

Original Article

Dietary intake of six minerals in relation to the risk of chronic obstructive pulmonary disease

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To investigate the relationship between dietary intake of minerals and the risk of chronic obstructive pulmonary disease (COPD), a case-control study was conducted in central Japan. A total of 278 referred patients (244 men and 34 women) aged 50-75 years with COPD diagnosed within the past four years and 340 community-based controls undertook spirometric measurements of lung function. A structured questionnaire was administered face-to-face to obtain information on demographics and habitual food consumption. Dietary intakes of six major minerals were derived from the Japanese food composition tables. The COPD patients had lower habitual energy-adjusted intakes of calcium, phosphorus and iron than controls, but not sodium. A significant reduction in prevalence of COPD was observed for calcium, with adjusted odds ratio 0.65 (95% confidence interval: 0.37-0.98) for the highest level versus lowest level of intake. A high iron intake was also inversely associated with the COPD risk. In conclusion, an inverse association was evident between dietary calcium intake and the risk of COPD for Japanese adults.

Key Words: calcium, chronic obstructive pulmonary disease, iron, lung function, minerals

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is now the fifth leading cause of morbidity worldwide and will be the third most frequent cause of death by 2020.¹ Cigarette smoking has been established as the principal risk factor. While 95% of COPD patients are or have been cigarette smokers, about 20% of smokers develop COPD.² Therefore, other factors such as dietary habits may protect against or contribute to the development of this disease.³

A mineral is "an element or chemical compound that is normally crystalline and that has been formed as a result of geological processes".⁴ Minerals are essential elements for the human body. A prospective cohort study in the United Kingdom observed that magnesium intake (mean 330, SD 79 mg per day) was positively associated with forced expiratory volume in one second (FEV1).⁵ But magnesium intake was not related to respiratory symptoms, wheeze⁵ and cough plus phlegm.⁶ A review study concluded that the beneficial effect of magnesium on lung function was unclear.⁷ Meanwhile, selenium intake was not associated with COPD mortality according to a large population-based cohort study,⁸ whereas another study in the USA found that serum selenium level was significantly associated with FEV1 among smokers.⁹

In view of the limited and inconsistent findings reported in the literature, the present case-control study aimed to ascertain whether dietary intake of minerals is

associated with lung function and the prevalence of COPD. This study is part of a research project assessing the role of dietary and lifestyle factors for the prevention of this major disease.

MATERIALS AND METHODS

Participants

Surveys for this case-control study were conducted in the Aichi, Gifu and Kyoto areas of central Japan in 2006. Details of the methodology have been described elsewhere.^{10,11} Data from a total of 278 COPD patients (244 men and 34 women), referred by respiratory physicians from six hospitals, were available for analysis. Diagnosis of COPD was confirmed by spirometry according to standard protocol with FEV1/FVC<0.7, where FVC = forced vital capacity.¹² Patients were included if they were 50-75 years of age and had COPD diagnosed as the primary functionally limiting illness within the past four

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years. Exclusion criteria were recent stroke, dementia or other health conditions that prohibited them from being interviewed.

The control group consisted of 340 community-dwelling adults (272 men and 68 women) recruited during the same period and from the same domain as the prevalent cases. To improve statistical power and compensate for the relatively low number of female COPD patients, the ratio of 1:2 was adopted for recruiting female controls. These controls were frequency matched to the cases by age (within 5 years) with the same exclusion criteria. All participants underwent spirometric measurements of respiratory function to ensure correct classification of their case-control status. Ethics approval was obtained from the Human Research Ethics Committee of Curtin University.

Interview and instruments

Face-to-face interviews of consented participants were conducted by the first author using a structured questionnaire. Confidentiality of the information provided and the right to withdraw without prejudice were ensured. In order to minimize recall error, interviews of the cases were undertaken in the presence of the next-of-kin, after making appointment through their respiratory physician. Each interview took about 30-45 minutes to complete and was held in the outpatient department for cases or the place of recruitment for controls.

