別紙1

『骨粗鬆症性骨折の実態調査および全国的診療データベース構築の研究』の同意説明文書

1. 研究の目的

この『骨粗鬆症（こつそしょうしょう）性骨折の実態調査および全国的診療データベース構築の研究』（以下調査研究）は，骨粗鬆症の診断や治療方法と将来的におきる骨折の関係を明らかにすることを目的としています。

骨粗鬆症は骨がへったり，もろくなって骨が折れやすくなる病気のことです。昔は，年をとって骨が弱くなることは老化現象（ろうかげんしょう；年のせい）の一つとされ，腰が曲がったり，痛みが出たりすることは，仕方がないことだとされてきました。ところが最近では，なぜ骨粗鬆症という病気になるのかがわかり，骨折を予防するため，いろいろなお薬がつかわれるようになってきています。しかしながら骨粗鬆症のなかでどんな人で骨折がおこりやすいか，はまだ十分には分かっておらず，今回の研究では，それを明らかにすることを目的としています。

2. 研究の内容に関して

この調査研究に参加することに同意していただいた場合は，診療のために必要とされて実施された，X線検査，身体測定，骨密度検査，採血および採尿の4年間のデータを用いさせていただきます。また，アンケート調査への記入をお願いします。アンケートは身体の調子や日常の生活の状況に関することを，ご自身でご記入していただきます。

そして骨粗鬆症と診断された場合には，あなたの骨の状態に合わせ，骨の量を増やしたり骨折を予防する効果のあるお薬で治療を行なってゆきます。その後も保険で認められた内容で，骨のチェックを行なってゆきます。

その治療期間中に骨折が起きた場合，その状況を確認させていただきます。もし，骨折が起きて他の病院に入院される場合には，そのことをお知らせください。また，その後の状況を調査担当医師が，電話にて確認することがありますのでご了承下さい。

4年間の調査が終了した段階で，再度調査をお願いする場合もありますが，その際には改めてあなたの参加同意をいただくようにします。

この調査研究は全国の 5000 人以上の骨粗鬆症患者さんにご参加いただく予定ですが，全員の結果が出そろった段階で解析を行ない，検査値やアンケート結果および治療と骨折の関連性を明らかにする予定です。最終的なまとめは2014年ごろに出る予定です。

3. あなたに対する不利益（ふりえき）に関して

この調査研究は通常の保険診療の範囲で行ない，特別な費用がかかる調査は行ないません。この調査研究に参加されることで，あなたに対する不利益を生じることはありません。また，あなたに参加いただくことにより，あなた自身や将来の患者さんのために，よりよい情報が得られるものと考えています。

4. 研究の組織と責任医師

この調査研究は厚生労働省によって認められ，助成が行なわれているものであり，主任研究者は折茂　肇（健康科学大学学長）です。この調査研究は全国の 10 ヶ所以上で同時に行なわれており，この施設の責任医師は＿＿＿＿＿＿＿＿です。この調査研究は，財団法人パブリックヘルスリサーチセンターの倫理委員会とこの施設の倫理委員会で内容の審査を受け，倫理上問題がないとされています。

これらの研究について何かわからなかったりすることがあって，相談する必要がある場合には調査担当医師に連絡してください。

5. 同意しない場合でも不利益をうけないこと

研究への参加はあくまでもあなたに決めていただくことであり，あなたの自由です。参加いただけない場合でも，今後の治療には全く影響はありません。

6. 同意したあとでもいつでも撤回できること

参加いただいたあとでも，何かの理由で参加をとりやめたくなられた場合は，いつでもやめることができますので，調査担当医師にご相談ください。

7. プライバシーは守られること

あなたの記録やデータなど，プライバシーをまもる工夫を十分行います。この研究を通じて得られたあなたを特定する情報は，この施設内のシステムに登録されますが，外部の集計担当者に送信される前の段階で匿名化されるようになっているため，調査担当医師以外の目に触れることはありません。すべての情報は匿名化した上で番号により管理します。

