Calcium Intake and Risk of Primary Hyperparathyroidism in Women: Prospective Cohort Study

BMJ

BMJ 2012;345:e6390 doi: 10.1136/bmj.e6390 (Published 18 October 2012)

RESEARCH

Calcium intake and risk of primary hyperparathyroidism in women: prospective cohort study

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Abstract

Objective To examine the association between calcium intake and risk of primary hyperparathyroidism in women.

Design Prospective cohort study.

Setting Nurses' Health Study I, which originally recruited participants from the 11 most populous states in the United States.

Participants 58 354 female registered nurses enrolled in the Nurses' Health Study I aged 39-66 years in 1986 and with no history of primary hyperparathyroidism. Calcium intake was assessed every four years using semiquantitative questionnaires on food frequency.

Main outcome measure Incident primary hyperparathyroidism, confirmed by medical record review.

Results During 22 years of follow-up, we recorded 277 incident cases of primary hyperparathyroidism. Women were divided into five equal groups, according to intake of dietary calcium. After adjusting for age, body mass index, race, and other factors, the relative risk of primary hyperparathyroidism for women in the group with the highest intake of dietary calcium was 0.56 (95% confidence interval 0.37 to 0.86, P=0.009 for trend), compared with the group with the lowest intake. The multivariable relative risk of primary hyperparathyroidism for women taking more than 500 mg/day of calcium supplements compared with no calcium supplements was 0.41 (95% confidence interval 0.29 to 0.60, P<0.001 for trend). Analyses restricted to participants with regular physical exams did not significantly change the association between calcium intake and risk of primary hyperparathyroidism.

Conclusion Increased calcium intake is independently associated with a reduced risk of primary hyperparathyroidism in women.

Introduction

Primary hyperparathyroidism is the most common cause of hypercalcemia[1] and the third most common endocrine disorder, with 100 000 new cases in the United States each year.[2] Up to 2% of postmenopausal women could have this condition.[3 4] Primary hyperparathyroidism is characterized by hypercalcemia with a high or insufficiently suppressed level of parathyroid hormone, and is caused by a solitary parathyroid adenoma in 85-90% of patients.[5 6] Associated morbidities and costly sequelae include decreased bone mineral density, fractures, and kidney stones.[7 8] However, little is known about risk factors for primary hyperparathyroidism.[9] Monogenic disorders (such as multiple endocrine neoplasia I and II)[10] account for fewer than 5% of cases,[11] and neck irradiation also accounts for only a small fraction of cases.[12]

Because the parathyroid adenoma of sporadic primary hyperparathyroidism is monoclonal,[13-15] factors that chronically stimulate parathyroid hormone and increase the probability of a parathyroid cell undergoing a somatic mutation and subsequent clonal proliferation could increase the risk for primary hyperparathyroidism.[11 14 16] Calcium intake is known to influence parathyroid hormone level[17-22] and therefore could be important in the pathogenesis of primary hyperparathyroidism. However, no study to date has prospectively explored the relation between calcium intake and risk of developing primary hyperparathyroidism.

To examine the association between calcium intake and the risk of incident primary hyperparathyroidism, we conducted a prospective study of 58 354 women in the Nurses' Health Study I without history of primary hyperparathyroidism at baseline.

Methods

Study population

The Nurses' Health Study I is an ongoing, prospective cohort study which began in 1976, enrolling 121 700 female registered nurses between 30 and 55 years of age and residing in 11 US states. The cohort is followed by using questionnaires mailed every two years that ask about lifestyle practices and newly diagnosed diseases. The average proportion of participants followed up has been more than 90%. The sample for our

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analysis was limited to the 58 354 women who answered either the 2006 or 2008 questionnaires, which included questions on lifetime history of primary hyperparathyroidism. The study protocol was reviewed and approved by the Brigham and Women's Hospital institutional review board.

