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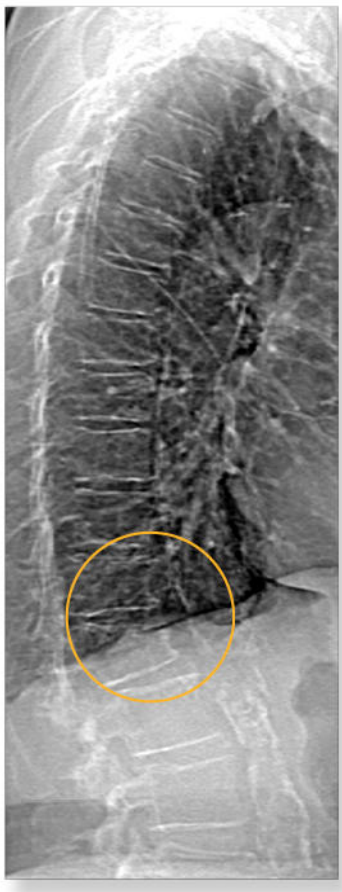

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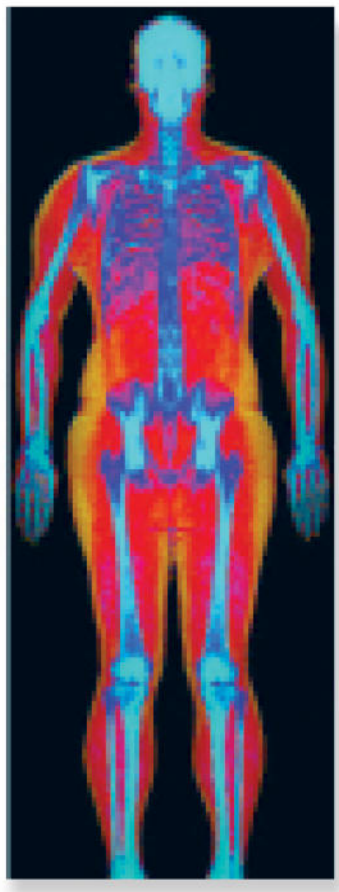

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ORIGINAL ARTICLE

JBMR

Milk Intake and Risk of Hip Fracture in Men and Women: A Meta-Analysis of Prospective Cohort Studies

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ABSTRACT

Milk contains calcium, phosphorus, and protein and is fortified with vitamin D in the United States. All these ingredients may improve bone health. However, the potential benefit of milk on hip fracture prevention is not well established. The objective of this study was to assess the association of milk intake with risk of hip fracture based on a meta-analysis of cohort studies in middle-aged or older men and women. Data sources for this study were English and non-English publications via Medline (Ovid, PubMed) and EMBASE search up to June 2010, experts in the field, and reference lists. The idea was to compare prospective cohort studies on the same scale so that we could calculate the relative risk (RR) of hip fracture per glass of milk intake daily (approximately 300 mg calcium per glass of milk). Pooled analyses were based on random effects models. The data were extracted by two independent observers. The results show that in women (6 studies, 195,102 women, 3574 hip fractures), there was no overall association between total milk intake and hip fracture risk (pooled RR per glass of milk per day = 0.99; 95% confidence interval [CI] 0.96–1.02; *Q*-test $p = .37$). In men (3 studies, 75,149 men, 195 hip fractures), the pooled RR per daily glass of milk was 0.91 (95% CI 0.81–1.01). Our conclusion is that in our meta-analysis of cohort studies, there was no overall association between milk intake and hip fracture risk in women but that more data are needed in men. © 2011 American Society for Bone and Mineral Research.

KEY WORDS: HIP FRACTURE; MILK INTAKE; META-ANALYSIS; COHORT STUDIES

Introduction

Milk is a major source of calcium and phosphorus and plausibly may reduce fracture risk through its calcium content. However, the most recent meta-analysis suggested a neutral effect of a high dietary calcium intake on hip fracture risk in men and women based on data from prospective cohort studies.[1] Furthermore, the same meta-analysis suggested no significant overall benefit of calcium supplementation on risk of nonvertebral fractures based on five double-blind, randomized, controlled trials (RCTs). Indeed, a possible adverse effect on hip fracture risk was found [among 6504 individuals and 139 hip fractures, pooled relative risk (RR) = 1.64; 95% confidence interval (CI) 1.02–2.64].[1]