最終的なまとめは，学会や学術雑誌にて公表する予定ですが，あなたのお名前や個人を特定できる内容が使われることはありません。ご希望があればこの調査研究で得られた結果はあなたにもお知らせいたします。

8. 遠慮せずに調査担当医師に質問してください

説明の中で，わからない言葉や，疑問に思われたこと，もう一度聞きたいことなどがありましたら，測定前に何でも調査担当医師に質問してください。

あなたの調査担当医師：＿＿＿＿＿＿＿＿＿＿＿＿

電話番号：＿＿＿＿＿＿＿＿＿＿＿＿

この研究の内容をご理解いただき，参加にご了解をいただける場合，最終ページの同意書にご署名ください。

年　月　日

施設名＿＿＿＿＿＿＿＿＿＿＿＿

責任医師名＿＿＿＿＿＿＿＿＿＿＿＿

施設名＿＿＿＿＿＿＿＿＿＿

責任医師名＿＿＿＿＿＿＿＿＿＿

＊＊＊同　意　書＊＊＊

研究名：『骨粗鬆症性骨折の実態調査および全国的診療データベース構築の研究』

私は，上記研究について，以下の項目について説明文書を用いて説明を受け，よく理解しましたので，本研究に参加します。

□　この研究の目的は，骨粗鬆症の診断と骨折発生の関係を確認するものであること

□　調査研究における依頼事項は身体測定，X線撮影，骨密度測定，採血，採尿，質問票への記入であること

□　骨折発生の場合，医療機関に連絡を入れていただくこと

□　参加されなくてもなんら不利益を受けないこと

□　プライバシーは保護されること

ご本人がご記入ください

同意日：　平成　　年　　月　　日

氏　名：＿＿＿＿＿＿＿＿＿＿

研究者記入欄

説明日：　平成　　年　　月　　日

調査担当医師名：＿＿＿＿＿＿＿＿＿＿

別紙 2

アンケート用紙

記入日＿＿＿＿年＿＿＿月＿＿＿日　お名前＿＿＿＿＿＿＿＿＿＿＿＿

年　齢＿＿＿＿＿歳

毎日の生活についてうかがいます。以下の（）内の質問に対し，あてはまるものに○をつけて，お答えください。質問が多くなっていますが，ご面倒でも全部の質問にお答えください。

・タバコを吸っていますか　（吸わない・吸ったことがある・吸っている）

・お酒を飲んでいますか　（飲まない・やめた・あまり飲まない・毎日飲んでいる）

毎日飲んでいる場合お答えください ↓

お酒を飲まれている量は１日どれくらいですか？

↓

日本酒	１合未満	・	1-2 合	・	２合以上
ビール	大ビン１本	・	1-2 本	・	２本以上
焼酎	１杯	・	1-2 杯	・	２杯以上
ウィスキー	W1 杯	・	1-2 杯	・	２杯以上
ワイン	１杯	・	1-2 杯	・	２杯以上

