Published in final edited form as:
Osteoporos Int. 2004 July ; 15(7): 552–559.

Vitamin A intake and the risk of hip fracture in postmenopausal women: the Iowa Women's Health Study

L.S. Lim
School of Public Health, Division of Epidemiology, University of Minnesota, Minneapolis, MN 55454, USA

Department of Internal Medicine, Division of Preventive and Occupational Medicine, Mayo Clinic, Rochester, MN 55905, USA

L.J. Harnack and **D. Lazovich**
School of Public Health, Division of Epidemiology, University of Minnesota, Minneapolis, MN 55454, USA

A.R. Folsom
School of Public Health, Division of Epidemiology, University of Minnesota, Minneapolis, MN 55454, USA E-mail: Folsom@epi.umn.edu Tel.: +1-612-6268862 Fax: +1-612-6240315

Abstract

Excessive intake of vitamin A is postulated to have a detrimental effect on bone by inducing osteoporosis. This may lead to an increased risk of fracture, particularly in persons who are already at risk of osteoporosis. However, few studies have specifically examined the association of vitamin A intake through diet and supplement use, with fractures in a cohort of older, community-dwelling women. We prospectively followed a cohort of 34,703 postmenopausal women from the Iowa Women's Health Study to determine if high levels of vitamin A and retinol intake through food and supplement use were associated with an increased risk of hip or all fractures. A semiquantitative food frequency questionnaire was used to obtain the participants' baseline vitamin A and retinol intake. Participants were followed for a mean duration of 9.5 years for incident self-reported hip and nonhip fractures. After multivariate adjustment, it was revealed that users of supplements containing vitamin A had a 1.18-fold increased risk of incident hip fracture (n = 525) compared with nonusers (95% CI, 0.99 to 1.41), but there was no evidence of an increased risk of all fractures (n = 6,502) among supplement users. There was also no evidence of a dose-response relationship in hip fracture risk with increasing amounts of vitamin A or retinol from supplements. Furthermore, our results showed no association between vitamin A or retinol intake from food and supplements, or food only, and the risk of hip or all fractures. In conclusion, we found little evidence of an increased risk of hip or all fractures with higher intakes of vitamin A or retinol among a cohort of older, postmenopausal women.

Keywords

Fracture; Hip fracture; Osteoporosis; Postmenopause; Retinol; Vitamin A

Introduction

Animal studies have shown that excessive vitamin A can have a detrimental effect on bone through decreased bone formation, increased bone resorption, and enhanced fracture probability [1]. Hypothesized mechanisms include retinol-induced osteoblastic inhibition [2],

Correspondence to: L.S. Lim.

osteoclastic stimulation [3], and vitamin D inhibition [4]. High vitamin A intake has also been shown to have a negative impact on human bone metabolism. Excessive vitamin A intake can cause skeletal deformities in fetuses [5]. Chronic vitamin A toxicity can also cause hypercalcemia [6], impairment of bone remodeling, and bone abnormalities in humans [7,8]. Furthermore, high intake of synthetic retinoids has been associated with decreased bone mass [9,10] and suppressed biochemical markers of bone turnover [11].

Several epidemiologic studies have examined the association between vitamin A intake and bone mass. Early studies examining the association of vitamin A intake via supplements or food with radial bone mass in postmenopausal women did not yield consistent results [12,13, 14,15]. This may have been related to cross-sectional rather than longitudinal study designs and the high intraindividual variance that exists for vitamin A intake [16]. More recent studies involving other skeletal sites have shown an inverse association between vitamin A intake and bone mass [17,18]. In a cross-sectional analysis of 175 women, retinol intake of greater than 1.5 mg/day was associated with a 10% reduction in femoral neck bone mineral density compared with intake of less than 0.5 mg/day [17]. This association was also seen at other skeletal sites including the lumbar spine and total body bone mineral density. In a prospective cohort study of 958 men and women, a log unit increase in dietary retinol intake among supplement users was associated with a 0.02 g/cm^2 lower bone mineral density (BMD) and 0.23% greater annual bone loss [18].

