Original Article

Folate intake associated with lung function, breathlessness and the prevalence of chronic obstructive pulmonary disease

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A case-control study was conducted in central Japan to investigate the relationship between dietary intake of folate and lung function, breathlessness and chronic obstructive pulmonary disease (COPD). 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 (272 men and 68 women) were assessed for dyspnoea and undertook spirometric measurements of lung function. A structured questionnaire was administered face-to-face to obtain information on demographics, lifestyle and habitual food consumption. Folate intake was derived from the Japanese food composition tables. The COPD patients had significantly lower habitual intake of folate (mean 231, SD 90 μg/day) than control subjects (mean 261, SD 110 μg/day), $p<0.001$. Lung function measures were found to be positively associated with dietary folate level. Reductions in prevalence of COPD and especially breathlessness were observed, the respective adjusted odds ratio (OR) being 0.74 (95% confidence interval (CI) 0.35 to 1.58) and 0.43 (95% CI 0.21 to 0.91) for the highest versus lowest quartile of folate intake. The corresponding tests for linear trend were also significant ($p<0.05$). In conclusion, an inverse association was evident between dietary folate intake and the prevalence of breathlessness for Japanese adults, together with a significant dose-response relationship for the COPD risk. Moreover, increased folate intake might be beneficial to lung function.

Key Words: breathlessness, chronic obstructive pulmonary disease, folate, Japan, lung function

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability in many Asia-Pacific countries especially China and Japan because of continued tobacco consumption.[1] It is characterized by a progressive decline in lung function, and encompasses chronic bronchitis and emphysema. The most common symptoms of COPD are breathlessness, excessive sputum production, and a chronic cough.[2] Although COPD commonly develops as a result of cigarette smoking, only about 20% of smokers develop COPD.[3] Therefore, environmental and dietary factors are likely to contribute to the etiology of this disease. Apart from tobacco abstinence, a good diet may offer protection and consequently, reduce the disease burden and health care costs associated with COPD. Our literature review of dietary factors suggested that increased vegetable consumption can reduce the risk of COPD while a high fish intake is beneficial to lung function. Fruit intake is also positively associated with lung function and inversely related to COPD mortality and respiratory symptoms.[4]

Folate (the naturally occurring form) and folic acid are forms of the water-soluble vitamin B9. Folate is essential for the syntheses of nucleic acids and to control gene expression epigenetically through one-carbon metabolism.[5] By methylating harmful homocysteine, folate reduces the risk of cardiovascular diseases.[6] Leafy vegetables such as spinach, asparagus, lettuces, dried/ fresh beans and peas, sunflower seeds and certain other fruits and vegetables are rich sources of dietary folate.[7] Liver and liver products also contain high amounts of folate.[7] Adequate folate levels have been associated with reduced risks of coronary artery disease, colorectal cancer, and dementia.[8] Recent evidence also suggested that high serum folate levels are associated with a lower risk of atopy and wheezing.[9] An inverse relationship between dietary folate intake and lung cancer especially for heavy smokers was reported in a large New York State cohort study comprising 57968 subjects.[10] However, folate supplement was unlikely to reduce the risk of developing lung cancer according to another prospective cohort study of 77,721 adults.[11]

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Although folate supplementation and fortification have become increasingly popular in 52 countries, limited information is available about the specific effects of folate on lung health. In particular, a comprehensive literature search found no published article on the relationship between folate and COPD. We have reported an inverse association between vegetable consumption and the risk of COPD for Japanese adults.[12] Recently, COPD patients were found to have high total homocysteine but low circulating folate levels.[13] The present study aimed to further investigate the effects of folate intake from food sources on lung function, breathlessness and the prevalence of COPD. We did not investigate antioxidants and other nutrients such as vitamin C, vitamin D and carotenes because they have been extensively assessed in the literature.[14] The study formed part of a research project assessing the role of nutritional factors for the prevention of this major disease.