・納豆を食べる習慣がありますか　（はい・いいえ）

・牛乳・乳製品をよくとりますか　（はい・いいえ）

・１日３食，食べていますか？　（はい・いいえ）

・カルシウム・ビタミンなどのサプリメントをとっていますか？　（はい・いいえ）

・定期的に運動していますか？　（はい・いいえ）

・日中よく外出しますか　（はい・いいえ）

・バスや電車を使って一人で外出ができますか　（はい・いいえ）

・日用品の買い物ができますか　（はい・いいえ）

・自分で食事の用意ができますか　（はい・いいえ）

・請求書の支払いができますか　（はい・いいえ）

・銀行預金，郵便貯金の出し入れが自分でできますか　（はい・いいえ）

・年金などの書類が書けますか　（はい・いいえ）

・新聞などを読んでいますか　（はい・いいえ）

・本や雑誌を読んでいますか　（はい・いいえ）

・健康についての記事や番組に関心がありますか　（はい・いいえ）

・友だちの家を訪ねることがありますか　（はい・いいえ）

・家族や友だちの相談にのることがありますか　（はい・いいえ）

・病人を見舞うことができますか　（はい・いいえ）

・若い人に自分から話しかけることがありますか　（はい・いいえ）

・この１年以内に転倒したことがありますか　（はい・いいえ）

・過去，ご本人が骨折したことがありますか　（はい・いいえ）

・過去，親族の誰かが骨折したことがありますか　（はい・いいえ）

↓はいの場合お答えください

それはどなたですか

↓

（母親・父親・同胞）

・ステロイドの薬剤を飲んでいますか　（はい・いいえ）

・腰背部痛はありますか　（はい・いいえ）

・身長の低下はありますか　（はい・いいえ）

・月経はありますか　（はい・いいえ）

以上です。ご協力ありがとうございました。

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LOCOMOTOR DISEASES

Association of hip fracture incidence and intake of calcium, magnesium, vitamin D, and vitamin K

Yumi Yaegashi · Toshiyuki Onoda · Kozo Tanno · Toru Kuribayashi · Kiyomi Sakata · Hajime Orimo

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Abstract *Objective* To analyze the association between hip fracture incidence in 12 regional blocks within Japan and dietary intake of four key nutrients: calcium, magnesium, vitamin D, and vitamin K. *Design* An ecological study. *Methods* Using data from the 2002 national survey on the incidence of hip fracture and the National Nutritional Survey of Japan, a standardized incidence ratio of hip fracture was calculated, and the association between the standardized incidence ratio and each nutritional intake was assessed for each region using Pearson's correlation coefficient and partial correlation analysis. *Results* There were significant correlations between the standardized incidence ratio by region and magnesium, vitamin D, and vitamin K in both men and women, and calcium in women. The strongest inverse correlations were found in vitamin K in both men and women ($r = -0.844$, $P = 0.001$, and $r = -0.834$, $P = 0.001$, respectively). After adjusting for calcium, magnesium, and vitamin D, the partial correlation between the standardized incidence ratio by regional block and vitamin K was strongest in both men and women (partial correlation coefficient, pcc $= -0.673$, $P = 0.04$; pcc $= -0.575$, $P = 0.106$, respectively). *Conclusions* The significant correlation between hip fracture incidence and vitamin K intake, and also regional variations in food patterns, suggest that increasing intake of vegetables and legumes might lead to a decrease in hip fracture incidence in the future. Further, this study suggests that a review of the dietary reference value of vitamin K from the perspective of osteoporosis would be useful.

Keywords Ecological study · Hip fracture · Nationwide survey · Nutrients · Regional difference · Vitamin K

Abbreviations

pcc	Partial correlation coefficient
BMD	Bone mass density

Introduction

Hip fracture is a major public health problem and the most serious outcome of osteoporosis, and is becoming more frequent as the average age of the world's population increases [1, 2]. Estimates suggest that in the absence of primary prevention the number of hip fractures worldwide will increase to approximately 2.6 million by the year 2025, and 4.5 million by the year 2050 [3]. Additionally, even if age-adjusted incidence rates for hip fracture remain stable, the estimated number of hip fractures worldwide will rise from 1.7 million in 1990 to 6.3 million in 2050 [1].

In Japan, hip fracture is a major cause of patients' becoming bedridden, which in turn severely decreases quality of life in the elderly, at the same time as adding costs to the health system. It is therefore an urgent problem in the rapidly aging Japanese population, and the development of measures against hip fracture is an urgent medical and social issue in Japan [4].

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Four nationwide surveys in 1987, 1992, 1997, and 2002 showed that the incidence of hip fracture was higher in the western areas than in the eastern areas of Japan. Further, the 2002 survey showed that the number of new cases of hip fracture continued to increase as the elderly population increased [5–8].