A few studies have found high levels of vitamin A intake to be associated with an increased risk of hip fracture [17,19]. In a prospective study of over 2,000 men, a serum retinol level in the highest quintile was associated with a 1.6-fold increased risk of any fracture and 2.5-fold increased risk of hip fracture relative to the middle quintile [20]. In a cohort study involving approximately 72,000 nurses, those in the highest quintiles of total vitamin A and retinol intakes were 1.5 and 1.9 times more likely to have a hip fracture respectively compared with those in the lowest quintiles of intake [19]. However, there are no published studies that examine the association of fracture with vitamin A intake through diet and supplement use in older, community-dwelling postmenopausal women. Forty-four percent of women aged 51–74 years report using a nutritional supplement [21]. About 65% of supplement users consume supplements containing vitamin A [22]. Chronic ingestion of large amounts of supplement-derived vitamin A may place older women at an increased risk for osteoporosis and fracture. Furthermore, the effect of exposure to high levels of vitamin A may be exacerbated in older persons by a diminished capacity for its clearance [23].

The purpose of this study was to determine if high levels of vitamin A and retinol intake through food or supplement use are associated with an increased rate of hip fracture in a cohort of postmenopausal women.

Methods

This study is based on a prospective cohort—the Iowa Women's Health Study (IWHS). The IWHS is a longitudinal investigation of 41,836 women aged 55–69 who were randomly selected from the 1985 Iowa driver's license registry. These participants responded to a baseline questionnaire that was mailed to 99,826 women in 1986 with a response rate of 42%. Nonrespondents were on average, 3 months younger than respondents, had a 0.4 kg/m^2 higher body mass index (BMI), and were more likely to live in a rural area [24].

The questionnaire included questions related to demography, lifestyle habits, medical history, reproductive and menstrual history, and body measurements. The following variables were dichotomized for statistical analysis: smoking history (ever smokers and never smokers), physical activity (moderate-to-high and low), level of formal education (high school or less

and greater than high school education), and medication use, including estrogen replacement of any duration (ever user and never user). Height and weight measurements were obtained by self-report and analyzed as continuous variables. Waist and hip measurements were obtained by using a standard tape measure that was provided. These measurement techniques have been shown to be valid and reliable [25]. The waist-to-hip ratio (WHR) and BMI were analyzed as continuous variables.

A semiquantitative food frequency questionnaire (FFQ) was used to assess diet. This FFQ was almost identical to the 1984 Nurses' Health Study dietary assessment [26] and included 127 food items and supplementary questions. The section on intake of vitamin supplements included questions on the name, frequency, and doses of multivitamins and of supplements containing only vitamin A. Multivitamins were coded individually to assign their contribution to vitamin A intake. Additional questions included the type of breakfast cereal consumed to determine the amount of vitamin A fortification. Daily intake of various dietary components including vitamin A (IU), retinol (IU), vitamin D (IU), calcium (mg), alcohol (g), caffeine (mg), and protein (g) were analyzed from the FFQ as either quintiles or continuous variables. The exposures of interest for this analysis were food and supplemental sources of baseline vitamin A (including both carotenoids and retinol) and retinol.

The accuracy of the FFQ for vitamin A intake was examined in an earlier study. The mean intakes from five 24-h dietary recalls were correlated with responses from the FFQ in a subgroup of 44 women [27]. The correlation coefficient of vitamin A intake from the two methods was found to be 0.14 from food only, and 0.56 from both food and supplements. For retinol intake, the correlation coefficient was 0.38 from food only, and 0.68 from both food and supplements. When the FFQ was re-administered 2 years after the baseline questionnaire, the correlation coefficients in the same 44 women were 0.64 and 0.58 for total vitamin A intake and vitamin A intake from food, respectively. The correlation coefficients for total retinol intake and retinol from food were 0.66 and 0.70, respectively.

Follow-up questionnaires were mailed out in 1987, 1989, 1992, and 1997. The response rates for each of these years were 91%, 89%, 83%, and 79%, respectively. These questionnaires obtained information on the vital status, residence, and self-reported medical conditions of the participants. The last included information on the occurrence of hip and nonhip fractures. The primary and secondary outcomes of interest were the first reported occurrences of hip and all fractures. Another study found a 91% agreement between self-reported hip fracture and medical chart review [28]. Reported nonhip fractures included fractures of the upper arm, forearm, wrist, ribs, and vertebrae. Follow-up time for cases of fracture was calculated as the number of years from completion of the baseline questionnaire to the midpoint between the year in which the first hip fracture was reported and the participant's previous questionnaire. For noncases, the follow-up time was calculated from the baseline questionnaire to the completion of the last questionnaire or death (through 1997). Deaths were identified through the Iowa State Health Registry and the National Death Index.

A subgroup analysis of participants who responded to the 1997 follow-up questionnaire showed that 54% of those who reported using multivitamins or supplements containing vitamin A in 1986 still reported using them in 1997. Twenty-six percent of participants who did not use multivitamins or supplements containing vitamin A in 1986 were using them in 1997.