MATERIALS AND METHODS

Participants

A case-control study was conducted in 2006, details of the methodology have been described elsewhere.[12] In total, 278 COPD patients (244 men and 34 women) were referred by respiratory physicians from six hospitals in the Aichi, Gifu and Kyoto areas of central Japan. Diagnosis of COPD was confirmed by spirometry using standard protocol[15] with FEV1/FVC<0.7, where FEV1 = forced expiratory volume in one second, and FVC = forced vital capacity. Inclusion criteria were 50-75 years of age and COPD being diagnosed as the primary functionally limiting illness within the past four years. Patients were excluded if they had a recent stroke, dementia or other health conditions that prohibited them from being interviewed.

The control group comprised of 340 adults (272 men and 68 women) recruited during the same period and from the same catchment areas as the prevalent cases. These community-based controls were frequency matched to the cases by age (within 5 years) using the same exclusion criteria. Spirometric measurements of respiratory function were taken from all participants to ensure correct classification of their disease status. Ethics approval was obtained from the Human Research Ethics Committee of Curtin University of Technology (approval number HR 90/2005) and the participating hospitals.

Interview and questionnaire

The first author conducted face-to-face interviews with consented participants using a structured questionnaire. Confidentiality of the information provided and the right to withdraw without prejudice were ensured after explaining the purpose of the study. Interviews of the cases were undertaken in the presence of their next-of-kin to minimise recall error. On average the interviews took 30-45 minutes to complete and were held in the outpatient department for cases and the place of recruitment for controls.

The first part of the questionnaire sought demographic and lifestyle characteristics 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 or ex-smoker; current smoker), smoking pack-years and alcohol drinking status (non-drinker; drinker). Information on habitual diet was then obtained using a 138-item food frequency questionnaire taken from the Japan Public Health Centre-based prospective study on cancer and cardiovascular disease.[16] Its validity and reproducibility had been established for the Japanese adult population.[17,18] The reference recall period for dietary variables was set at five years before interview. Since all prevalent cases were recruited within four years of confirmed COPD diagnosis, their dietary exposure information was captured before the onset of the disease. The frequency of food intake was classified by nine categories ranging from 'almost never' to 'seven 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. Eating utensils and photographs of foods were displayed to clarify size and amount.

The third part of the questionnaire consisted of two screening instruments to assess the breathlessness symptom of each individual: "dyspnoea" scale of the Medical Research Council[19] and the "Feeling Short of Breath" scale of the Australian Lung Foundation.[20]

Statistical analysis

The quantity of folate contained in each food item was obtained from the Japanese food composition tables[7, 16] and reproduced in Table 1. For each participant, dietary intake of folate 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 (kcal) was similarly estimated by summing the energy intake across individual food items.

Descriptive statistics were first applied to summarise participant characteristics and lung function measures. After comparing the folate intake between case and control groups, unconditional logistic regression analyses were performed to assess the effects of folate on COPD risk and the prevalence of breathlessness with adjustment for total energy intake. The quantitative folate variable was subjected to a linear trend test and further categorised into quartiles based on the empirical distribution of controls or participants without the breathlessness symptom. The lowest 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/height^2) of five years before interview, education level, cigarette smoking, smoking pack-years and alcohol drinking status. These variables were either established risk factors or plausible confounders from the literature.[4] All statistical analyses were conducted using the SPSS package version 13.