Milk also may reduce fracture risk through vitamin D fortification, which is done routinely in the United States (100 IU vitamin D per 8-oz/237-mL glass of milk) and Sweden (45 IU vitamin D in a 300-mL glass of fat-reduced milk). The effects of

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oral vitamin D supplementation on nonvertebral fractures have been summarized in a 2009 meta-analyses of 12 double-blind RCTs ($n = 42,279$).[2] The results show that vitamin D at a received dose greater than 400 IU per day reduces the risk of any nonvertebral fracture by 20% and those at the hip by 18% independent of age, type of dwelling (community-dwelling versus nursing home), and concomitant calcium supplementation among seniors aged 65 years and older. This important dose-dependent benefit of vitamin D in nonvertebral fracture prevention was smaller in two meta-analyses published in 2007[3,4] and one 2010 patient-based meta-analysis of 7 large trials[5] using alternative inclusion criteria that permitted open-design trials,[3–5] use of intramuscular vitamin D,[5] and a less comprehensive[3,4] or no[5] accounting for adherence to treatment, which may result in more conservative estimates.

Much of Europe does not add vitamin D to milk, which is particularly noteworthy in Northern European countries, where sunshine exposure capable of producing vitamin D in the skin is limited. However, in the SENECA (Survey in Europe on Nutrition and the Elderly; A Concerted action) study, the lowest 25-hydroxyvitamin D concentrations were measured among seniors living in the Mediterranean, likely owing to sun avoidance by older individuals.[6] Another possible beneficial effect of milk intake on fracture risk may be increases in blood concentrations of insulin-like growth factor 1, which is likely caused in part by the high protein content of milk and has been positively associated with bone mass and muscle mass.[7–9]

Since the effect of milk intake on hip fracture risk has not been examined in an RCT and is not well established from individual observational studies, we conducted a systematic review and a meta-analysis of prospective cohort studies addressing the relationship between milk intake and hip fracture risk. We chose to focus on prospective cohort studies to minimize any bias in the assessment of milk intake with respect to hip fracture incidence.

Methods

Search strategy and data extraction

We conducted a systematic search for relevant English and non-English publications using Medline (ie, Ovid and PubMed) for the period January 1960 to June 2010 and EMBASE for January 1991 to June 2010. We also contacted experts in the field and searched reference lists and abstracts presented at the American Society for Bone and Mineral Research annual meetings from 1995 to 2009. Medical subject headings (MeSH) terms included "cohort studies," "prospective studies," or "retrospective studies"; "fracture" or "hip fracture"; "calcium," "calcium analogues or derivates," "calcium carbonate," "calcium citrate," "calcium gluconate," or "calcium phosphate"; and "milk" or "dairy products." Eligibility and exclusion criteria were prespecified. Data extraction was conducted independently by two investigators (HAB-F and JH).

Eligible studies

We included only prospective cohort studies that required milk intake to be assessed prior to the hip fracture event. Our primary outcome was first incident hip fracture in middle aged or older men and women (Fig. 1). For the Nurses Health data, we received an update of the latest published data from 2003[10] extending the follow-up from 18 to 26 years (Diane Feskanich, personal communication).

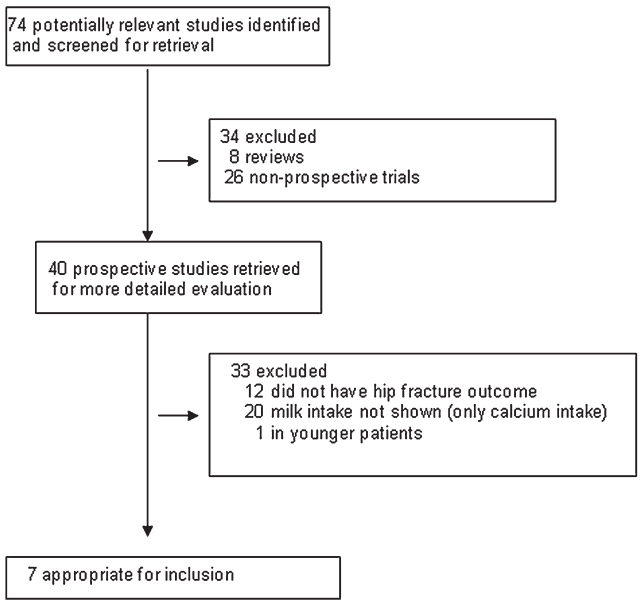

Fig. 1. QUOROM flow diagram of prospective cohort studies (996 articles found; of these, 922 could be excluded based on abstract).