Statistical analysis

Women were excluded if they were premenopausal at the time of the baseline questionnaire (n = 569); if they had implausible energy intakes of less than 600 kcal or greater than 5,000 kcal, or failed to complete a substantial portion (≥30 missing items) of the FFQ (n = 3,102);

or if they had reported a history of cancer other than skin cancer (n = 3,830). These exclusions were not mutually exclusive and the remaining number of participants was 34,703.

The age- and multivariate-adjusted relative risks for hip and all fractures were computed for supplement users (those who reported using a vitamin A–containing supplement) versus nonusers. Supplement users were categorized into three levels of vitamin A and retinol intake (less than 5,000 IU, 5,000 to 9,999 IU, and 10,000 IU or more), and the risks of hip and all fractures were calculated relative to the nonsupplement group. The age- and multivariate-adjusted relative risk of hip and all fractures were also computed for quintiles of total and food-only vitamin A and retinol referenced against the lowest quintile. In order to make comparisons with a similar recent study, age-adjusted relative risks also were computed for five categories of vitamin A intake using cutoffs from the Nurses' Health Study [19].

Analysis of covariance (ANCOVA) was conducted to identify possible confounding variables, adjusting for age. Variables that were associated with vitamin A intake at $p < 0.2$ for the F-test for overall difference were selected for inclusion in proportional hazards (Cox) regression analysis. Covariates were retained in the multivariate model using improvement-of-fit criteria ($p < 0.05$). All multivariate models included adjustment for energy intake as a continuous variable. All analysis was performed using PC SAS version 8.2 (SAS Institute, Cary, NC, USA).

Results

The analysis involved a total of 34,703 predominantly white (99.3%) women with a median age of 61 years. There were 525 incident hip fractures, and a total of 6,502 hip and nonhip fractures. The mean length of follow-up was 9.5 person-years. Slightly over one third of the participants (35%) used supplements containing vitamin A at baseline (n = 12,293). Supplement users were slightly younger, less obese, physically more active, more educated, and less likely to have diabetes compared with nonusers (Table 1). They were also more likely to use thyrotropic, sedative, and steroid medications, and estrogen replacement therapy. The energy-adjusted mean intakes of protein, calcium, and vitamin D were higher, whereas the mean caffeine intake was lower among supplement users compared with nonusers. The mean total vitamin A intake was 6,920 IU higher among supplement users compared with nonusers. There were generally similar differences among the subjects grouped by quintiles of total vitamin A intake (extreme quintile results shown in Table 1).

In the age-adjusted model, vitamin A supplement users had a 17% higher risk of hip fracture compared with nonusers (95% CI, −2% to +39%) (results not shown). The relative risk was similar after adjusting for age, BMI, WHR, diabetes mellitus, physical activity, steroid medication, and estrogen replacement therapy (RR = 1.18, 95% CI, 0.99 to 1.41). Vitamin A supplement use was not associated with risk of all fractures (RR = 1.00, 95% CI, 0.95 to 1.05, after adjusting for age, BMI, education, diabetes mellitus, cirrhosis, and use of sedative, thyrotropic, seizure, and steroid medications). When analyzed according to quantity of vitamin A obtained from supplements, risk of hip fracture was slightly greater than 1.0 for each level of vitamin A from supplement use compared with nonusers (Table 2). However, these relative risks were not statistically significant, and a dose-response relationship was not observed. Similarly null results were seen with increasing amounts of retinol intake from supplements for hip fracture and for all fractures (Table 2).

Table 3 shows the relative risk of hip and all fractures by quintiles of total vitamin A and retinol intake, with the covariates adjusted for, indicated in Table 3 footnotes. Other dietary factors such as calcium or vitamin D were not found to be independent risk factors for fracture in the models and were not included. There were no significant dose-response relationships across

quintiles of total vitamin A or retinol intake and hip fracture risk. There also was no association between total vitamin A or retinol intake and risk of any fracture. Two supplemental analyses were run (not shown). First, we confirmed that very high levels were not especially risky, as the RR of hip fracture for the highest decile of vitamin A intake compared with the lowest decile was 1.15 (95% CI, 0.76 to 1.76). When cut points (< 1,250 μg/day [< 6,250 IU/day], 1,250–1,699 μg/day [6,250–8,499 IU/ day], 1,700–2,249 μg/day [8,500–11,249 IU/day], 2,250–2,999 μg/day [11,250–14,999 IU/day], and ≥3,000 μg/day [≥15,000 IU/day]) from the Nurses' Health Study were used [19], there still was no association.