It is well known that hip fracture is associated with osteoporosis, a skeletal disorder characterized by compromised bone strength [9], and that some micronutrients play an important role in the prevention and treatment of osteoporosis. Calcium, the most studied nutrient in the area of bone health, is known for its effectiveness in retarding bone loss in postmenopausal women [10, 11]. Magnesium and vitamin D play important roles in calcium and bone metabolism. Vitamin K, originally recognized as a factor required for normal blood coagulation, is beginning to receive more attention for its role in bone metabolism [10, 12–14]. Vitamin K is a family of structurally similar, fat soluble, 2-methyl-1, 4-naphthoquinones, including phylloquinone (K1) and menaquinones (K2). Phylloquinone (K1) is found in higher plants and algae, with the highest concentration in green leafy vegetables. Menaquinones (K2) also occur naturally, but are produced by an array of bacteria. In vitro studies show vitamin K2 is far more active than K1 in bone formation [15]. According to Schurgers et al. [16], both menaquinone-7 (K2) and vitamin K1 were absorbed well, with peak serum concentrations at 4 h after intake. However, menaquinone-7 (K2) showed a very long half-life time compared to vitamin K1 [16]. It is reported that the half-life time of vitamin K1 is 1–2 h and that of menaquinone-7 is approximately 3 days [17].

Though the frequency and the regional differences of hip fracture in Japan have been reported previously, the potential association with nutritional factors has not been reported in a comprehensive manner. The purpose of this study is to analyze the associations between the incidence of hip fracture and intake of four key nutrients—calcium, magnesium, vitamin D, and vitamin K—using data from the 2002 nationwide survey on the incidence of hip fracture and the National Nutritional Survey of Japan.

Subjects and methods

The 2002 nationwide survey on the incidence of hip fracture

To estimate the number of patients with hip fracture nationwide, hospitals and clinics including or specializing in orthopedics throughout Japan were divided into strata according to the number of beds, resulting in 10 strata in total. A total of 16% of clinics with 19 or fewer beds and all hospitals with 20 or more beds were included in the survey (Table 1).

In previous nationwide surveys, hospitals with 199 or fewer beds were stratified by the number of beds and were randomly selected by Neyman's allocation method. This survey was conducted using the same method and further obtained the accurate incidence of hip fracture by regional block.

A questionnaire was sent to all participating or selected hospitals and clinics asking for information on the number of new patients with hip fracture between January 1 and December 31, 2002, and each patient's sex, age, and place of residence. The number of new patients with hip fracture was estimated by the following formula:

$$\text{Number of patients} = \sum \frac{N_i}{n_i} \cdot P_i$$

where N_i is the number of surveyed institutions, n_i is the number of responding institutions, and P_i is the summation of the number of new patients.

To evaluate the influence of regional differences in the incidence of hip fracture, the country was divided into 12 regional blocks and a standardized incidence ratio was calculated following the same procedure used for calculating

Table 1 Number of responding institutions and response rate by stratum

Stratum no.	No. of beds	No. of subject institutions	Sample no. (rate)	No. of responding institutions	Response rate (%)
Total		9,422	5,919 (62.8%)	3,723	62.9
1	–19	4,168	665 (16.0%)	437	65.7
2	20–49	567	567 (100%)	340	60.0
3	50–99	1,364	1,364 (100%)	882	64.7
4	100–149	863	863 (100%)	556	64.4
5	150–199	702	702 (100%)	481	68.5
6	200–299	629	629 (100%)	353	56.1
7	300–399	477	477 (100%)	274	57.4
8	400–499	244	244 (100%)	144	59.0
9	500–599	155	155 (100%)	95	61.3
10	600–	253	253 (100%)	161	63.6

the standardized mortality ratio, based on regional classifications used in the National Nutritional Survey in Japan (Fig. 1).

Incidence by sex and age was calculated based on the estimated number of new patients derived from the response to the survey. This incidence was multiplied by the population of the sex and age groups in each regional block to obtain the expected number of new patients (Table 2). Population figures from the 2000 national census were used to calculate the incidence of hip fracture and the standardized incidence ratio by region.

Intake of nutrients

The National Nutrition Survey [18] is carried out annually in Japan to monitor health conditions and dietary intakes in order to allow more effective nutrition policy making, to clarify the relationships between nutrition and health outcomes, and to evaluate their economic effect. The dietary survey procedure was conducted by both the food weighing method and the method of proportional distribution, which meant estimating the amount of food per household member according to the proportion of eating. The survey procedure is based on the revision of the Japanese Standard Food Composition Table (5th edition, revised in 2001). Intake of four nutrients related to bone metabolism—calcium, magnesium, vitamin D, and vitamin K—has been surveyed annually in Japan since 2001. We analyzed intake of the four nutrients by each regional block using data from the National Nutrition Survey 2001.