Ineligible studies

We excluded cross-sectional and case-control studies and animal investigations. We excluded studies that did not provide separate data for men and women[11] or did not provide separate data on hip fractures.[12]

Studies identified

A total of seven separate studies were identified: six that provided data from women separately and three that provided data from men separately (Table 1).

Statistical methods

Gender-specific analyses were conducted because men and women differ in fracture risk[13] and total calcium intake.[14] However, we also performed an analysis that included both men and women because the relative benefit of milk may be independent of the underlying difference in fracture risk and calcium intake. The primary outcome of the pooled analysis was the RR of hip fracture for an increment of 1 glass (approximately 300 mg of calcium[15]) of total milk intake per day.

For the highest and lowest open-ended milk intake categories, we chose predefined values for the corresponding medians, which are 30% lower than the lowest cutoff and 30% higher than the upper cutoff. RRs adjusted for multiple covariates were used whenever available.

To compare studies on the same scale in the pooled analysis, we calculated the RR for a 1 glass per day increment in total milk intake, assuming a log-linear association of intake with risk. Since

Table 1. Prospective Cohort Studies That Assessed Milk Intake and Hip Fracture Risk

Author	Mean duration of follow-up, years	Population	Gender (men/ women)	Mean age, years (range)	Total cases	Milk intake assessment	Covariates adjustment
Owusu[23] (1997)[a,b]	8	Health Professionals Follow-up Study	M = 43,063	54 (40–75)	M = 56	FFQ	Age, body mass index, smoking, physical activity, total energy, alcohol intake, vitamin D intake
Cumming[22] (1997)[a,b]	6.6	Study of Osteoporotic Fractures (SOF Study)	W = 9704	71 (65 +)	W = 306	FFQ	Age, clinic, weight, history of fracture since age 50, fall in past 12 months, protein intake, caffeine intake, recreational physical activity, walking for exercise, use of vitamin D supplements and Tums antacids
Meyer[25] (1997)[b]	13.8	National Health Screening Norway	M = 20035 W = 19752	47.1 (40–53)	M = 49 W = 154	FFQ	Age, height, body mass index, physical activity, diabetes, disability pension, marital status , smoking
Michaelsson[24] (2003)[a]	13	Swedish Mammography Screening Study	W = 60689	53.6 (40–74)	W = 1535	FFQ	Age, body mass index, energy intake, protein intake, retinol intake, meat consumption, marital status, nulliparity, education level
Feskanich[10] (2003—update 2010)[a,b]	26	Nurses' Health Study	W = 74672	53.7 (34–59)	W = 1151	FFQ	Recreational activity; body mass index; smoking, intakes of calcium from supplements, vitamin D from supplements, retinol from supplements, vitamin K, alcohol, caffeine, and total energy; meat consumption; use of thiazide diuretics and hormone-replacement therapy; incident diagnoses of osteoporosis and cancer over follow-up; activity and vitamin use during teenage years; body mass index at age 18; height
Kanis[27] (2004)	3–8 depending on cohort	Pooled meta-analysis of a multicenter study including six cohort studies from Europe, Australia, and Canada	W= 27298 M = 12265	66.7 (58.9–80.0)	W= 330 M = 83	Crude assessment with dichotomized variable: less than 1 glass or more	Age
Fujiwara[26] (1997)[a,b]	14	Japanese Adult Health Study	W = 2987	W = 58.6 (11.6)	W = 49	FFQ	Age, alcohol, body mass index, prevalent vertebral fracture, number of children, age at menarche

FFQ = food frequency questionnaire.
[a]Excluded subjects with prior hip fracture.
[b]Excluded high-trauma fractures.

the RRs within each cohort study depend on a common reference group, they are correlated. Thus we used a method developed by Greenland and colleagues that yields an efficient point estimator and a consistent variance estimate under these circumstances[16] to calculate for each study the RR of hip fracture per 1 glass of total milk intake. Results from all studies were then pooled using random-effects models.[17]