Among nonusers of supplements, there also was no association of increasing quintiles of vitamin A or retinol intake from food with the risk of hip fracture (Table 4). In fact, women in the highest quintile of retinol intake had 26% fewer hip fractures than those in the first quintile (95% CI, −50% to +8%). Among supplement nonusers, increasing quintiles of food-derived vitamin A were inversely associated with all fracture types (*p* value for test of trend = 0.01). A similar trend was not observed for increasing quintiles of food-derived retinol, and there was no evidence of an increased risk of any fracture beyond the first quintile of retinol intake. Among supplement users, no effect of food-derived vitamin A or retinol on hip or all fractures was seen as well (results not shown).

Discussion

Epidemiologic evidence from previous studies has suggested that consuming vitamin A in excessive amounts may be detrimental to bone mass and may even be a risk factor for osteoporotic fractures. The results from our study largely fail to confirm this association for total, food only, and supplemental vitamin A. Only supplemental vitamin A users had a small, elevated risk of hip fracture compared with nonusers (RR = 1.18, 95% CI, 0.99 to 1.41). However, hip fracture incidence showed no dose-response increase with the amount of supplemental vitamin A. Results were similarly null when the intake of supplemental retinol (the biologically active form of vitamin A) was examined. Risk of all fractures also was not increased among supplement users compared with nonusers. Among supplement nonusers, there was a trend toward a reduced risk of all fractures with increasing quintiles of vitamin A intake from food, which was not seen for food-related retinol intake. These results, overall, suggest that the risk of fracture is not related to the intake of vitamin A or retinol in this cohort.

Even though 35% of women used supplements containing vitamin A, supplement users also tended to consume slightly more vitamin A from food sources, compared with nonusers of supplements. The mean intake of vitamin A from food only was 12,293 IU for supplement users and 11,933 IU for nonusers. As the former consumed an average of 7,000 IU more total vitamin A than the latter group, supplement use in this cohort may be an indicator of vitamin A overuse.

In the only other published study of vitamin A intake and fracture risk in postmenopausal women, the Nurses' Health Study, the risk of hip fracture was 1.5 times greater in the highest quintile of daily vitamin A intake compared with the lowest quintile [19]. The increased risk was primarily attributed to retinol (RR = 1.89 for highest vs lowest quintile). There was a trend toward increased hip fracture risk (RR = 1.40, 95% CI, 0.99 to 1.99) among women who used vitamin A supplements, compared with those who never used them. Among nonusers of supplements, the highest quintile of retinol intake from food had a 1.7 times increased risk of hip fracture compared with the lowest quintile. Apart from the slightly increased risk of hip fracture among users of vitamin A supplements, we were not able to confirm the other results from Nurses' Health Study. The Nurses' Health Study was a larger study (*n* = 72,337), had longer follow-up (18 years), and included a broader range of ages (34 to 77 years). The racial composition and the initial proportion of participants who used vitamin supplements were

similar in both studies. The mean total daily vitamin A intake among our study participants was 14,429 IU, which was higher than the mean intake of 11,325 IU observed in the Nurses' Health Study. One major difference is that in the Nurses' Health Study, the amount of vitamin A and retinol was determined from an average of five FFQs, which probably provided a more accurate estimate of intake. Because we only had one FFQ, our vitamin A measures undoubtedly suffered from more random error, which would tend to attenuate our relative risk estimates toward the null.

Other limitations to our study include the following: Subjects who quit completing follow-up questionnaires were censored at death or the time of the last questionnaire, which made fracture ascertainment impossible. This could lead to a biased relative risk if these subjects had a different vitamin A association with fracture. As stated above, the semiquantitative FFQ was obtained only once at baseline and dietary vitamin A has a high intraindividual variation, which may lead to some imprecision in measuring the exposure variables. The correlations for vitamin A and retinol were low in the validation study, which may in part reflect the limited utility of five 24-h dietary recalls (the criterion measure) for assessing the intake of nutrients such as vitamin A that have a very high intraindividual variation in intake. A cause of high variation includes fluctuating or seasonal dietary patterns. Dietary habits or supplement use may also change over a long period of time, leading to misclassification of the exposure variables. However, the validity of the FFQ was more acceptable if supplements were included with dietary sources ($r = 0.56$). Furthermore, it was found to be moderately reliable on repeat administration [27]. In spite of that, it is possible that exposure misclassification may have obscured a weak association with the outcome. Although verification of the reported fracture was not undertaken in this study, self-reported hip fracture appears to be reasonably valid [28]. We were unable to distinguish between traumatic and spontaneous hip fractures. However, most hip fractures in this age group are associated with osteoporosis [29]. There are limits to the generalizability of our study to other populations as it was conducted predominantly on white women.