Statistical analysis

Pearson's correlation coefficient was used to assess the associations between the standardized incidence ratio and the four nutrients: calcium, magnesium, vitamin D, and vitamin K. Further, we calculated the partial correlation coefficient (pcc) for each nutrient after adjusting for the remaining variables as covariates. In all analyses, two-sided P values <0.05 were considered to be statistically significant.

Table 2 Estimated incidence rate by block (per 10,000)

Block	Total	Men	Women
1 Hokkaido	8.55	4.31	12.44
2 Tohoku	8.57	3.93	12.92
3 Kanto I	7.08	3.24	10.96
4 Kanto II	8.60	3.99	13.11
5 Hokuriku	11.01	4.88	16.78
6 Tokai	9.16	3.89	14.31
7 Kinki I	9.49	4.11	14.57
8 Kinki II	10.43	4.37	16.09
9 Chugoku	12.58	5.33	19.25
10 Shikoku	13.84	6.18	20.76
11 Kitakyushu	12.89	5.06	19.94
12 Minamikyushu	12.91	5.40	19.71
Total	9.47	4.14	14.57
95% CI	9.25–9.70	4.02–4.23	14.25–14.95

Results

The incidence of hip fracture in 2002

Among 9,422 orthopedic institutions in Japan, 5,919 were selected to estimate the incidence of hip fracture by region. Replies were obtained from 3,723 institutions, a response rate of 62.9%. The response rate was highest for the Tohoku region (71.4%), and lowest for the Kanto I region (52.7%) (Table 2).

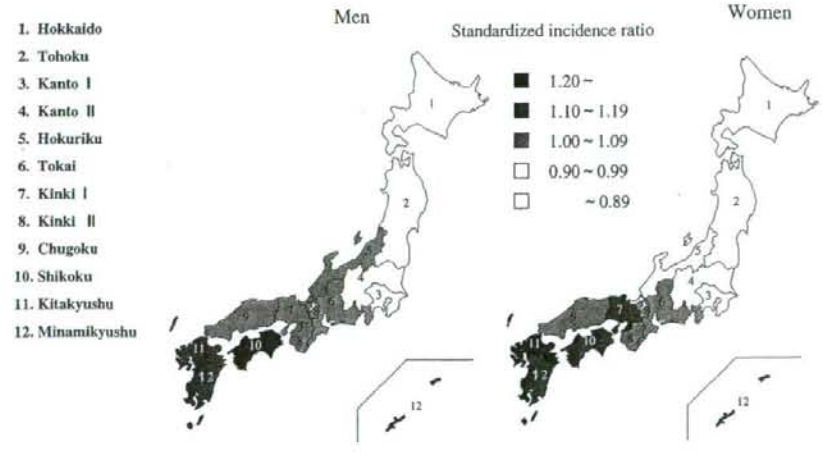

Fig. 1 Standardized incidence ratio of hip fracture

The estimated number of new hip fracture patients in 2002 was 118,500 in total (95% CI: 115,900–121,500), 25,400 (24,600–25,900) in men and 93,100 (91,200–95,700) in women. Crude incidence of hip fracture per 10,000 by regional block was highest in men in the western areas of Japan (Shikoku: 6.18 per 10,000, Minamikyushu: 5.40 per 10,000 and Chugoku: 5.33 per 10,000) compared with the eastern areas (Kanto I: 3.24 per 10,000, Tokai: 3.89 per 10,000, and Tohoku: 3.93 per 10,000). The pattern in women was similar, with the highest rate in Shikoku (20.76 per 10,000), Kitakyushu (19.94 per 10,000) and Minamikyushu (19.71 per 10,000) in the western areas and lower rates in the eastern areas: Kanto (10.96 per 10,000), Hokkaido (12.44 per 10,000) and Tohoku (12.92 per 10,000) (Table 2).