RESULTS

Sample characteristics of the participants are summarised in Table 2. The mean age was about 66 years and the majority of participants had high school or below education. The mean BMI (five years ago) of cases was lower than that of controls, and over 20% of them continued to smoke after the diagnosis of COPD. It is therefore not

Table 1. Folate content in Japanese foods and beverages[16]

	Food/Beverages	Folate (μg)		Food/Beverages	Folate (μg)
1	Well-milled rice	7	38	Pacific saury, mackerel	2
2	Vitamin supplemented rice	7	39	Dried small fish	9
3	Rice mixed with other grains	7	40	Cod roe	47
4	Miso-soup	3	41	Eel	17
5	Sake	0	42	Squid	16
6	Shochu, awamori	0	43	Octopus	24
7	Beer	6	44	Prawn	15
8	Whisky	0	45	Short-necked clam, crab shell	16
9	Wine	1	46	Vivipara	1
10	Steaks	7	47	Chikuwa (fish paste product)	4
11	Grilled beef	7	48	Kamaboko (fish paste product)	4
12	Stewed beef	10	49	Carrot	14
13	Stir-fried pork	4	50	Spinach	194
14	Deep-fried pork	3	51	Pumpkin	16
15	Stewed pork, Western style	9	52	Cabbage	43
16	Stewed pork, Japanese style	4	53	Chinese radish	28
17	Pork in soup	4	54	Salted pickles of Chinese radish	17
18	Pork liver	212	55	Salted pickles of green leafy vegetables	118
19	Grilled chicken	11	56	Pickled plum	2
20	Deep-fried chicken	4	57	Pickled Chinese cabbage	24
21	Chicken liver	738	58	Pickled cucumber	1
22	Ham, loin	3	59	Pickled egg plant	20
23	Sausage, Weiner	2	60	Sweet pepper	22
24	Bacon	2	61	Tomato	15
25	Luncheon meat	5	62	Chinese chive	105
26	Milk	5	63	Garland chrysanthemum	77
27	Egg	47	64	Komatsuna	194
28	Cheese	7	65	Broccoli	71
29	Yogurt	7	66	Onion	19
30	Salted fish	14	67	Cucumber	14
31	Dried fish	2	68	Chinese cabbage	66
32	Canned tuna	5	69	Bean sprout	61
33	Salmon, trout	14	70	Snap bean	37
34	Bonito, tuna	7	71	Lettuce	56
35	Cod, flat fish	5	72	Chingensai	79
36	Sea bream	15	73	Leaf mustard	159
37	Horse mackerel, sardine	8	74	Bitter gourd	72

surprising that their lung function was weaker than their counterparts without the disease, as reflected by lower FEV1 and FVC measures.

The COPD patients had significantly lower habitual intake of folate (mean 231.2, SD 90.2 μg/day) than control subjects (mean 261.3, SD 109.8 μg/day), according to independent samples t-test ($p<0.001$). In particular, the mean folate intake of 222.8 μg per day by male COPD patients was below the Japanese government recommended daily allowance of 240 μg.[21] They also had significantly less total energy intake ($p=0.024$) than male controls whereas both groups were similar in terms of total energy intake for females ($p=0.743$).

The relationship with lung function was next investigated. Both lung function measures FEV1 and FVC (ml) were positively associated with dietary folate level, with regression coefficient 1.02 (95% confidence interval [CI] 0.35 to 1.70) and 0.84 (95% CI 0.13 to 1.55), respectively, after adjustment for total energy intake and other confounding factors.

Table 3 summarises logistic regression results for dietary folate intake in relation to COPD and the breathlessness symptom. Reductions in prevalence of COPD were observed by increasing daily folate intake. The corresponding test for linear trend was also significant ($p=0.022$). The prevalence of breathlessness was significantly higher among cases (66%) than controls (12%) (Table 2) and their median dyspnoea scores were also different ($p<0.001$). The observed Spearman rank correlation of 0.7 confirmed a good agreement between the two scales. Logistic regression result in Table 3 further suggested an inverse relationship between dietary folate intake and the prevalence of breathlessness, with a 57% reduction in risk (adjusted OR=0.43) for the highest versus lowest quartile of intake, p for trend =0.014. Indeed, participants with breathlessness had significantly less ($p<0.001$) folate intake (mean 223.2, SD 82.5 μg/day) than others without the symptom (mean 262.7, SD 110.1 μg /day). In view of the gender imbalance in the sample, female participants were subsequently removed to assess the sensitivity of the analysis. As shown in Table 3, reductions in risk of COPD and breathlessness by increasing folate intake were still evident among the male participants.