The structured questionnaire solicited demographic and lifestyle information including age, gender, current height (m) and weight (kg) and weight (kg) 5 years ago, education level (high school or below; college or university), cigarette smoking (never smoker; ex-smoker; current smoker), smoking pack-years and alcohol drinking status (non-drinker; drinker). Information on habitual diet was obtained using a 138-item food frequency questionnaire taken from the Japan Public Health Center-based prospective study on cancer and cardiovascular disease.¹³ Its validity and reproducibility (of nutrients intake) had been established for the Japanese adult population.^{14,15} The reference recall for dietary variables was set at five years before interview, because estimation beyond five years would be difficult for the elderly participants and all prevalent cases were recruited within four years of con-

firmed COPD diagnosis. The frequency of food intake was classified by nine categories ranging from 'almost never' to '7 or more times per day'. Standard portion size consumed per meal was specified for each item, with amount expressed as small (50% smaller), medium, and large (50% larger) and quantified in terms of grams per day. Utensils and photographs of foods were shown to clarify size and amount whenever necessary. A test-retest was also conducted two weeks apart on 24 participants randomly selected from our sample. For the 138 food items considered, the mean Kappa statistic was 0.85 (SD 0.18) for frequency and 0.79 (SD 0.23) for amount of intake, suggesting good agreement of responses based on the food frequency questionnaire.

Statistical analysis

The quantity of minerals contained in each food item was obtained from the National Cancer Center of Japan.¹³ The minerals available for analysis from the nutrient database were calcium, phosphorus, iron, sodium, potassium and selenium. For each participant, dietary intake of each mineral was derived by adding the corresponding food items and multiplying the portion size (in grams) by frequency of consumption per day. Daily total energy intake (kJ) was similarly estimated by summing the energy intake across individual food items. Salt consumption in terms of salt and soy sauce added to foods was not quantified and thus excluded in the calculation of sodium intake.

Descriptive statistics were first applied to summarize participant characteristics and lung function measures. After comparing the energy-adjusted minerals intake pattern between case and control groups, unconditional logistic regression analyses were conducted to assess the effects of specific dietary mineral on the COPD risk with adjustment for total energy intake. Each quantitative mineral variable was subjected to a linear trend test and further categorized into tertiles on the basis of the empirical distribution among controls. The lowest energy-adjusted intake level was taken as the reference category in each model. Other independent variables included in the multivariable models were age, gender, body mass index (BMI=weight/height²) of five years ago, education level, cigarette smoking, smoking pack-years and alcohol drinking status. These variables were either established risk

Table 1. Characteristics of participants by gender and case-control status

Variable	COPD patients		Controls	
	Male (n=244)	Female (n=34)	Male (n=272)	Female (n=68)
Gender				
Mean age (years)	66.5 (SD 6.82)	66.1 (SD 6.13)	65.2 (SD 5.41)	66.1 (SD 5.76)
Current mean body mass index (kg/m ²)	21.9 (SD 3.56)	21.1 (SD 3.79)	23.5 (SD 2.81)	23.0 (SD 2.93)
Mean body mass index 5 years ago (kg/m ²)	22.1 (SD 2.94)	20.7 (SD 3.89)	23.6 (SD 2.85)	23.3 (SD 3.25)
Education: High school or below	195 (80.2%)	26 (78.8%)	166 (61.9%)	47 (70.1%)
Alcohol drinkers	150 (61.5%)	8 (23.5%)	202 (74.5%)	21 (30.9%)
Current smokers	53 (21.7%)	9 (26.5%)	63 (23.2%)	2 (2.9%)
Ex-smokers	189 (77.5%)	21 (61.7%)	134 (49.3%)	3 (4.4%)
Never smokers	2 (0.8%)	4 (11.8%)	75 (27.6%)	63 (92.6%)
Mean smoking (pack-years)	65.0 (SD 24.9)	43.3 (SD 31.7)	30.9 (SD 28.8)	2.0 (SD 9.68)
FEV1	1.64 (SD 0.69)	1.15 (SD 0.47)	2.56 (SD 0.51)	1.76 (SD 0.35)
FVC	3.08 (SD 0.83)	2.07 (SD 0.52)	3.31 (SD 0.60)	2.17 (SD 0.41)
FEV1% predicted	56.7 (SD 22.3)	56.5 (SD 19.4)	86.5 (SD 14.0)	93.9 (SD 13.8)
Mean total energy intake (kJ)	4879 (SD 1849)	4792 (SD 1925)	5273 (SD 2058)	4675 (SD 1569)