Figure 1 shows the east–west regional differences expressed by standardized incidence ratios. The similarity in the pattern in both men and women is noteworthy.

Correlation between the standardized incidence ratio by block and each nutritional intake

Figures 2–5 show the correlations between the standardized incidence ratio by regional block and intake of each nutrient. There was a significant correlation between the standardized incidence ratio by regional block and calcium in women ($r = -0.636$, $P = 0.026$), but not in men (Fig. 2). For magnesium (Fig. 3), and vitamin D (Fig. 4), significant correlations were observed in both men and women ($r = -0.706$, $P = 0.010$, and $r = -0.797$, $P = 0.002$, respectively, for magnesium and $r = -0.723$, $P = 0.008$, and $r = -0.814$, $P = 0.001$, respectively, for vitamin D). The strongest inverse correlations were found between the standardized incidence ratio by regional block and vitamin K in both men and women ($r = -0.844$, $P = 0.001$, and $r = -0.834$, $P = 0.001$, respectively) (Fig. 5). Eastern areas such as Tohoku and Kanto, which had higher vitamin K intake than the western areas, showed a lower incidence ratio of hip fracture. Conversely, western areas such as Shikoku and Kyushu, which had lower vitamin K intake, showed the opposite results.

The data were also analyzed by Spearman's correlation coefficient. The results were similar to those of Pearson's coefficient.

Partial correlation adjusting for other covariates

Table 3 shows partial correlation coefficients and P values after adjusting for the other three covariates. There was no