DISCUSSION

This was the first study to investigate the effects of habitual folate intake on lung function, breathlessness and the prevalence of COPD for Japanese adults. The majority (80%) of the patients had COPD diagnosed within the

Table 1. Folate content in Japanese foods and beverages (continue)[16]

	Food/Beverages	Folate (μg)		Food/Beverages	Folate (μg)
75	Chard, Swiss chard	14	112	Shiitake mushroom	33
76	Loofah	5	113	Enokitake, Shimeji	28
77	Mugwort	177	114	Wakame	24
78	Papaya	38	115	Hijiki	25
79	Mardarin orange	20	116	Nori	718
80	Other oranges	32	117	Butter for spread	3
81	Apple	0	118	Margarine for spread	1
82	Persimmon	8	119	Salad dressing	4
83	Strawberries	18	120	Mayonnaise	6
84	Grapes	4	121	Worchester Sauce	4
85	Melon	6	122	Ketchup	13
86	Watermelon	2	123	Soy milk	2
87	Peach	3	124	Green tea (sencha)	1
88	Pear	8	125	Green tea (bancha, genmaicha)	1
89	Kiwifruit	38	126	Oolong tea	5
90	Pineapple	11	127	Tea	5
91	Banana	19	128	Coffee except canned	0
92	Breads	77	129	Canned coffee	0
93	Udon	4	130	Soup	6
94	Soba	16	131	Lactic acid bacteria beverage	0
95	Okinawa soba	8	132	100% orange juice	27
96	Chinese noodles	8	133	100% apple juice	0
97	Mochi	1	134	Tomato juice	20
98	Japanese-style confectionery	16	135	Calcium fortified soft drink	0
99	Cake	5	136	Beta-carotene fortified soft drink	0
100	Biscuit, cookie	43	137	Soft drink	0
101	Chocolate	9	138	Power drinks (vitamin fortified)	0
102	Peanuts	145	139	Tap or well water	0
103	Tofu for miso-soup	15	140	Mineral water and filtered water	0
104	Tofu for other dishes	15	141	Sugar for tea	0
105	Yushi-dofu	6	142	Sugar for coffee	0
106	Freeze-dried tofu	1	143	Cream for tea	0
107	Deep-fried tofu	27	144	Cream for coffee	0
108	Natto	8	145	Cooking oil	0
109	Sweet potato	14	146	Cooking salt (sodium)	0
110	Potato	13	147	Salt (sodium) in noodle-soup	0
111	Taro	9			

Table 2. 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)
Mean age (years)	66.5 (SD 6.8)	66.1 (SD 6.1)	65.2 (SD 5.4)	66.1 (SD 5.8)
Mean BMI five years ago (kg/m^2)	22.1 (SD 2.9)	20.7 (SD 3.9)	23.6 (SD 2.9)	23.3 (SD 3.3)
Education: High school or below	195 (80%)	26 (79%)	166 (62%)	47 (70%)
Alcohol drinkers	150 (62%)	8 (24%)	202 (75%)	21 (31%)
Current smokers	53 (22%)	9 (27%)	63 (23%)	2 (3%)
Mean smoking (pack-years)	65.0 (SD 24.9)	43.3 (SD 31.7)	30.9 (SD 28.8)	2.0 (SD 9.7)
FEV1 (ml)	1640 (690)	1150 (470)	2560 (510)	1760 (350)
FVC (ml)	3080 (830)	2070 (520)	3310 (600)	2170 (410)
Breathlessness	157 (66%)	20 (66%)	33 (12%)	7 (10%)
Mean total energy intake (kcal)	1166.1 (SD 441.8)	1145.3 (SD 460.1)	1260.3 (SD 491.8)	1117.3 (SD 374.9)
Mean folate intake (μg/day)	222.8 (SD 83.2)	291.1 (SD 114.1)	256.6 (SD 109.4)	279.8 (SD 110.2)

past two years and all 278 prevalent cases were interviewed within four years of confirmed COPD diagnosis, thus enabling accurate capture of their dietary exposure information. Another strength was the spirometric measurement of lung function taken for all participants to ensure correct classification of their disease status.