FEV1, forced expiratory volume in one second. FVC, forced vital capacity.

factors or plausible confounders from the literature.³ All statistical analyses were performed using the SPSS package version 15.

RESULTS

Table 1 presents the characteristics of the participants by gender and case-control status. The mean age was about 66 years and most participants had high school or below education, but the mean BMI (five years ago) of COPD patients was lower than that of controls ($p < 0.001$). For the case group, 220 patients (80%) had their COPD diagnosed within the past two years. It is alarming that some patients (21.7% for male and 26.5% for female) continued to smoke after their diagnosis of COPD and as expected, they had lower lung function measures than their counterparts without the disease. The COPD patients also had lower total energy intake for males ($p = 0.02$) but similar to control subjects for females ($p = 0.74$).

Table 2 shows the dietary intake of minerals by participants five years ago. The COPD patients had lower daily crude intake of calcium, phosphorus, iron, potassium and selenium than controls except sodium. However, their differences in energy-adjusted intakes were not significant for potassium and selenium. Habitual intakes of minerals by control subjects were generally comparable with those of the Japanese adult population aged over 50 years,¹⁶ but calcium and phosphorus intakes by some participants were below the recommended levels.¹⁷

The relationship with lung function was next investigated for all participants. As shown in Table 3, observed lung function measures (FEV1, FVC and FEV1% predicted) were positively correlated with calcium, phosphorus, iron, potassium and selenium but negatively correlated with sodium, though the magnitude of the Pearson correlation coefficients were low.

Table 4 summarizes logistic regression results for dietary minerals intake in relation to the COPD prevalence.

Correlation between the six minerals intake ranged from 0.46 to 0.91. To avoid potential collinearity problem, the effect of each mineral was assessed using separate logistic regression models. A 35% reduction in risk was evident by increasing daily calcium level, the adjusted odds ratio (OR) being 0.65 (95% confidence interval (CI) 0.37 to 0.98) for the highest versus lowest category of energy-adjusted intake, and p for trend = 0.02. Decrease in COPD risk was also associated with higher energy-adjusted intakes of iron but to a lesser extent, OR 0.68, 95% CI 0.39 to 0.99, the corresponding test for linear trend was significant ($p = 0.01$). However, little association with the COPD prevalence was found for the other minerals.

DISCUSSION

This was the first study to investigate the effects of habitual dietary minerals intake on the risk of COPD for the Japanese population. The sample size of 618 subjects (278 COPD patients, 340 controls) provided sufficient statistical power for the multivariable analysis. Moreover, lung function spirometry was performed for each participant to ensure correct classification of the case-control status. The majority (80%) of the patients had COPD diagnosed within the past two years and all 278 prevalent cases were interviewed within four years of confirmed COPD diagnosis. It is possible that patients with COPD have nutritional deficiencies because of reduced appetite and food intake. Therefore, the reference recall for dietary variables was set at five years before interview. Although relatively small numbers of female participants were recruited, the gender ratio was typical of the COPD population in Japan.