A strength of this study is the large size, which allowed an adequate number of relatively rare events to be captured, and good statistical power. The mailed questionnaires, rather than face-to-face visits at a study center, enabled a fairly large representation of community-based women to participate.

Conclusion

There was a slightly increased risk of hip fracture among users of supplements containing vitamin A (RR = 1.18; 95% CI, 0.99 to 1.41), but no apparent dose-response. Otherwise, we found little relation of hip fracture incidence with vitamin A or retinol intake.

Acknowledgements

The Iowa Women's Health Study was funded by research grant R01 CA39742 from the National Cancer Institute. Special thanks to Ching-Ping Hong for her statistical support and William Thomas, PhD, for his comments and feedback.

References

1. Binkley N, Krueger D. Hypervitaminosis A and bone. Nutr Rev 2000;58:138–144. [PubMed: 10860393]
2. Togari A, Kondo M, Arai M, et al. Effects of retinoic acid on bone formation and resorption in cultured mouse calvaria. Gen Pharmacol 1991;22:287–292. [PubMed: 2055423]
3. Scheven BA, Hamilton NJ. Retinoic acid and 1,25-dihydroxyvitamin D3 stimulate osteoclast formation by different mechanisms. Bone 1990;11:53–59. [PubMed: 2331432]

4. Rohde CM, Manatt M, Clagett-Dame M, et al. Vitamin A antagonizes the action of vitamin D in rats. J Nutr 1999;129:2246–2250. [PubMed: 10573558]
5. Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high vitamin A intake. N Engl J Med 1995;333:1369–1373. [PubMed: 7477116]
6. Frame B, Jackson CE, Reynolds WA, et al. Hypercalcemia and skeletal effects in chronic hypervitaminosis A. Ann Intern Med 1974;80:44–48. [PubMed: 4810349]
7. Hathcock JN, Hattan DG, Jenkins MY, et al. Evaluation of vitamin A toxicity. Am J Clin Nutr 1990;52:183–202. [PubMed: 2197848]
8. Bendich A, Langseth L. Safety of vitamin A. Am J Clin Nutr 1989;49:358–371. [PubMed: 2492745]
9. DiGiovanna JJ, Sollitto RB, Abangan DL, et al. Osteoporosis is a toxic effect of long-term etretinate therapy. Arch Dermatol 1995;131:1263–1267. [PubMed: 7503569]
10. Okada N, Nomura M, Morimoto S, et al. Bone mineral density of the lumbar spine in psoriatic patients with long term etretinate therapy. J Dermatol 1994;21:308–311. [PubMed: 8051315]
11. Kindmark A, Rollman O, Mallmin H, et al. Oral isotretinoin therapy in severe acne induces transient suppression of biochemical markers of bone turnover and calcium homeostasis. Acta Derm Venereol 1998;78:266–269. [PubMed: 9689293]
12. Sowers MF, Wallace RB. Retinol, supplemental vitamin A and bone status. J Clin Epidemiol 1990;43:693–699. [PubMed: 2370577]
13. Yano K, Heilbrun LK, Wasnich RD, et al. The relationship between diet and bone mineral content of multiple skeletal sites in elderly Japanese-American men and women living in Hawaii. Am J Clin Nutr 1985;42:877–888. [PubMed: 3877451]
14. Freudenheim JL, Johnson NE, Smith EL. Relationships between usual nutrient intake and bone-mineral content of women 35–65 years of age: longitudinal and cross-sectional analysis. Am J Clin Nutr 1986;44:863–876. [PubMed: 3491533]
15. Sowers MR, Wallace RB, Lemke JH. Correlates of midradius bone density among postmenopausal women: a community study. Am J Clin Nutr 1985;41:1045–1053. [PubMed: 3873171]
16. Willett, W. Nutritional epidemiology. Oxford University Press; New York: 1998. Nature of variation in diet; p. 33-49.
17. Melhus H, Michaelsson K, Kindmark A, et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. Ann Intern Med 1998;129:770–778. [PubMed: 9841582]
18. Promislow JH, Goodman-Gruen D, Slymen DJ, et al. Retinol intake and bone mineral density in the elderly: the Rancho Bernardo Study. J Bone Miner Res 2002;17:1349–1358. [PubMed: 12162487]
19. Feskanich D, Singh V, Willett WC, et al. Vitamin A intake and hip fractures among postmenopausal women. JAMA 2002;287:47–54. [PubMed: 11754708]
20. Michaelsson K, Lithell H, Vessby B, et al. Serum retinol levels and the risk of fracture. N Engl J Med 2003;348:287–294. [PubMed: 12540641]
21. Koplan JP, Annest JL, Layde PM, et al. Nutrient intake and supplementation in the United States (NHANES II). Am J Public Health 1986;76:287–289. [PubMed: 3484909]
22. Stewart ML, McDonald JT, Levy AS, et al. Vitamin/ mineral supplement use: a telephone survey of adults in the United States. J Am Diet Assoc 1985;85:1585–1590. [PubMed: 4067153]
23. Whiting SJ, Lemke B. Excess retinol intake may explain the high incidence of osteoporosis in northern Europe. Nutr Rev 1999;57:192–195. [PubMed: 10439632]
24. Folsom AR, Kaye SA, Prineas RJ, et al. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am J Epidemiol 1990;131:794–803. [PubMed: 2138863]
25. Kushi LH, Kaye SA, Folsom AR, et al. Accuracy and reliability of self-measurement of body girths. Am J Epidemiol 1988;128:740–748. [PubMed: 3421240]
26. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–199. [PubMed: 3337073]
27. Munger RG, Folsom AR, Kushi LH, et al. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am J Epidemiol 1992;136:192–200. [PubMed: 1415141]