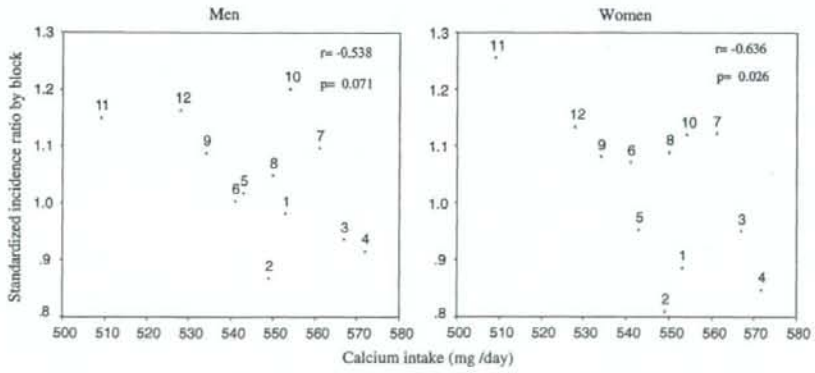

Fig. 2 Correlation between standardized incidence ratio and calcium

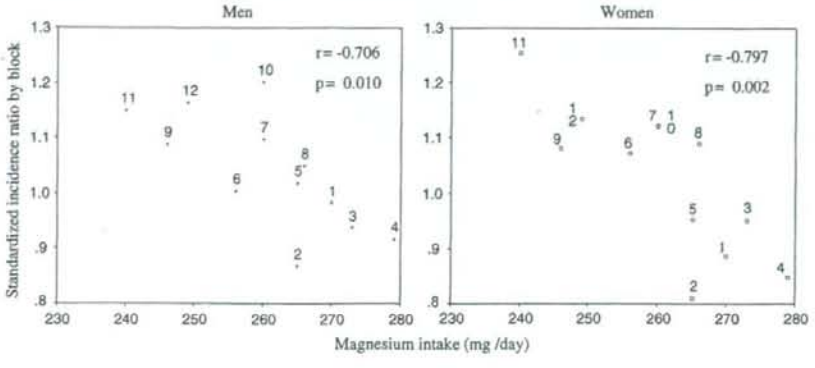

Fig. 3 Correlation between standardized incidence ratio and magnesium

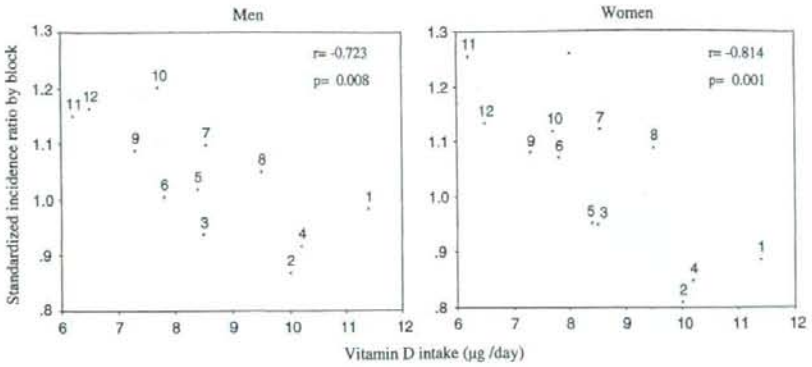

Fig. 4 Correlation between standardized incidence ratio and vitamin D

significant correlation between the standardized incidence ratio by regional block and intake of calcium, magnesium, or vitamin D, respectively. Only vitamin K was significant in men after adjusting for vitamin D, magnesium, and calcium (pcc $= -0.673$, $P = 0.047$). In women, the partial correlation between the standardized incidence ratio by regional block and vitamin K was the strongest (pcc $= -0.575$, $P = 0.106$), although it was still statistically insignificant.

Discussion

With the exception of calcium intake in men, we found significant inverse associations between the standardized hip fracture incidence ratio by block for each nutrient. The strongest associations were found for vitamin K in both men and women, followed by vitamin D and magnesium.

After adjusting for calcium, magnesium, and vitamin D as covariates, vitamin K in men was correlated with the standardized incidence ratio by block. Though the difference in women was not statistically significant, partial correlation between the standardized incidence ratio by region was the strongest for vitamin K. There was also a striking pattern of high intake of vitamin K and low incidence of hip fracture in eastern areas of Japan, with the opposite pattern—a low intake of vegetables rich in vitamin K and a high incidence of hip fracture—in western areas. These findings lend support to the idea that vitamin K is an important factor explaining regional differences in the incidence of hip fracture.

Though calcium has been perceived as the most important nutrient relating to bone metabolism, we observed weak or null associations between the standardized incidence ratio and its intake. One possible explanation is that most Japanese people recognize the importance of calcium and consciously include it in their diet. However, magnesium deficiency alters calcium metabolism, resulting in hypocalcemia, vitamin abnormalities, and neuromuscular hyperexcitability [10]. Several small epidemiologic studies have found that higher magnesium intake was associated with higher bone mass density (BMD) in elderly men and women [19]. Although there is little evidence linking intake of magnesium to the prevention of osteoporosis in the general population [11], in this study we found a stronger correlation between the standardized incidence ratio and magnesium intake than that of calcium. Therefore, it appears possible that magnesium might have an effect on regional differences in hip fracture incidence.

As vitamin D has been recognized as a critical factor in calcium metabolism, the effect of calcium and vitamin D supplementation on bone density has been reported in various studies. According to a meta-analysis by Bischoff-

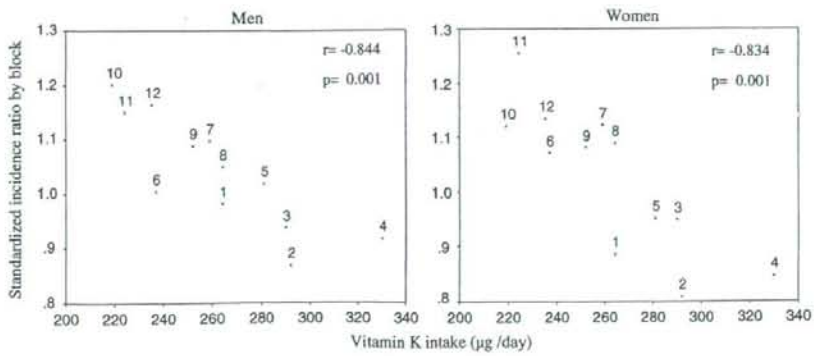

Fig. 5 Correlation between standardized incidence ratio and vitamin K

Table 3 Results of partial correlation analysis adjusting the other factors

	Men		Women	
	pcc[a]	*P*	pcc[a]	*P*
Calcium	0.218	0.574	0.192	0.621
Magnesium	−0.040	0.919	−0.149	0.702
Vitamin D	−0.381	0.312	−0.480	0.191
Vitamin K	−0.673	0.047	−0.575	0.106

pcc[a] = partial correlation coefficient

Ferrari et al. [20], oral vitamin D supplementation in the range of 700–800 IU/day reduces the relative risk of hip or any non-vertebral fracture by approximately 25% [20].