Assessment of dietary intake

To assess the participants' diet, we used semiquantitative questionnaires on food frequency that asked about the average intake of more than 130 individual food items and 22 individual beverages during the previous year. The participants were asked to complete food frequency questionnaires in 1986, 1990, 1994, 1998, 2002, and 2006. Intake of specific dietary factors was computed from the reported frequency of consumption of each specified unit of food and from US Department of Agriculture data on the content of the relevant nutrient in specified portions. Nutrient values were adjusted for total energy intake to determine the nutrient composition of the diet independent of the total amount of food eaten. The food frequency questionnaire also asked about the use of calcium supplements, vitamin D supplements, and multivitamins. The intake of supplemental calcium, vitamin A, and vitamin D in multivitamins or in isolated form were determined by the brand, type, and frequency of reported use.

The food frequency questionnaire has been extensively validated.[23] In a sample of 173 participants in the Nurses' Health Study I, nutrient intake reported on two food frequency questionnaires was compared with four seven-day records kept by the nurses who weighed and measured everything they ate or drank.[24] The values for the nutrient data on the two food frequency questionnaires and the food diaries were highly correlated, and the degree of reproducibility was not modified by obesity or other personal characteristics. For example, correlation coefficients were 0.81 for skim or low fat milk and 0.94 for yogurt.[24]

Assessment of non-dietary factors

Age, body mass index, smoking status (never, past, current), physical activity (in metabolic equivalent task scores), history of diabetes, hypertension, diuretic use, menopausal status, and postmenopausal hormone use were ascertained from the biennial questionnaires. Self reported weight was highly reliable (r=0.97) among a subset of participants who underwent direct measurement of their weight.[25] Physical activity reported on the questionnaires has been previously validated against physical activity diaries (r=0.79).[26] Self reported hypertension[27] and diabetes[28] were previously validated in this cohort. Self reported age at menopause and type of menopause were previously validated in the Nurses' Health Study I and shown to be highly accurate.[29] Race was self reported and categorized in this analysis as white and non-white.

Assessment of cases

Participants were asked about a diagnosis of hyperparathyroidism on the 2006 and 2008 questionnaires. On the 2008 questionnaire, nurses were also asked about lifetime history of hyperparathyroidism. To identify primary (v secondary) hyperparathyroidism, we subsequently obtained the medical records of all participants who gave consent. We confirmed cases of primary hyperparathyroidism by pathology report of a resected adenoma or by elevated serum concentrations of calcium (≥10.6 mg/dL; 1 mg/dL=0.25 mmol/L) with high or insufficiently suppressed parathyroid hormone[30-34] (≥50 pg/mL; 1 pg/mL=1 ng/L). The medical record confirmation rate was 75%. Cases were rejected after medical record review for a variety of reasons, most commonly incomplete data or identification of secondary hyperparathyroidism from vitamin D deficiency or renal insufficiency.

We included in the analysis only cases of primary hyperparathyroidism that were diagnosed during the 22 years between the date on which the 1986 questionnaire was returned and 31 May 2008. Participants with a history of primary hyperparathyroidism at baseline were excluded from the study.

Statistical analyses

The study design was prospective; information on diet was collected before the diagnosis of primary hyperparathyroidism. For each participant, we counted person months of follow-up from the date on which the 1986 questionnaire was returned to the date on which primary hyperparathyroidism was diagnosed or death occurred, or 31 May 2008, whichever occurred first. Information on exposures of interest that was recorded in response to the 1986 questionnaire was updated on subsequent questionnaires. We allocated person time of follow-up according to exposure status at the start of each follow-up period. Dividing the cohort into five equal groups of nutrient intake allowed us to examine a wide range of nutrient intake while maintaining enough participants in the highest and lowest categories. If complete information on diet was missing at the start of a time period, the participant was excluded from that time period.

