitamin A activity, we examined intakes of alpha carotene and beta cryptoxanthin and

Table 2. Characteristics of the Study Population of Postmenopausal Women (n = 72 337) by Quintiles of Vitamin A Intake, Nurses' Health Study, 1980-1998*

	Quintiles of Vitamin A Intake									
	Food and Supplements					Food Only				
	1	2	3	4	5	1	2	3	4	5
Age, mean, y	58.3	59.3	59.7	60.0	60.5	59.0	60.0	60.6	61.1	61.7
Body mass index, mean, kg/m ²	26.0	26.0	25.9	25.8	25.7	26.0	26.0	26.0	26.1	26.0
Physical activity, mean, h/wk	2.4	2.7	2.9	3.0	3.2	2.4	2.7	2.9	3.0	3.4
Current smoker, %	26	20	18	18	17	23	18	16	15	14
Daily intake, mean										
Vitamin A, $\mu\text{g}\ddagger$										
Food and supplements	965	1442	1890	2491	4274	1415	1789	2037	2388	3108
Food only	940	1310	1553	1757	2045	811	1146	1427	1763	2507
Retinol, μg										
Food and supplements	487	763	1085	1607	3206	1000	1201	1319	1516	1852
Food only	429	605	733	854	985	425	553	666	802	1014
Beta carotene, μg										
Food and supplements	2664	3824	4673	5295	6747	2852	3789	4419	5188	6996
Food only	2647	3775	4586	5147	6378	2705	3627	4258	5006	6793
Calcium, mg \ddagger	719	827	887	947	1058	800	902	932	970	1018
Protein, g	70	74	75	77	80	70	73	75	77	80
Vitamin D, $\mu\text{g}\ddagger$	4.2	5.6	7.1	9.5	13.8	6.8	7.9	8.1	8.6	9.2
Vitamin K, μg	140	169	187	204	233	132	163	181	203	254
Alcohol, g	7.4	6.6	6.4	6.3	5.6	8.2	6.8	6.4	5.8	5.0
Caffeine, mg	370	350	338	326	307	352	332	324	314	301
Current use, %										
Postmenopausal hormones	29	30	33	34	34	34	36	36	36	34
Thiazide diuretics	13	13	13	14	13	12	13	13	13	13
Multivitamin supplements	17	26	38	54	67	38	42	43	45	45
Vitamin A supplements	0.6	1.1	1.9	3.4	15	3.1	3.7	4.0	4.4	6.1
Beta carotene supplements	0.8	1.6	2.5	4.5	11	3.7	4.2	4.2	4.8	5.4

*Values are standardized to the age distribution of the study population during follow-up. Vitamin A and other dietary variables were assessed in 1980, 1984, 1986, 1990, and 1994, intakes were cumulatively averaged over time.

†Vitamin A is measured in micrograms of retinol equivalents (1500 μg RE = 5000 IU).

‡Calcium and vitamin D include intake from food and supplements.

found no appreciable increase in risk of hip fracture with higher intakes of either of these carotenoids (data available on request from the authors).

Consumption of liver and carrots, the major food sources of retinol and beta carotene, respectively, in this population, confirmed the results we observed in the nutrient analyses. Women who consumed liver 1 or more times per week had an elevated although non-significant RR of 1.69 (95% CI, 0.95-3.04) for hip fracture compared with women who never consumed liver. For

women who consumed carrots 1 or more times per day compared with less than once per week, the RR was 1.05 (95% CI, 0.61-1.82).

Using intake as a continuous variable, for every additional 500-µg/d increase in retinol intake, hip fracture risk increased significantly: 15% (95% CI, 8%-22%) for retinol from food plus supplements and 33% (95% CI, 9%-64%) for retinol from food only. For a 2000-µg daily increase in beta carotene, the increase in fracture risk was not statistically significant: 7% (95% CI,

-1% to 15%) for total beta carotene and 2% (95% CI, -10% to 17%) for beta carotene from food only.