28. Bush TL, Miller SR, Golden AL, et al. Self-report and medical record report agreement of selected medical conditions in the elderly. Am J Public Health 1989;79:1554–1556. [PubMed: 2817172]

29. National Osteoporosis FoundationFast facts on osteoporosis2003National Osteoporosis FoundationWashington, DC http://www.nof.org/osteoporosis/stats.htm. Cited 22 May 2003

Table 1

Age-adjusted characteristics of vitamin A supplement users and nonusers, and between the 1st and 5th quintiles of total vitamin A intake, Iowa Women's Health Study, 1986

	Vitamin A supplement			Total vitamin A intake		
	users	**nonusers**	***p*Value**	**1st Quintile**	**5th Quintile**	***p*Value[a]**
Number	12,293	22,410	–	6940	6940	–
Mean total vitamin A intake (IU)	18,976	11,934	<0.0001	5,113	29,239	–
Range of vitamin A intake (IU)	631–236,991	221–215,392	–	221–7,055	19,893–236,991	–
Age (years)	61.7	61.5	<0.01	61.2	61.8	<0.0001
Body mass index (kg/m^2)	26.6	27.2	<0.0001	27.1	26.9	0.36
Waist-to-hip ratio	0.83	0.84	<0.0001	0.84	0.83	<0.0001
Diabetes mellitus (%)	5.5	6.4	0.001	5.8	6.3	0.77
Ever cigarette smoking (%)	34.2	33.8	0.42	38.0	30.6	<0.0001
Physically active (%)[b]	56.4	49.2	<0.0001	40.0	62.0	<0.0001
Prior fracture (%)	14.1	13.4	0.06	13.4	14.0	0.91
Thyrotropic medication (%)[c]	16.7	13.1	<0.0001	13.7	15.6	<0.0001
Sedative medication (%)[c]	43.0	38.0	<0.0001	39.6	39.1	0.11
Diuretic medication (%)[c]	35.3	34.7	0.27	34.4	35.3	0.37
Steroid medication (%)[c]	6.9	5.4	<0.0001	5.6	6.2	0.11
Estrogen replacement (%)[c]	43.6	35.8	<0.0001	36.3	40.8	<0.0001
Greater than high school education (%)	42.6	38.2	<0.0001	31.5	46.6	<0.0001
Mean protein intake[d] (g/day)	81.3	80.6	0.0001	76.9	85.5	<0.0001
Mean calcium intake[d] (mg/day)	1295	984	<0.0001	874	1,318	<0.0001
Mean caffeine intake[d] (mg/day)	236	273	<0.0001	307	219	<0.0001
Mean alcohol intake[d] (g/day)	3.8	3.7	0.22	4.5	2.9	<0.0001
Mean vitamin D intake[d] (IU/day)	671	269	<0.0001	219	632	<0.0001

[a] *p* Value for *F*-test of overall difference

[b] Moderate to high levels of physical activity

[c] Ever use

[d] Adjusted for age and energy (calories)

Table 2

Relative risks of hip and all fractures according to supplemental vitamin A and retinol intake versus supplement nonusers, Iowa Women's Health Study, 1986–1997