The relative risk—the incidence among women in a particular category of intake divided by the corresponding rate in the comparison category—was used as the measure of association. We used the Mantel extension test to evaluate linear trends across categories of calcium intake. We used a proportional hazards model to simultaneously adjust for several risk factors. The variables considered in these models were age; body mass index (<22, 22-24.9, 25-29.9, and ≥30); race (white or non-white); physical activity level (divided into five equal groups of differing levels); alcohol intake (none, 0.1-4.9, 5-14.9, ≥15 g/day); use of thiazide or loop diuretics (yes or no); supplemental calcium intake (none, 1-500, >500 mg/day); supplemental vitamin D intake (none, 1-400, >400 IU/day); dietary intakes of calcium, vitamin D, vitamin A, and protein (total and animal protein intake); self reported diabetes; self reported hypertension; menopausal status; postmenopausal hormone use; and physical exam during the prior two years. Owing to the high correlation between the dietary intakes of calcium and phosphorus (r≥0.68 for all follow-up periods), we excluded phosphorus from the multivariable models. We calculated 95% confidence intervals for all relative risks. All P values were two tailed.

Results

Dietary calcium intake

During 1 475 978 person years of follow-up over a 22 year period, we confirmed 277 cases of incident primary hyperparathyroidism. Table 1⇓ shows the characteristics of the cohort, divided into five equal groups according to energy adjusted intake of dietary calcium in 1986. For our analyses, however, the updated dietary values were used for each time period. The mean daily intake of vitamin D, magnesium, total protein, animal protein, and vitamin A, and the physical activity level increased with increasing dietary calcium intake. The average daily alcohol intake and the percentage of current smokers decreased with increasing calcium intake. The percentage of nurses with self reported diabetes or hypertension

or who were taking thiazide diuretics and the mean daily intake of supplemental calcium was similar across the five groups.

After adjusting for age, a higher intake of dietary calcium was associated with a reduced risk of primary hyperparathyroidism (table 2⇓). The relative risk for women in the group with the highest intake of dietary calcium compared with women with the lowest intake was 0.61 (95% confidence interval 0.42 to 0.90, P=0.03 for trend).

After further adjusting for body mass index, race, smoking status, calcium supplement use, intake of vitamin D, dietary intake of vitamin A and protein, alcohol intake, and diuretic use, the adjusted relative risk for women in the group with the highest intake of dietary calcium compared with women with the lowest intake was 0.56 (95% confidence interval 0.37 to 0.86, P=0.009 for trend). The association between dietary calcium and risk of primary hyperparathyroidism was similar for calcium intakes not adjusted for energy.

Total calcium intake

After adjusting for age, higher total daily intake of calcium (including dietary and supplemental calcium) was associated with a reduced risk of primary hyperparathyroidism (table 2). For women in the group with the highest intake of total calcium compared with women in the group with the lowest intake, the relative risk was 0.48 (95% confidence interval 0.33 to 0.69, P<0.001 for trend), and the multivariable relative risk was 0.41 (0.27 to 0.63, P<0.001 for trend).

Supplemental calcium intake

We also studied the relation between supplemental calcium intake and risk of primary hyperparathyroidism. Because of an insufficient number of cases of primary hyperparathyroidism among the different categories of supplemental calcium use in the earlier time periods, our analysis on the relation between supplemental calcium intake and primary hyperparathyroidism began in 1994 with follow-up until 2008. During 985 628 person years of follow-up over a 14 year period, we documented 257 cases of incident primary hyperparathyroidism.

Higher supplemental calcium intake was associated with a reduced risk of primary hyperparathyroidism (table 3⇓). After adjusting for age, the relative risk for women taking more than 500 mg/day of calcium supplements compared with those not taking calcium supplements was 0.69 (95% confidence interval 0.50 to 0.94, P<0.001 for trend). The multivariable relative risk for the same comparison, including adjustment for dietary calcium, was 0.41 (0.29 to 0.60, P<0.001 for trend).

Additional analyses

Since cases of primary hyperparathyroidism can be incidentally detected after routine measurement of serum chemistry panels,[35] we performed analyses with additional adjustment for having a physical exam (yes or no) during the prior two years of each time period in our multivariable analysis. The association between increased calcium intake and lower risk of primary hyperparathyroidism was similar after adjusting for regular physical exams, and was similar in analyses restricted to women who had a physical exam during the prior two years of each time period.