To assess heterogeneity, we calculated the *Q* statistic, a measure of the statistical significance of heterogeneity, and the I^2 index, a measure of the extent of heterogeneity.[18] To assess potential publication bias, we used Begg's and Egger's tests and Begg's funnel plot[19,20]; no evidence of bias was seen. Statistical analysis was performed by using STATA Version 7.0 (Stata Corp., College Station, TX, USA), including assessment of the influence of a single study on the summary-effect estimate.[21]

Results

Table 1 shows characteristics of the seven prospective cohort studies that met our inclusion criteria. We identified seven studies overall—six studies including 195,102 women sustaining 3574 fractures and three studies including 75,149 men sustaining 195 hip fractures. The median age at baseline ranged from 47 to 71 years. Mean follow-up varied between 3 and 26 years. Three studies were from the United States,[10,22,23] two from Scandinavia,[24,25] one from Japan,[26] and one multicenter pooled project from 11 cohorts around the world (Europe, Australia, and Canada).[27]

Primary analyses

Figure 2*A* shows the Forest plots for the RR of hip fracture for a 1 glass increment of total daily milk intake among women. The 95% confidence interval (CI) for each of the studies included 1.00, and there was no overall association between milk intake and hip fracture risk (pooled RR per glass of milk per day = 0.99, 95% CI 0.96–1.02).

Despite the absence of significant heterogeneity (*Q* test $p = .37$), we explored the influence of individual studies on the summary effect in Fig. 2*B*. This analysis suggested that the findings among women were strongly influenced by the study of Michaelsson and colleagues[24] among Swedish women. Excluding this study, there was a marginally significant 5% lower hip fracture risk per glass of milk daily (pooled RR = 0.95, 95% CI 0.90–1.00, $p = .049$, *Q* test $p = .97$). The I^2, the proportion of total variation in study estimates that was due to heterogeneity, was 25% (low) when including all studies among women and 0% when excluding the Swedish study by Michaelsson and colleagues.[24]