Results from analyses using only the 1980 baseline diet to characterize nutrient intakes over the 18 years of follow-up were weaker than the results from the Table 3 analyses in which nutrient intakes were cumulatively updated over time. In these baseline analyses, the RRs for hip fracture in the highest quintiles of intake were 1.10 (95% CI, 0.82-1.47) for baseline vitamin A from food plus supplements and

Table 3. Relative Risk (RR) of Hip Fracture by Quintiles of Vitamin A, Retinol, and Beta Carotene Intakes Among Postmenopausal Women in the Nurses' Health Study, 1980-1998*

	Quintiles of Consumption†					P for Trend‡
	1	2	3	4	5	
Vitamin A§						
Food and supplements, µg/d	<1250	1250-1699	1700-2249	2250-2999	≥3000	
Cases	118	103	121	124	137	
Age-adjusted RR (95% CI)	1.00	0.79 (0.60-1.02)	0.89 (0.69-1.14)	0.88 (0.69-1.14)	0.94 (0.74-1.21)	.55
Multivariate RR (95% CI) ¶	1.00	0.92 (0.70-1.22)	1.13 (0.85-1.49)	1.24 (0.92-1.68)	1.48 (1.05-2.07)	✓.003
Food only, µg/d#	<1000	1000-1299	1300-1599	1600-1999	≥2000	
Cases**	22	30	25	32	30	
Age-adjusted RR (95% CI)	1.00	1.33 (0.77-2.31)	1.16 (0.66-2.05)	1.34 (0.77-2.34)	1.40 (0.81-2.42)	.53
Multivariate RR (95% CI) ¶	1.00	1.51 (0.86-2.66)	1.37 (0.74-2.51)	1.74 (0.96-3.14)	1.82 (0.97-3.40)	.24
Retinol						
Food and supplements, µg/d	<500	500-849	850-1299	1300-1999	≥2000	
Cases	102	122	111	122	146	
Age-adjusted RR (95% CI)	1.00	1.12 (0.86-1.46)	0.99 (0.76-1.30)	1.08 (0.83-1.40)	1.25 (0.97-1.60)	✗.03
Multivariate RR (95% CI) ¶	1.00	1.25 (0.95-1.65)	1.18 (0.88-1.59)	1.43 (1.04-1.96)	1.89 (1.33-2.68)	✗<.001
Food only, µg/d#	<400	400-549	550-699	700-999	≥1000	
Cases	31	36	29	42	52	
Age-adjusted RR (95% CI)	1.00	1.20 (0.74-1.94)	0.92 (0.55-1.53)	1.34 (0.84-2.15)	1.67 (1.07-2.61)	✗.05
Multivariate RR (95% CI) ¶	1.00	1.27 (0.77-2.07)	0.96 (0.57-1.63)	1.41 (0.86-2.32)	1.69 (1.05-2.74)	✗.05
Beta Carotene						
Food and supplements, µg/d	<2550	2550-3549	3550-4649	4650-6299	≥6300	
Cases, No.	121	129	106	127	120	
Age-adjusted RR (95% CI)	1.00	1.00 (0.78-1.29)	0.79 (0.61-1.03)	0.92 (0.72-1.18)	0.83 (0.65-1.07)	.27
Multivariate RR (95% CI) ¶	1.00	1.18 (0.91-1.53)	1.03 (0.77-1.37)	1.27 (0.96-1.69)	1.22 (0.90-1.66)	.10
Food only, µg/d#	<2500	2500-3449	3450-4549	4550-6099	≥6100	
Cases, No.	41	35	42	34	38	
Age-adjusted RR (95% CI)	1.00	0.92 (0.58-1.44)	1.09 (0.71-1.68)	0.95 (0.61-1.48)	1.11 (0.71-1.72)	.78
Multivariate RR (95% CI) ¶	1.00	1.06 (0.66-1.69)	1.36 (0.85-2.16)	1.12 (0.67-1.87)	1.36 (0.81-2.30)	.94

*A total of 72 337 women contributed 860 355 person-years to this analysis; the hip fracture cases count was 603. CI indicates confidence interval.
 †Diet was assessed in 1980, 1984, 1986, 1990, and 1994 and nutrient intakes were cumulatively updated during analysis. Quintile cut-points varied somewhat with each dietary assessment; values listed here are approximate.
 ‡Test for trend for linear increase in nutrient intake.
 §Vitamin A is measured in micrograms of retinol equivalents.
 ¶Risk estimates were adjusted for age and follow-up cycle.
 ¶Risk estimates were adjusted for age, follow-up cycle, body mass index, use of postmenopausal hormones, smoking (including years since quitting for past smokers and cigarettes/d for current smokers), hours of leisure-time activity per week, use of thiazide diuretics, and intakes of calcium, protein, vitamin D, vitamin K, alcohol, and caffeine.
 #In analyses of nutrients from food sources only, women were excluded from further follow-up when they reported taking a multivitamin, a vitamin A supplement, or a beta carotene supplement. A total of 34 386 women contributed 313 138 person-years to this analysis; the hip fracture cases count was 190.
 **Does not include follow-up from 1980-1984 due to lack of data from the 1980 dietary questionnaire for vitamin A from food only; 28 676 women contributed 217 635 person-years to this analysis; the hip fracture cases count was 139.