It is well known that sun exposure is related to activation of vitamin D. In Japan, day length in western areas exceeds that in eastern areas, but incidence of hip fracture in western areas is higher than that in eastern areas. However, vitamin D intake, mainly from fish to fish products, is much higher in the eastern areas of Hokkaido and Tohoku than in any regions in western areas [18]. This suggests that vitamin D intake itself, more than day length, might explain the lower incidence of hip fracture.

Regarding vitamin K, we found the strongest correlations between the standardized incidence of hip fracture by regional block and its intake in partial correlation analysis as well as in correlation analysis. The percentage of vitamin K intake from vegetables is 94%, with 59% from various vegetables and 26% from legumes. In turn, fermented soybeans ('natto') account for 87% of legumes. There were no distinct regional differences in terms of intake of vegetables and legumes by regional block in the 2001 study [18]. However, we found a big difference in natto consumption by region. According to the Household Expenditure Survey of 2002, annual natto consumption was highest in eastern areas (Tohoku, followed by Kanto and Hokkaido) and lowest in western areas (Shikoku and Kinki); expenditure on natto in Tohoku was 2.3 times that in Shikoku [21]. Because regional classifications differed between the National Nutritional Survey and the Household Expenditure Survey, we were unable to rank regions directly. However, the rankings of natto consumption were almost identical to those of vitamin K intake.

Though Japan is a relatively small group of islands, it is characterized by striking differences in patterns of food consumption. A previous study of consumption of fermented soybeans in a few regions showed a large geographic difference in serum vitamin K2 levels in postmenopausal women, and also suggested a relationship between natto intake and the incidence of hip fracture [22]. Our results, covering all regions of Japan, are entirely consistent with these earlier findings.

If the associations suggested by our study are, in fact, present, there is a possibility of decreasing the incidence of hip fracture by encouraging increased consumption of green and yellow vegetables in general, and natto in particular.

However, our study has some limitations. First, in the National Nutrition Survey, data on the intake of each nutrient are provided by sex and age group, but the data by regional block are not divided by sex and age group. Second, this is an ecological study and therefore cannot confirm a causal linkage between the incidence of hip fracture and intake of vitamin K.

Nevertheless, because of the unique situation in Japan, where the food culture varies significantly between regions, the opportunity to study these important associations is unequaled anywhere in the world. The finding that consumption of natto, high in vitamin K2, appears to be associated with a lower incidence of hip fracture offers a readily available solution. Increasing intake of green vegetables and legumes, especially fermented soybeans rich in vitamin K2, might lead to a decreased incidence of hip fracture in the future. Further, we noted the difference in dietary reference value of vitamin K or other types of vitamin K intake by country, although the methodological approaches were not standardized. The dietary reference value in Japan is a maximum of 65 μg/day for men and 55 μg/day for women [23]. The adequate intake in the USA/Canada is a maximum of 120 μg/day for men and 90 μg/day for women. The recommended nutrient intake in France is a maximum of 65 μg/day for both men and women. In the UK, safe intake is set at 1 μg/kg for adults [24]. Since regions which consumed a lot of vitamin K, especially vitamin K2, showed a low incidence of hip fracture, we considered that vitamin K intake, not absorption, of over 300 μg/day would be helpful to reduce the incidence of hip fracture. However, as for regions in which intake of vitamin K1 is comparatively high (as in Europe and the USA), overall vitamin K intake significantly exceeding 300 μg/day might be more effective to decrease the incidence of hip fracture.

Our study suggests that a review of the dietary reference value of vitamin K from the perspective of osteoporosis would be useful. However, to confirm these associations, further research using more robust epidemiological methods is warranted.

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