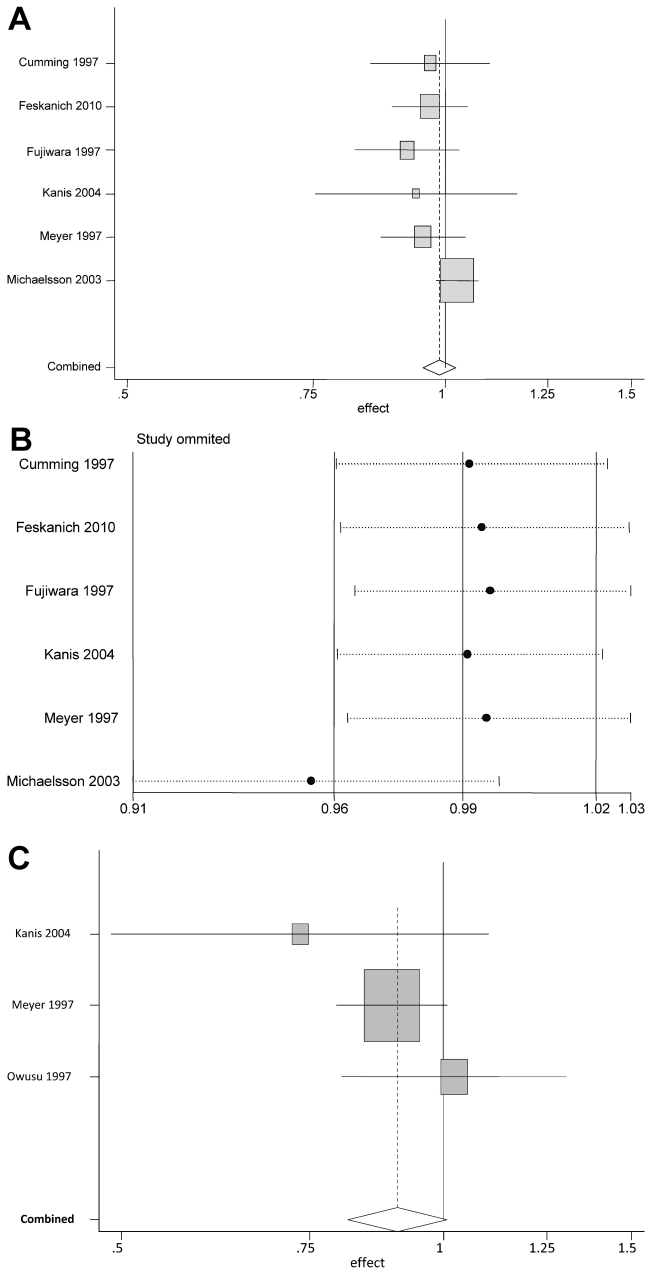

Fig. 2. (*A*) Relative risk of hip fracture for an increase of 1 glass of total milk intake per day in women. Forest plot for odds ratio of hip fracture for an increase of 1 glass of total milk intake per day. Size of squares is proportional to the inverse of the variance. Error bars represent the 95% confidence intervals. The confidence limits for the pooled RR is indicated by the diamond-shaped figure. There was no significant heterogeneity (*Q* test = .37). Among women, the pooled RR per 1 glass of milk per day was 0.99 (95% CI 0.96–1.02). (*B*) Examining the influence of single studies among women. The graph shows the influence of individual studies on the effect estimate. The influence analysis illustrates the pooled estimates omitting one study at a time. The results show the pooled estimates odds ratio of hip fracture for an increase of 1 glass of total milk intake per day. Based on this graph, the results among women are somewhat dominated by the study by Michaelsson and colleagues, although the test for heterogeneity did not reach significance including all studies (see panel *A*). Excluding the study by Michaellson and colleagues, there was a marginally significant 5% reduction of hip fracture risk per glass of milk intake per day (pooled RR = 0.95, 95% CI 0.90–1.00, $p = .049$, *Q* test $p = .97$). (*C*) Relative risk of hip fracture for an increase of 1 glass of total milk intake per day in men. Forest plot for odds ratio of hip fracture for an increase of 1 glass of total milk intake per day. Size of squares is proportional to the inverse of the variance. Error bars represent the 95% confidence intervals. The confidence limits for the pooled RR are indicated by the diamond-shaped figure. There was no significant heterogeneity (*Q* test $p = 0.356$). Among men, the pooled RR per 1 glass of milk per day was 0.91 (95% CI 0.81–1.01).

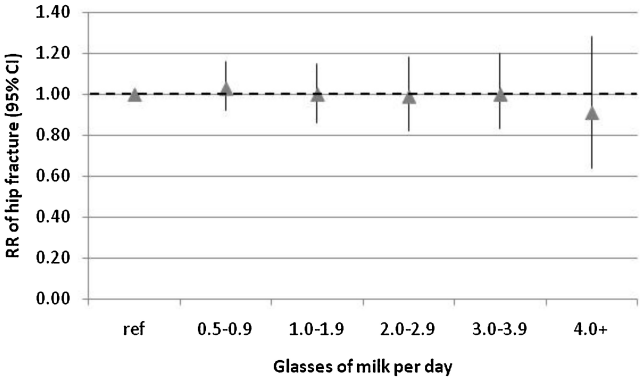

Fig. 3. Pooled analysis for categories of milk intake and hip fracture risk among women. Relationship between milk intake and hip fracture risk among women. RRs for categories of total milk intake and hip fracture risk were pooled across cohorts using the lowest category in each cohort as a reference. The reference categories in different studies ranged from 0 to 0.7 glass of total milk intake per day. Cohorts contributed only to the categories for which they had results for the same or similar range of milk intake (ie, the result for 5 to 7 glasses/week in the Nurses' Health Study contributed to the meta-analysis in category 0.5 to 0.9 glasses/day).

In men, as illustrated in Fig. 2*C*, the 95% CI for each of the individual studies also includes 1.00, and the pooled RR per daily glass of milk was 0.91 (95% CI 0.81–1.01), suggesting a borderline significant benefit in men. In men, the *Q* test for heterogeneity was not significant ($p = .36$).