Since the incidence of primary hyperparathyroidism seems to increase with age,[36 37] we also performed stratified analysis by age (≥65 and <65 years). The association between increased calcium intake and reduced risk of primary hyperparathyroidism was similar in older and younger women (P=0.21 for interaction); it was also similar after adjusting for menopausal status and use of postmenopausal hormone use. Since calcium absorption can depend on vitamin D status, we also performed analyses stratified by median total intake of vitamin D. The associations between higher calcium intake and decreased risk of primary hyperparathyroidism were similar among participants above and below this median level.

We also examined the association between cumulative calcium intake and risk of primary hyperparathyroidism, and the results were similar. Because we could not exclude the possibility that physicians stopped calcium supplements in participants with higher serum calcium concentrations shortly before primary hyperparathyroidism diagnosis, we also performed analyses with a four year lag between assessment of supplemental calcium use and primary hyperparathyroidism. In multivariable lag analyses, the relative risk of primary hyperparathyroidism was 0.79 (95% confidence interval 0.57 to 1.09) for women taking 1-500 mg/day of supplemental calcium and 0.71 (0.50 to 1.00) for those taking more than 500 mg/day of supplemental calcium, compared with women not taking supplemental calcium (P=0.12 for trend).

Discussion

To our knowledge, we report results from the first prospective study of the relation between calcium intake and risk of primary hyperparathyroidism. In women, increased dietary and supplemental calcium intake was associated with a reduced risk for developing primary hyperparathyroidism, independent of age, body size, diet, and other factors.

Comparison with other studies

Several studies have examined the effect of calcium intake in patients already diagnosed with primary hyperparathyroidism, with differing results.[38-41] Insogna and colleagues[39] found that calcium intake of 1000 mg/day compared with 400 mg/day suppressed the mean fasting level of parathyroid hormone by 19% among 18 study participants with primary hyperparathyroidism. Jorde and colleagues[40] found that the level of parathyroid hormone decreased after four weeks in 17 of 24 participants with primary hyperparathyroidism who were given calcium supplementation. On the other hand, Locker and colleagues[41] found no significant effect of dietary calcium intake on serum parathyroid hormone level among 71 participants already diagnosed with primary hyperparathyroidism. However, no study has prospectively examined the association between calcium intake and risk of developing primary hyperparathyroidism.

Limitations of the study

There are several limitations to our study. Firstly, since our study population was female and almost entirely white, our findings are not necessarily generalizable to men or other races. Secondly, we cannot exclude selection bias. We only included cases confirmed by medical record review, and we could not obtain medical records for all women who self reported primary hyperparathyroidism. Thirdly, although the food frequency questionnaires have been well validated, calcium intake was not perfectly assessed in this study. However, because of the prospective design, any misclassification would be random with respect to case status, and therefore would probably underestimate the magnitude of the inverse association between calcium intake and risk of primary hyperparathyroidism. Fourthly, many cases of primary hyperparathyroidism may be asymptomatic and detected by routine blood work. However,

in subanalyses restricted to women who had regular physical exams, the inverse relation between calcium intake and risk of developing primary hyperparathyroidism remained robust. Fifthly, since we conducted an observational study, there could be unknown confounders that we did not control for in our analysis. Finally, the magnitude of the association between higher supplemental calcium intake and lower risk of primary hyperparathyroidism was attenuated in lag analyses. Thus, we cannot exclude the possibility that some women with higher values of serum calcium on routine bloodwork were told to stop taking calcium supplements before their diagnosis of primary hyperparathyroidism.