In this study, COPD patients had lower dietary crude intakes of five major minerals except sodium than participants without the disease. It is of concern that their calcium and phosphorus intakes were substantially below the recommended levels for older adults. Their sodium

Table 2. Comparison of habitual dietary minerals intake between case and control groups

Crude mineral intake per day	COPD patients (n=278)		Controls (n=340)		t-test†	Population ¹⁶ >50 years	Recommended level ¹⁷	
	Mean	SD	Mean	SD			<i>p</i>	Average range
Calcium (mg)	463	210	545	245	0.002	533-586	650	2300
Phosphorus (mg)	794	297	884	331	0.017	919-1142	900	3000
Iron (mg)	7.39	2.84	8.38	3.43	0.036	8.2-9.5	7.5	50
Sodium (mg)	2952	1621	2806	1369	0.019	4173-5078‡	600	3600
Potassium (mg)	2519	981	2827	1175	0.092	2392-2800	2000	3000
Selenium (µg)	81.3	35.5	88.4	39.1	0.558	100	30	260

† mean difference between cases and controls based on energy-adjusted mineral intakes

‡ including salt and soy sauce added to foods

Table 3. Correlations between dietary minerals intake and lung function measures

Mineral intake	Lung function		
	FEV1	FVC	FEV1% predicted
Calcium (mg)	0.084 ($p = 0.040$)	0.022 ($p = 0.598$)	0.177 ($p < 0.001$)
Phosphorus (mg)	0.101 ($p = 0.014$)	0.080 ($p = 0.052$)	0.131 ($p = 0.002$)
Iron (mg)	0.064 ($p = 0.122$)	0.020 ($p = 0.627$)	0.143 ($p = 0.001$)
Sodium (mg)	-0.112 ($p = 0.006$)	-0.069 ($p = 0.092$)	-0.056 ($p = 0.174$)
Potassium (mg)	0.054 ($p = 0.191$)	0.008 ($p = 0.851$)	0.136 ($p = 0.001$)
Selenium (µg)	0.070 ($p = 0.090$)	0.078 ($p = 0.058$)	0.067 ($p = 0.107$)

Table 4. Dietary minerals intake and prevalence of COPD for Japanese adults

Energy-adjusted mineral intake per day	Cases n (%)	Controls n (%)	Crude		Adjusted †		Test for trend
			OR	95% CI	OR	95% CI	
Calcium (mg)							<i>p</i> =0.02
≤ 384	127(45.7)	112(33.2)	1.0		1.0		
385-517	80(28.8)	113(33.6)	0.62	0.43-0.92	0.79	0.47-1.32	
≥ 518	71(25.5)	112(33.2)	0.56	0.38-0.83	0.65	0.37-0.98	
Phosphorus (mg)							<i>p</i> =0.06
≤ 680	114(41.0)	112(33.2)	1.0		1.0		
681-801	87(31.3)	113(33.6)	0.76	0.52-1.11	0.94	0.56-1.57	
≥ 802	77(27.7)	112(33.2)	0.68	0.46-1.00	0.82	0.47-1.41	
Iron (mg)							<i>p</i> =0.01
≤ 6.15	122(43.9)	112(33.2)	1.0		1.0		
6.16-7.89	80(28.8)	113(33.6)	0.65	0.44-0.96	0.71	0.42-1.20	
≥ 7.90	76(27.3)	112(33.2)	0.62	0.42-0.92	0.68	0.39-0.99	
Sodium (mg)							<i>p</i> =0.94
≤ 1789	78(28.1)	112(33.2)	1.0		1.0		
1790-2587	87(31.3)	113(33.6)	1.13	0.75-1.68	0.75	0.58-1.11	
≥ 2588	113(40.6)	112(33.2)	1.46	0.99-2.16	0.89	0.52-1.53	
Potassium (mg)							<i>p</i> =0.05
≤ 2101	128(46.0)	112(33.2)	1.0		1.0		
2102-2587	65(23.4)	113(33.6)	0.50	0.34-0.75	0.58	0.34-1.00	
≥ 2588	85(30.6)	112(33.2)	0.66	0.45-0.97	0.59	0.34-1.04	
Selenium (µg)							<i>p</i> =0.16
≤ 61.4	97(34.9)	112(33.2)	1.0		1.0		
61.5-80.1	88(31.7)	113(33.6)	0.90	0.61-1.33	0.70	0.42-1.16	
≥ 80.2	93(33.4)	112(33.2)	0.96	0.65-1.41	0.95	0.56-1.60	

OR, odds ratio. CI, confidence interval.