1.17 (95% CI, 0.87-1.58) for baseline retinol from food plus supplements.

To examine the relative contributions of total retinol and beta carotene to the risk of hip fractures, we put both nutrient intakes in the same multivariate model. Results were similar to those reported from separate models (data available on request from the authors). We also examined the association between beta carotene and hip fractures within strata of retinol intake. Since absorption of beta carotene and its conversion to retinol is greater when retinol intake is low, any elevated risk of hip fracture with higher beta carotene intake might be seen most clearly among women with the lowest retinol intakes. However, among women in the lowest tertile of retinol intake from food plus supplements, those in the highest compared with the lowest quintile of beta carotene intake from food plus supplements had an RR of hip fracture of 0.94 (95% CI, 0.53-1.68). We performed other stratified analyses by intakes of calcium (<800 vs \geq 800 mg/d) and vitamin D (<5 vs \geq 5 μ g/d) and by smoking status (never, past, or current) and observed no significant differences in associations between hip fractures and vitamin A, retinol, or beta carotene intakes within the strata (data available on request from the authors).

We also examined intakes of vitamin A, retinol, and beta carotene stratified by postmenopausal hormone use. For retinol from food plus supplements, the risk

of hip fracture was significantly elevated only among the women not using postmenopausal hormones (TABLE 4). In comparison to the reference group of current hormone users in the lowest quintile of retinol intake, the RRs in the highest retinol quintiles were 2.52 (95% CI, 1.48-4.31) among women not using postmenopausal hormones and only 1.26 (95% CI, 0.68-2.33) among current hormone users. Unlike retinol, higher beta carotene intake did not confer a greater risk of hip fracture among the women not using postmenopausal hormones (data available on request from the authors).

Associations between hip fractures and use of multivitamins, vitamin A supplements, and beta carotene supplements are shown in TABLE 5. Risk of hip fracture was elevated with current use of either vitamin A supplements (RR, 1.40; 95% CI, 0.99-1.99) or multivitamins (RR, 1.32; 95% CI, 1.04-1.67), although we did not observe a linear increase in risk with longer duration of use for either one. Risk also was elevated among past users, though time since last use was low: 41% of past multivitamin users and 31% of past vitamin A supplement users had quit within the 2-year period since the previous questionnaire. Multivitamins are a source of vitamin D and calcium as well as retinol; therefore, these analyses were controlled for total vitamin D and calcium intakes. Risk of hip fracture was even greater for current vitamin A supplement users (RR, 1.75; 95%

CI, 1.09-2.80) and multivitamin users (RR, 1.59; 95% CI, 1.12-2.26) among women with low intakes of retinol from food sources (<600 μ g/d). Use of beta carotene supplements did not confer any increase in risk of hip fractures.

COMMENT

In this prospective cohort study of postmenopausal women, the risk of hip fracture was almost doubled among women with retinol intakes of about 2000 μ g/d or more compared with those with intakes of less than about 500 μ g/d. Current use of vitamin A supplements alone was associated with a 40% (nonsignificant) increase in risk. In contrast with retinol, higher intakes of beta carotene did not significantly increase the risk of hip fracture.

Our results are consistent with those reported by Melhus et al in Sweden.¹⁰ In that nested case-control study with 247 hip fracture cases among women aged 40 to 76 years, the risk of fracture was doubled for a retinol intake of greater than 1500 μ g/d compared with an intake of less than 500 μ g/d, and risk was found to increase linearly ($P=.006$). With calcium in the model, the odds ratio was reduced to 1.54 but remained statistically significant. Using the same comparison groups, we found a similar RR of 1.64.