	Supplement nonusers	Vitamin A from supplements (IU)			Retinol from supplements (IU)		
		<5,000	5,000–9,999	≥10,000	<5,000	5,000–9,999	≥10,000
Hip fractures (*n*)	324	67	106	38	100	75	36
Person-years	213,062	37,362	56,722	22,665	55,554	39,285	21,910
Age-adjusted RR	1.00	1.17	1.20	1.09	1.17	1.23	1.07
(95% CI)		(0.90–1.52)	(0.96–1.49)	(0.78–1.52)	(0.93–1.46)	(0.96–1.58)	(0.76–1.51)
Multivariate-adjusted RR[a]	1.00	1.17	1.22	1.12	1.18	1.24	1.10
(95% CI)		(0.90–1.53)	(0.98–1.52)	(0.80–1.57)	(0.94–1.48)	(0.96–1.59)	(0.78–1.55)
All fractures (*n*)	4,159	774	1,116	453	1,139	761	443
Person-years	190,741	33,157	50,871	20,293	49,389	35,330	19,603
Age-adjusted RR	1.00	1.07	1.00	1.02	1.05	0.98	1.03
(95% CI)		(0.99–1.15)	(0.94–1.07)	(0.93–1.12)	(0.99–1.12)	(0.91–1.06)	(0.94–1.14)
Multivariate-adjusted RR[b]	1.00	1.04	0.98	0.99	1.03	0.96	1.00
(95% CI)		(0.97–1.13)	(0.91–1.04)	(0.90–1.09)	(0.97–1.10)	(0.89–1.03)	(0.91–1.10)

[a] Adjusted for age (continuous), body mass index (continuous), waist-to-hip ratio (continuous), diabetes mellitus (yes, no), physical activity (moderate-high, low), steroid medication (current/prior, never), and estrogen replacement therapy (current/prior, never)

[b] Adjusted for age (continuous), body mass index (continuous), diabetes mellitus (yes, no), cirrhosis (yes, no), thyrotropic medication (current/prior, never), antiepileptic medication (current/prior, never), sedative medication (current/prior, never), steroid medication (current/prior, never), and education (less than or equal to high school, greater than high school)

Table 3

Relative risks of hip and all fractures by quintiles of total vitamin A and retinol intake, Iowa Women's Health Study, 1986–1997

	Vitamin A quintiles					Retinol quintiles				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Number	6,940	6,941	6,940	6,942	6,940	6,940	6,941	6,941	6,941	6,940
Intake, mean (IU)	5,113	8,771	12,256	16,764	29,239	912	2,031	3,857	5,768	12,610
Range (IU)	221–7,055	7,056–10,484	10,485–14,209	14,210–19,892	19,893–236,991	28–1,405	1,406–2,952	2,953–4,655	4,656–7,001	7,002–211,051
Hip fractures *(n)*	93	122	102	99	119	109	84	116	101	125
Person-years	64,989	65,688	66,434	66,724	66,068	65,807	67,194	65,468	66,052	65,290
Age-adjusted RR	1.00	1.26	1.03	0.97	1.17	1.00	0.72	1.03	0.88	1.10
(95% CI)		(0.96–1.65)	(0.78–1.37)	(0.73–1.29)	(0.89–1.54)		(0.54–0.96)	(0.79–1.33)	(0.67–1.15)	(0.85–1.42)
Test for trend *(p)*			0.85					0.21		
Multivariate-adjusted RR[a]	1.00	1.27	1.08	1.02	1.25	1.00	0.69	1.03	0.86	1.10
(95% CI)		(0.97–1.67)	(0.81–1.44)	(0.76–1.37)	(0.94–1.68)		(0.52–0.93)	(0.79–1.34)	(0.65–1.14)	(0.84–1.43)
Test for trend *(p)*			0.49					0.19		
All fractures	1,298	1,319	1,256	1,311	1,319	1,324	1,238	1,346	1,270	1,324
Person-years	58,073	58,672	59,622	59,717	58,979	58,648	60,455	58,304	59,129	58,527
Age-adjusted RR	1.00	1.00	0.93	0.97	0.98	1.00	0.90	1.01	0.94	0.99
(95% CI)		(0.92–1.06)	(0.86–1.01)	(0.89–1.04)	(0.91–1.06)		(0.83–0.97)	(0.94–1.09)	(0.87–1.01)	(0.91–1.06)
Test for trend *(p)*			0.43					0.86		
Multivariate-adjusted RR[b]	1.00	0.98	0.92	0.94	0.95	1.00	0.89	1.00	0.92	0.96
(95% CI)		(0.91–1.06)	(0.85–0.99)	(0.87–1.02)	(0.87–1.03)		(0.82–0.96)	(0.93–1.08)	(0.85–1.00)	(0.89–1.04)
Test for trend *(p)*			0.098					0.61		