† Adjusted odds ratios from logistic regression models including age, gender, body mass index (5 years ago), education level (high school or below; college or university), alcohol drinking (non-drinker; drinker), cigarette smoking (never/ex-smoker; current smoker), smoking pack-years, and daily total energy intake.

intake from foods also appeared high even without accounting for salt consumption in the diet.

Lung function was found to be positively associated with dietary calcium, phosphorus, iron and potassium but appeared to decline with increasing sodium intake. However, the observed correlations were low. There is some evidence suggesting that a high sodium intake may accentuate airway reactivity and reduce flows,^{18,19} while a previous study reported that serum selenium level was significantly associated with FEV1 among smokers.⁹

A new finding was that increased calcium intake could lead to a significant reduction in the prevalence of COPD. Epidemiological evidence also indicated a possible inverse association between dietary iron intake and COPD risk. Calcium intake from diet has been similarly shown to be protective against lung cancer,²⁰ while iron intake was also associated with a reduced lung cancer risk.²¹ Both calcium and iron are required for cellular function. Therefore, individuals with low intakes of these minerals may be unable to combat the carcinogenic effects from cigarette smoking. Nevertheless, more clinical research is needed to understand the biological mechanism underlying their protective effects.

Several limitations should be taken into account when interpreting the findings. Firstly, only six major minerals derived from the Japanese diet were available from the nutrient database.¹³ Consequently, effects of other minerals such as magnesium and zinc could not be evaluated. Secondly, salt consumption was difficult to quantify and excluded in the calculation of sodium intake. Nevertheless, case and control participants were similar in their habits of adding salt (*p*=0.06) and soy sauce (*p*=0.21) to

foods. The under-estimation of sodium intake was thus expected to be consistent within and between groups and should not affect the validity of the results.

The present case-control study was retrospective in design so that the possibility of recall bias could not be denied. Although habitual diet was assessed using a validated and reliable food frequency questionnaire for the Japanese population, the self-reported information was subjected to measurement errors. Face-to-face interviews were thus conducted to help interpretation and to improve the accuracy of their answers. Moreover, the same investigator (Hirayama) conducted all interviews to eliminate inter-interviewer bias. The control subjects were recruited during the same period and from the same catchment area as the cases. They should therefore provide valid estimates of minerals intake. But the inherent selection bias was unavoidable because of their voluntary participation in the study. Information bias was unlikely, because the effects of dietary minerals were not established for COPD and all participants were blinded to the study hypothesis. Nevertheless, residual confounding might still present even though plausible confounding factors were controlled for in the multivariable analyses.

In conclusion, an inverse association was found between dietary calcium intake and the risk of COPD for Japanese adults, together with a significant dose-response relationship.

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AUTHOR DISCLOSURES

None declared for all authors.

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Original Article

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六種礦物質攝取量與慢性阻塞性肺疾之風險相關

為探究膳食礦物質攝取量與慢性阻塞性肺病(COPD)風險之相關性，在日本中部進行一病例對照研究。病例組共 278 位(男性 244 位，女性 34 位)，年齡 50-75 歲，均在過去四年內被診斷患有慢性阻塞性肺病。對照組來自相同社區，共 340 人。所有參與者都經肺功能檢查，並接受面訪以結構式問卷獲得基本人口學資料及慣常的食物攝取。再根據日本食物成分表，量化 6 種主要礦物質之攝取量。以能量校正後，COPD 病例組與對照組相比，有較低的鈣、磷及鐵攝取，而鈉則相反。結果也發現，鈣攝取量最高組與最低組相比，COPD 盛行率之勝算比顯著較低(OR=0.65；95% CI: 0.37- 0.98)。鐵的高攝取量與 COPD 風險亦呈負相關。綜合以上，日本成年人膳食鈣攝取量與慢性阻塞性肺病風險，呈現顯著負相關。

關鍵字：鈣、慢性阻塞性肺病、鐵、肺功能、礦物質