Among the postmenopausal women in the NHS cohort, we observed a strong positive association between retinol intake and hip fractures only among those

Table 4. Relative Risk (RR) of Hip Fracture by Postmenopausal Hormone Use and Quintiles of Retinol Intake From Food and Supplements Among Postmenopausal Women in the Nurses' Health Study, 1980-1998*

Quintiles of Retinol (μ g/d)†	Postmenopausal Hormone Users†				Non-Postmenopausal Hormone Users†			
	Person-Years	Cases, No.	Age-Adjusted RR (95% CI)§	Multivariate RR (95% CI)¶	Person-Years	Cases, No.	Age-Adjusted RR (95% CI)§	Multivariate RR (95% CI)¶
1 (<500)	49 370	22	1.00 (Referent)	1.00 (Referent)	107 223	63	1.10 (0.67-1.79)	1.09 (0.67-1.78)
2 (500-849)	51 353	22	0.88 (0.49-1.58)	0.95 (0.52-1.72)	105 590	80	1.32 (0.82-2.12)	1.44 (0.89-2.33)
3 (850-1299)	55 543	21	0.74 (0.41-1.35)	0.87 (0.47-1.61)	104 864	76	1.23 (0.76-1.98)	1.43 (0.87-2.36)
4 (1300-1999)	57 470	30	0.99 (0.57-1.71)	1.29 (0.71-2.32)	100 754	79	1.29 (0.80-2.08)	1.66 (0.99-2.78)
5 (\geq 2000)	58 501	28	0.81 (0.46-1.41)	1.26 (0.68-2.33)	94 819	97	1.60 (1.00-2.56)	2.52 (1.48-4.31)

*The reference category is current postmenopausal hormone users in the lowest quintile of retinol intake. CI indicates confidence interval.

†Postmenopausal hormone use was updated every 2 years over follow-up.

‡Diet was assessed in 1980, 1984, 1986, 1990, and 1994 and retinol intake was cumulatively updated during analysis. Quintile cut-points varied somewhat with each dietary assessment; values listed here are approximate.

§Risk estimates were adjusted for age and follow-up cycle.

¶Risk estimates were adjusted for age, follow-up cycle, body mass index, smoking (including years since quitting for past smokers and cigarettes/d for current smokers), hours of leisure-time activity per week, use of thiazide diuretics, and intakes of calcium, protein, vitamin D, vitamin K, alcohol, and caffeine.

not currently using postmenopausal hormones. We had no prior hypothesis for this finding; therefore, it needs to be examined in other studies.

Due to the high rate of absorption and the large storage capacity for retinol in the human body,²¹ vitamin A toxicity can result from acute ingestion of a very high dose, generally more than 100 000 IU,²² or from repeated exposure for several weeks or months to lesser dosages (eg, between 25 000 and 50 000 IU/d)⁶ (1 IU = 0.3 µg of retinol). Vitamin A toxicity has not been observed with excessive intakes of beta carotene,²³ presumably because of limitations on its absorption and conversion to retinol.²⁴

Excess vitamin A is known to have teratogenic effects on bone growth in mice^{25,26} and is likely to affect human fetal bone development as well.²⁷ In growing animals, hypervitaminosis A can produce bone fractures²⁸⁻³⁰ and other skeletal anomalies.^{31,32} Isolated cases of hypervitaminosis A in humans were associated with bone pain, hypercalcemia, and increased bone resorption.⁶ Also, patients undergoing long courses of treatment with retinoids, such as isotretinoin and etretinate for skin conditions, have experienced progressive calcification of ligaments, modeling abnormalities of long bones, and osteoporosis.^{33,34} Direct effects of vitamin A on bone osteoclasts and osteoblasts have been demonstrated in vitro that increase bone resorption and decrease formation.^{3,4,29,35} If this mechanism occurs in vivo, long-term exposure to high vitamin A amounts could plausibly lead to low bone density and fractures. This may be exacerbated in older adults with diminished capacity to clear high levels of ingested retinol.³⁶ A deleterious effect of vitamin A on bone may also operate through its antagonistic relationship with vitamin D. In a recent study in humans, a vitamin A dose corresponding to about 1 serving of liver was shown to severely diminish the ability of vitamin D to increase intestinal calcium absorption.³⁷

Melhus et al¹⁰ noted that hip fracture incidence in Europe is highest in

Sweden and Norway, countries that also have the highest intakes of vitamin A, primarily from fish oils and dairy foods. In the United States, high consumption is also common and easily attainable. Due to the loss of vitamin A with the removal of fat, skim and low-fat milk are fortified to at least 350 µg/c (1500 µg/L). One tbsp (15 mL) of fortified margarine also contains about 150 µg of vitamin A and breakfast cereals are often fortified with up to 375 µg per serving. In addition, multivitamins may contain 1500 µg of retinol per tablet, although in more recent formulations part of the vitamin A content may be contributed by beta carotene. It is also possible to purchase vitamin A supplements in doses of 3000 µg.