[a] Adjusted for age (continuous), body mass index (continuous), waist-to-hip ratio (continuous), diabetes mellitus (yes, no), past irregular menstrual duration (yes, no), physical activity (moderate-high, low), steroid medication (current/prior, never), estrogen replacement (current/prior, never), and energy intake (continuous)

[b] Adjusted for age (continuous), body mass index (continuous), diabetes mellitus (yes, no), cirrhosis (yes, no), past irregular menstrual duration (yes, no), thyrotropic medication (current/prior, never), sedative medication (current/prior, never), steroid medication (current/prior, never), antiepileptic medication (current/prior, never), diuretic medication (current/prior, never), education (less than or equal to high school, greater than high school), alcohol use (continuous), and energy intake (continuous)

Table 4

Relative risks of hip and all fractures by quintiles of vitamin A and retinol intake from food-only among supplement nonusers, Iowa Women's Health Study, 1986–1997

	Vitamin A quintiles					Retinol quintiles				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Number	4,482	4,482	4,482	4,482	4,482	4,482	4,481	4,483	4,483	4,481
Intake, mean (IU)	4,440	7,223	10,043	13,793	24,163	744	1,424	2,356	3,967	6,878
Range (IU)	221–5,975	5,976–8,544	8,545–11,699	11,700–16,431	16,432–215,392	28–1,086	1,087–1,790	1,791–3,260	3,261–4,660	4,661–209,573
Hip fractures*(n)*	61	67	70	61	65	73	61	60	72	58
Person-years	41,812	42,333	42,813	43,111	42,994	42,329	43,047	43,544	42,086	42,056
Age-adjusted RR	1.00	1.05	1.07	0.91	0.95	1.00	0.79	0.76	0.95	0.76
(95% CI)		(0.74–1.48)	(0.76–1.51)	(0.64–1.30)	(0.67–1.35)		(0.56–1.11)	(0.54–1.07)	(0.68–1.31)	(0.54–1.07)
Test for trend*(p)*			0.56					0.35		
Multivariate-adjusted RR[a]	1.00	1.09	1.13	0.98	1.08	1.00	0.78	0.73	0.94	0.74
(95% CI)		(0.77–1.55)	(0.79–1.61)	(0.68–1.43)	(0.73–1.59)		(0.55–1.10)	(0.51–1.05)	(0.67–1.32)	(0.50–1.08)
Test for trend *(p)*			0.91					0.32		
All fractures	829	848	844	814	824	863	795	815	879	807
Person-years	37,355	37,988	38,204	38,697	38,497	37,701	38,723	39,187	37,464	37,666
Age-adjusted RR	1.00	1.00	0.99	0.93	0.94	1.00	0.89	0.90	1.01	0.92
(95% CI)		(0.91–1.10)	(0.90–1.09)	(0.85–1.03)	(0.86–1.04)		(0.81–0.98)	(0.81–0.99)	(0.92–1.11)	(0.84–1.02)
Test for trend*(p)*			0.096					0.74		
Multivariate-adjusted RR[b]	1.00	0.98	0.97	0.91	0.91	1.00	0.89	0.88	1.01	0.91
(95% CI)		(0.89–1.08)	(0.88–1.07)	(0.82–1.01)	(0.82–1.02)		(0.80–0.98)	(0.80–0.98)	(0.91–1.11)	(0.82–1.01)
Test for trend *(p)*			0.037					0.61		

[a] Adjusted for age (continuous), body mass index (continuous), waist-to-hip ratio (continuous), diabetes mellitus (yes, no), past irregular menstrual duration (yes, no), physical activity (moderate-high, low), steroid medication (current/prior, never), estrogen replacement (current/prior, never), and energy intake (continuous)

[b] Adjusted for age (continuous), body mass index (continuous), diabetes mellitus (yes, no), cirrhosis (yes, no), past irregular menstrual duration (yes, no), thyrotropic medication (current/prior, never), sedative medication (current/prior, never), steroid medication (current/prior, never), antiepileptic medication (current/prior, never), diuretic medication (current/prior, never), education (less than or equal to high school, greater than high school), alcohol use (continuous), and energy intake (continuous)

Osteoporos Int. Author manuscript; available in PMC 2007 October 15.