To examine the relationship between milk intake and hip fracture risk in more detail, we pooled RRs for categories of total milk intake and hip fracture risk among women from each cohort study (Fig. 3) using the lowest category as a reference and corresponding RRs for higher intake categories. Figure 3 confirms the findings suggested by the analysis in Fig. 2*A*, with no apparent association between higher milk intake and hip fracture risk, even with intakes as high as 3 or 4 glasses per day. The limited data for men did not allow useful categorical dose-response analyses.

If cohorts of both women and men were analyzed jointly, there was a weak and nonsignificant overall inverse association between milk intake and hip fracture risk (pooled RR per glass of milk per day = 0.97, 95% CI 0.93–1.01, *Q* test p =.26).

Variation in milk intake

All studies but the Nurses' Health Study used only a single milk intake assessment despite long follow-ups in some of the studies. In the updated follow-up over 26 years in the Nurses' Health Study, milk intake was assessed from 1980, 1984, 1986, 1990, 1994, 1998, and 2002 using a cumulative average over time. The investigators of the Nurses' Health Study provided correlation coefficients of milk intake across time based on their data as well as the contribution of milk to total dietary calcium intake (Diane Feskanich, personal communication). Using log-transformed data for total milk intake, milk intake at baseline correlated moderately with future intake of milk within the Nurses' Health Study: Correlation of milk intake in 1986 and 1990 = 0.63; correlation in 1986 and 1994 = 0.58; and correlation in 1986 and 1998 = 0.52. In 1986 and in 2002, milk, cheese, and yoghurt contributed 54% of dietary calcium intake in the Nurses' Health Study, whereas milk alone accounted for 30% to 36% of dietary calcium or 54% of dairy calcium intake.

Discussion

Based on a meta-analysis of prospective cohort studies, we found no overall association between milk intake and hip fracture risk in women, even at high milk intakes. Only if one influential study from Sweden was excluded was a higher milk intake associated with a 5% reduced risk of hip fracture per daily glass of milk. Among men, with limited data available, a possible benefit of a higher milk intake could not be excluded.

In prospective cohort studies, a lack of overall association between total milk intake and hip fracture risk in women has several possible explanations. Milk intake was imperfectly measured in the cohort studies, with little uniformity of intake measurement and an update of intake only assessed in one study (26-year follow-up date of the Nurses' Health Study). Another possible explanation is that patients with recognized osteoporosis generally are advised to increase their calcium intake. This confounding by indication may mask an inverse association between milk intake and hip fracture risk in women in particular because they are more likely to receive advice to increase their calcium intake.[28] However, this issue most likely relates to the use of calcium supplements and less to an increased milk intake. Consistent with this idea, in the Nurses' Health Study, the exclusion of women with a history of diagnosed osteoporosis did not appreciably affect the association between milk intake and fracture risk.[29] Further, in data provided by Feskanich and colleagues for the Nurses' Health Study, milk accounted for 54% of dairy calcium intake, although this may be lower in some European countries where cheese is a stronger contributor to dairy calcium intake.[30–32] However, a lower dairy intake from milk in Europe would not have affected the results of this meta-analysis provided that milk intake is a relevant predictor of hip fracture risk overall.

If the active ingredient of milk is primarily calcium, our overall findings confirm an earlier meta-analysis with most of the same studies showing a neutral association of calcium intake and hip fracture risk in both men and women.[1] Notably, the same meta-analysis also summarized data from double-blind RCTs of calcium supplementation without vitamin D and did not find a benefit on fracture risk compared with placebo at doses of 800 to 1600 mg of calcium per day. Based on five studies of 5666 primarily postmenopausal women plus 1074 men with 814 nonvertebral fractures, the pooled RR for nonvertebral fractures comparing calcium supplementation with placebo was 0.92 (95% CI 0.81–1.05). Based on four studies with separate results for hip fracture including 6504 individuals with 139 hip fractures, the pooled RR comparing calcium with placebo was 1.64 (95% CI 1.02–2.64). Thus calcium alone may not prevent nonvertebral fractures and hip fractures.