Areas for future research

Calcium intake could have a role in the pathogenesis of primary hyperparathyroidism by influencing the production of parathyroid hormone.[17-22] The monoclonal nature of the single parathyroid adenoma that causes the large majority of cases of primary hyperparathyroidism[13-15] suggests a neoplasm that originates from single cells with a growth-conferring mutation. Because factors that cause parathyroid hyperplasia, such as lower calcium intake, increase the probability that a parathyroid cell will undergo a somatic mutation and subsequent clonal proliferation, such factors could increase the risk for developing primary hyperparathyroidism.[11 14 16] The peak disease incidence occurring later in life also suggests that risk factors for primary hyperparathyroidism could be due to a chronic stimulus over time.[42] Future research should examine other environmental and lifestyle risk factors that could chronically stimulate the parathyroid gland and thereby affect subsequent development of primary hyperparathyroidism.

We thank the participants in the Nurses' Health Study for their continuing cooperation. An abstract of this work was presented at the annual meeting of the American Society of Bone and Mineral Research on 19 September 2011.

Contributors: JP is the guarantor and takes responsibility for the integrity of the work as a whole, from inception to publication; contributed to the study conception and design, acquisition of data, analysis, interpretation of data, and drafting of the article; and approved the final version of the manuscript. GC contributed to the conception and design, interpretation of data, critical revisions of the article, and approved the final version of the manuscript. ET contributed to the conception and design, acquisition of data, interpretation of data, critical revisions of the article, and approved the final version of the manuscript.

Funding: This research was supported by the US National Institutes of Health grants DK084707, HL092947, DK91417, and CA087969.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from the US National Institutes of Health; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The institutional review board at the Brigham and Women's Hospital approved this study.

Data sharing: Requests for access to data, statistical code, questionnaires, and technical processes may be made by contacting the corresponding author at jmpaik@partners.org.

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What is already known on this topic

Calcium intake is known to influence parathyroid hormone levels and therefore could be important in the pathogenesis of primary hyperparathyroidism

No study to date has prospectively explored the relation between calcium intake and risk of developing primary hyperparathyroidism

What this study adds

Increased calcium intake, including both dietary and supplemental calcium, is independently associated with a reduced risk of developing primary hyperparathyroidism in women

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Accepted: 10 September 2012

Cite this as: *BMJ* 2012;345:e6390

Tables

Table 1| Age standardized baseline characteristics of women according to energy adjusted intake of dietary calcium in 1986

	Dietary calcium intake				
	Group 1 (n=11 490)	Group 2 (n=11 808)	Group 3 (n=11 818)	Group 4 (n=11 740)	Group 5 (n=11 498)
Age (years)*	51.3	51.4	51.7	51.8	52.4
Body mass index	25.0	25.1	25.2	25.3	25.2
Physical activity (MET/week)	11.9	13.9	14.6	15.4	16.1
Dietary calcium intake (mg/day)†	431	564	672	811	1115
Calcium supplement intake (mg/day)	352	351	360	357	335
Calcium supplement use (% (No))	55 (6351)	56 (6654)	58 (6833)	58 (6775)	55 (6370)
Total (dietary and supplemental) vitamin D intake (IU/day)†	254	287	322	366	465
Magnesium intake (mg/day)†	265	285	300	314	334
Total protein intake (gm/day)†	70.1	72.5	74.4	76.8	81.3
Animal protein intake (gm/day)†	50.3	51.7	53.5	56.2	62.1
Total (dietary and supplemental) vitamin A intake (mcg/day)†	1842	2051	2205	2329	2493
Alcohol intake (gm/day)	8.8	6.7	5.8	5.0	4.0
Smoking status (% (No))					
Never smoker	43 (4955)	46 (5374)	46 (5458)	47 (5470)	50 (5760)
Past smoker	33 (3776)	34 (4068)	37 (4358)	37 (4375)	35 (4052)
Current smoker	24 (2758)	20 (2366)	17 (2002)	16 (1895)	15 (1686)
Self reported diabetes (% (No))	2 (247)	2 (258)	2 (281)	3 (349)	3 (352)
Self reported hypertension (% (No))	24 (2722)	22 (2620)	22 (2615)	23 (2648)	22 (2584)
Thiazide use (% (No))‡	13 (1517)	12 (1392)	12 (1459)	12 (1450)	12 (1374)
Loop diuretic use (% (No))§	1 (171)	2 (181)	2 (195)	1 (171)	2 (196)

Data are mean values, or the percentages (and numbers) of participants that are standardized to the age distribution of the study population. Study population divided into five equal groups according to intake of dietary calcium. MET=metabolic equivalent task scores.