Supplements contribute significantly to vitamin A intake in the United States. In a sample of adult women in NHANES III, the mean intake of vitamin A from supplements was 1338 µg/d,²⁰ and in the NHS cohort, more than

20% of the vitamin A in the diet was provided by multivitamins and about 5% came from vitamin A supplements. However, multivitamins contain other essential nutrients and have been associated with lower risk of coronary disease,³⁸ colon cancer,³⁹ and breast cancer⁴⁰ in this same cohort. Also, the findings from this study do not imply that supplementation with vitamin A should be discontinued when used for conditions such as retinitis pigmentosa, for which benefits have been documented,⁴¹ although monitoring of bone health may be appropriate.

This study was conducted in a mostly white population of women and results may not be generalizable to other racial/ethnic groups. Results are also limited to self-reported hip fractures with no further identification of exact fracture site. The strengths of this study are the 90% follow-up rate over 18 years and the repeated assessment of diet and supplement use. Results were greatly at-

Table 5. Relative Risk (RR) of Hip Fracture for Multivitamin, Vitamin A, and Beta Carotene Supplement Use Among Postmenopausal Women in the Nurses' Health Study, 1980-1998*

	Person-Years	Cases, No.	Age-Adjusted RR (95% CI)†	Multivariate RR (95% CI)‡
Multivitamin use				
Never	301 182	176	1.00	1.00
Past	167 361	121	1.11 (0.87-1.40)	1.25 (0.97-1.61)
Current§	348 618	262	1.13 (0.93-1.37)	1.32 (1.04-1.67)
<5 y	71 187	39	0.96 (0.68-1.36)	1.05 (0.74-1.49)
5-9 y	54 335	33	1.05 (0.72-1.53)	1.25 (0.83-1.85)
10-14 y	36 471	24	1.03 (0.67-1.57)	1.29 (0.81-2.05)
≥15 y	58 025	42	0.98 (0.70-1.38)	1.28 (0.86-1.91)
P for trend			.87	.34
Vitamin A supplement use				
Never	713 096	462	1.00	1.00
Past	64 023	61	1.17 (0.89-1.53)	1.34 (1.01-1.76)
Current§	40 020	36	1.32 (0.94-1.85)	1.40 (0.99-1.99)
<3 y	13 859	10	1.14 (0.61-2.13)	1.23 (0.65-2.30)
≥3 y	14 275	12	1.34 (0.75-2.37)	1.31 (0.72-2.39)
P for trend			.76	.80
Beta carotene supplement use				
No	607 663	419	1.00	1.00
Yes	28 137	21	0.85 (0.55-1.32)	0.91 (0.57-1.44)

*Supplement use was assessed every 2 years beginning in 1980 for multivitamins and vitamin A and in 1984 for beta carotene. Past use of multivitamins and vitamin A supplements was assessed at baseline; past use of beta carotene was not assessed at baseline; therefore, past use and duration of use were not calculated. CI indicates confidence interval.

†Risk estimates were adjusted for age and follow-up cycle.

‡Risk estimates were adjusted for age, follow-up cycle, body mass index, use of postmenopausal hormones, smoking (including years since quitting for past smokers and cigarettes/d for current smokers), hours of leisure-time activity per week, use of thiazide diuretics, and intakes of calcium, protein, vitamin D, vitamin K, alcohol, and caffeine.

§For multivitamins and vitamin A supplements, risk of hip fracture was calculated for all current users and by duration of use among continuous users. Never use was the reference group for all categories of current use.

||Test for trend for linear increase in duration of current use.

tenuated when only the initial reported diet was used for analyses because of real changes in diet over time and random error from a single measure, which is reduced when dietary intakes are cumulatively averaged with each new assessment.

Our findings provide further evidence that chronic intake of excessive vitamin A, particularly from retinol, may contribute to the development of osteoporotic hip fractures in women. The amounts of retinol in fortified foods

and vitamin supplements may need to be reassessed since these add significantly to total retinol consumption in the United States.

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Acquisition of data: Feskanich, Willett.

Analysis and interpretation of data: Feskanich, Willett, Colditz.

Drafting of the manuscript: Feskanich, Willett.

Critical revision of the manuscript for important intellectual content: Feskanich, Singh, Willett, Colditz.

Statistical expertise: Feskanich, Willett.

Obtained funding: Singh, Willett.

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Study supervision: Colditz.

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