However, milk also contains phosphorus and protein and is fortified with vitamin D in the United States, so milk may be superior to calcium supplementation for the prevention of hip

fractures in older individuals who often have nutritional deficiencies, such as in vitamin D and phosphate intake, owing to low protein intake.[33] A balanced calcium/phosphate ratio is needed for bone mineralization, and phosphate deficiency (defined as an intake below 70% of the adult Recommended Daily Allowance [RDA]; 700 mg/day) is found in 10% of US women over 60 years of age and in 15% of US women over 80 years of age (National Health and Nutrition Examination Survey [NHANES] III[34]). While calcium supplements may decrease phosphate absorption,[35] which may augment bone resorption,[35,36,37] milk provides both calcium and phosphate. For protein, a recent meta-analysis found a small positive effect of protein supplementation on lumbar spine bone mineral density (BMD) in randomized, placebo-controlled trials but no benefit of a higher protein intake on hip fracture risk from cohort studies,[3] although recent data from the Framingham cohort study suggested a protective effect of a higher protein intake on hip fracture risk.[39]

Vitamin D fortification of milk as practiced in the United States (100 IU per glass) or greater exposure to vitamin D by residence at lower latitudes may modulate the benefit of milk on hip fracture prevention. Vitamin D deficiency is common in older individuals at risk of hip fracture,[40] and vitamin D supplementation appears to reduce the risk of hip fracture[2] and the risk of falling.[41] Further, in two recent population-based studies in Iceland[42] and the United States,[43] 25-hydroxyvitamin D status appeared to be the stronger predictor of both parathyroid hormone suppression[42] and higher hip bone density[43] than calcium intake. Unfortunately, a useful subgroup analysis by vitamin D exposure relative to milk intake was not possible because of the limited data available. Given the northern latitude and small amount of vitamin D fortification in only fat-reduced milk in Sweden, however, decreased vitamin D exposure may explain in part the influence of the Swedish study toward a neutral association between milk intake and hip fracture risk.

In men, the overall relation between milk intake and hip fracture risk was inverse and of borderline significance. If, in reference to the preceding paragraph, an adequate vitamin D exposure is required for a benefit of milk on hip fracture prevention, the possibly stronger benefit of higher milk intake in men may be explained, in part, by their generally higher 25-hydroxyvitamin D levels.[43,44]

The strengths of this meta-analysis of prospective cohort studies are the large number of cases and long follow-ups provided, up to 26 years in the update of the Nurses' Health Study. Furthermore, prospective cohort studies have the least potential for selection and information bias compared with other observational study designs because exposure data (milk intake) is assessed prior to the event (hip fracture). In the absence of RCT data, these cohort studies provide the strongest level of evidence. A limitation of our study is that milk intake was assessed only once in most of the studies and in the Nurses' Health Study was only moderately correlated and stable over long periods of follow-up. Our study also was limited by the absence of baseline 25-hydroxyvitamin D levels (exposure data on vitamin D) and information on physical activity. Both factors potentially could modify the associations between milk intake and fracture risk.[33,45,46] Finally, all the component studies of this meta-analysis were observational and thus subject to uncontrolled confounding and other potential biases.

In summary, our results do not support an overall benefit of a higher milk intake in reducing the risk of hip fractures in adult women. Thus future studies of hip fracture prevention in women may consider milk intake plus vitamin D supplementation. Among men, our results could not exclude a possible overall benefit of a higher milk intake in reducing the risk of hip fractures, and more data are needed.

Disclosures

All funding sources were independent and had no influence on the study design, the data extraction, analyses, interpretation of the data, writing of this article, or in the decision to submit the article for publication. All the authors state that they have no conflicts of interest.

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References

1. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr. 2007;86:1780–1790.
2. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized, controlled trials. Arch Intern Med. 2009;169:551–561.
3. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative meta-analysis of randomized, controlled trials. J Clin Endocrinol Metab. 2007;30:30.
4. Cranny A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess (Full Rep.). 2007 Aug (158):1–235. Review.
5. Patient level pooled analysis of 68,500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 340:b5463.
6. van der Wielen RP, Lowik MR, van den Berg H, et al. Serum vitamin D concentrations among elderly people in Europe. Lancet. 1995;346: 207–10.
7. Heaney RP, McCarron DA, Dawson-Hughes B, et al. Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc. 1999;99:1228–1233.
8. Heaney RP, McCarron DA, Dawson-Hughes B, et al. Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc. 1999;99:1228–1233.
9. Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998;128:801–809.
10. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr. 2003;77:504–511.