*Not adjusted by age.

†Energy adjusted.

‡From 1988.

§From 1994.

Table 2| Age adjusted and multivariable relative risks for incident primary hyperparathyroidism according to dietary and total calcium intake*

	Group 1	Group 2	Group 3	Group 4	Group 5	P for trend
Dietary calcium intake						
Median within group (mg/day)	443	564	670	806	1070	—
No of cases of primary hyperparathyroidism	69	57	57	50	44	—
No of person years	290 985	296 872	298 068	297 109	292 944	—
Age adjusted relative risk (95% CI)	1.0	0.81 (0.57 to 1.15)	0.80 (0.56 to 1.14)	0.70 (0.49 to 1.01)	0.61 (0.42 to 0.90)	0.03
Multivariable relative risk (95% CI)†	1.0	0.79 (0.55 to 1.13)	0.78 (0.54 to 1.11)	0.66 (0.45 to 0.98)	0.56 (0.37 to 0.86)	0.009
Total calcium intake						
Median within group (mg/day)	522	737	999	1276	1794	—
No of cases of primary hyperparathyroidism	86	61	43	42	45	—
No of person years	289 554	294 850	297 322	298 933	295 321	—
Age adjusted relative risk (95% CI)	1.0	0.69 (0.50 to 0.96)	0.48 (0.33 to 0.69)	0.45 (0.31 to 0.65)	0.48 (0.33 to 0.69)	<0.001
Multivariable relative risk (95% CI)‡	1.0	0.64 (0.46 to 0.91)	0.42 (0.28 to 0.62)	0.39 (0.25 to 0.58)	0.41 (0.27 to 0.63)	<0.001

Population divided into five equal groups according to intake of calcium.

*For illustrative purposes, medians within each group for intake of dietary and total calcium were derived from responses to the 1986 dietary questionnaire. However, the period specific medians were used for the 1986-2008 analysis. Relative risks are for the risk of primary hyperparathyroidism compared with the group that had the lowest intake of dietary or total calcium (that is, group 1).

†Multivariable model includes age, body mass index (categories: <22, 22-24.9, 25-29.9, ≥30), race, smoking status (past, current, or never), calcium supplement intake, total vitamin D intake, dietary intakes of vitamin A and protein, alcohol intake, and diuretic use (thiazide or loop diuretic use).

‡Multivariable model includes age, body mass index (categories: <22, 22-24.9, 25-29.9, ≥30), race, smoking status (past, current, or never), total vitamin D intake, dietary intakes of vitamin A and protein, alcohol intake (categories: none, 0.1-4.9, 5-14.9, ≥15 g/day), and diuretic use (thiazide or loop diuretic use).

Table 3| Age adjusted and multivariable relative risks for incident primary hyperparathyroidism according to supplemental calcium intake

	Supplemental calcium intake (mg/day)			
	None	1-500	>500	P for trend
No of cases of primary hyperparathyroidism	85	86	86	—
No of person years*	294 279	293 762	397 587	—
Age adjusted relative risk (95% CI)	1.0	0.99 (0.73 to 1.34)	0.69 (0.50 to 0.94)	<0.001
Multivariable relative risk (95% CI)†	1.0	0.82 (0.59 to 1.15)	0.41 (0.29 to 0.60)	<0.001

*Follow-up started in 1994 because of insufficient number of cases of primary hyperparathyroidism in participants taking supplemental calcium from 1984-93.
†Multivariable model includes: age, body mass index (categories: <22, 22-24.9, 25-29.9, ≥30), race, smoking status (past, current, never), dietary calcium intake, total vitamin D intake, dietary intakes of vitamin A and protein, alcohol intake (categories: none, 0.1-4.9, 5-14.9, ≥15 g/day), and diuretic use (thiazide or loop diuretic use).