11. Wickham CA, Walsh K, Cooper C, et al. Dietary calcium, physical activity, and risk of hip fracture: a prospective study. BMJ. 1989;299: 889–892.
12. Huopio J, Kroger H, Honkanen R, Saarikoski S, Alhava E. Risk factors for perimenopausal fractures: a prospective study. Osteoporos Int. 2000;11:219–227.
13. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev. 1985;7:178–208.
14. Bischoff HA, Dietrich T, Orav JE, Dawson-Hughes B. Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger and older US adults. Abstract; Annual Meeting of the Americal College of Rheumatology 2002 2002.
15. USDA. http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17a301.pdf. USDA National Nutrient Database for Standard Reference, Release 17.
16. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135:1301–1309.
17. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. Stat Med. 1995;14:395–411.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–560.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–634.
20. Egger M, Smith GD, Altman DG. Systemic Reviews in Health Care: Meta-analysis in context. BMJ Books. 2001;211–217.
21. Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care: Meta-analysis in context. BMJ Books. 2003; 361.
22. Cumming RG, Cummings SR, Nevitt MC, et al. Calcium intake and fracture risk: results from the study of osteoporotic fractures. Am J Epidemiol. 1997;145:926–934.
23. Owusu W, Willett WC, Feskanich D, Ascherio A, Spiegelman D, Colditz GA. Calcium intake and the incidence of forearm and hip fractures among men. J Nutr. 1997;127:1782–1787.
24. Michaelsson K, Melhus H, Bellocco R, Wolk A. Dietary calcium and vitamin D intake in relation to osteoporotic fracture risk. Bone. 2003;32:694–703.
25. Meyer HE, Pedersen JI, Loken EB, Tverdal A. Dietary factors and the incidence of hip fracture in middle-aged Norwegians. A prospective study. Am J Epidemiol. 1997;145:117–123.
26. Fujiwara S, Kasagi F, Yamada M, Kodama K. Risk factors for hip fracture in a Japanese cohort. J Bone Miner Res. 1997;12:998–1004.
27. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of milk intake and fracture risk: low utility for case finding. Osteoporos Int. 2005;16:799–804.
28. Dawson-Hughes B, Harris SS, Dallal GE, Lancaster DR, Zhou Q. Calcium supplement and bone medication use in a US Medicare health maintenance organization. Osteoporos Int. 2002;13:657–662.
29. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr. 2003;77:504–511.
30. Dumartheray EW, Krieg MA, Cornuz J, Whittamore DR, Lanham-New SA, Burckhardt P. Energy and nutrient intake of Swiss women aged 75–87 years. J Hum Nutr Diet. 2006;19:431–435.
31. Johnell O, Gullberg B, Kanis JA, et al. Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. J Bone Miner Res. 1995;10:1802–1815.
32. Kanis J, Johnell O, Gullberg B, et al. Risk factors for hip fracture in men from southern Europe: the MEDOS study. Mediterranean Osteoporosis Study. Osteoporos Int. 1999;9:45–54.
33. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992;327: 1637–1642.
34. Alaimo K, McDowell MA, Briefel RR, et al. Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. Adv Data. 1994; 1–28.
35. Heaney RP, Nordin BE. Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. J Am Coll Nutr. 2002;21:239–244.
36. Raisz LG, Niemann I. Effect of phosphate, calcium and magnesium on bone resorption and hormonal responses in tissue culture. Endocrinology. 1969;85:446–452.
37. Lotz M. The diagnostic importance of hypophosphatemia. Med Times. 1968;96:1166–1168.
38. Darling AL, Millward DJ, Torgerson DJ, Hewitt CE, Lanham-New SA. Dietary protein and bone health: a systematic review and meta-analysis. Am J Clin Nutr. 2009;90:1674–1692.
39. Misra D, Berry SD, Broe KE, et al. Does dietary protein reduce hip fracture risk in elders? The Framingham osteoporosis study. Osteoporos Int. 2011;22:345–349.
40. Cauley JA, Lacroix AZ, Wu L, et al. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. Ann Intern Med. 2008; 149:242–250.
41. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009;339:b3692.
42. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA. 2005;294: 2336–41.
43. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U. S. adults. J Bone Miner Res. 2009;24:935–942.
44. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670–676.
45. Specker BL. Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. J Bone Miner Res. 1996;11:1539–1544.
46. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337:670–676.