In this study, male patients with COPD had lower dietary folate level than participants without the disease. It is concerning that their folate intakes were below the level recommended for older adults of 240 μg per day.[21] However, folate intake was not corrected for polyglutamyl folate, which is the major dietary folate and only 60% effective compared with monoglutamyl folate.[22]

Lung function was observed to be positively associated with dietary folate intake. The epidemiological evidence also indicated that increased folate intake could lead to reductions in the prevalence of COPD and breathlessness with significant dose-response relationships. Folate intake from diet has been similarly shown to be beneficial against lung cancer.[10] It is possible that a high

Table 3. Dietary folate intake and prevalence of COPD and breathlessness for Japanese adults

Folate intake (μg/day)	Yes n (%)	No n (%)	Crude OR	Crude 95% CI	Adjusted † OR	Adjusted † 95% CI
Both genders	COPD					
≤ 190	97 (34.9)	84 (24.9)	1		1	
191-244	70 (25.2)	84 (24.9)	0.72	(0.47, 1.11)	0.75	(0.42, 1.35)
245-308	58 (20.9)	85 (25.2)	0.59	(0.38, 0.92)	0.61	(0.32, 1.16)
≥ 309	53 (19.1)	84 (24.9)	0.55	(0.35, 0.86)	0.74	(0.35, 1.58)
Test for trend					$p = 0.022$	
Men only	COPD					
≤ 183	88 (36.1)	67 (24.9)	1		1	
184-241	66 (27.0)	68 (25.3)	0.74	(0.46, 1.18)	0.74	(0.40, 1.37)
242-293	43 (17.6)	67 (24.9)	0.49	(0.30, 0.80)	0.56	(0.28, 1.11)
≥ 294	47 (19.3)	67 (24.9)	0.53	(0.33, 0.87)	0.75	(0.34, 1.66)
Test for trend					$p = 0.022$	
Both genders	Breathlessness					
≤ 190	79 (36.6)	97 (25.1)	1		1	
191-244	61 (28.2)	96 (24.8)	0.78	(0.50, 1.21)	0.90	(0.54, 1.51)
245-318	51 (23.6)	98 (25.3)	0.64	(0.41, 1.00)	0.80	(0.45, 1.43)
≥ 319	25 (11.6)	96 (24.8)	0.32	(0.19, 0.54)	0.43	(0.21, 0.91)
Test for trend					$p = 0.014$	
Men only	Breathlessness					
≤ 183	72 (38.1)	79 (25.2)	1		1	
184-242	55 (29.1)	78 (24.8)	0.77	(0.48, 1.24)	0.99	(0.56, 1.69)
243-298	32 (16.9)	78 (24.8)	0.45	(0.27, 0.76)	0.58	(0.31, 1.11)
≥ 299	30 (15.9)	79 (25.2)	0.42	(0.25, 0.71)	0.66	(0.31, 1.39)
Test for trend					$p = 0.021$	

†Adjusted odds ratios from logistic regression models including age, gender, BMI (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 of folate can offer some protection against tobacco carcinogens. More experimental research is needed to understand the underlying biological mechanism.

Several limitations should be taken into account. Recall bias was inherent in the present case-control study due to its retrospective design, especially since the reference recall period was set at five years before interview. Although habitual diet was assessed using a validated and reliable food frequency questionnaire for the Japanese population, measurement errors could be introduced in the self-reported information. Therefore, face-to-face interviews were conducted to assist interpretation and to improve the accuracy of their responses. The first author conducted all interviews to eliminate inter-interviewer bias. Control subjects were recruited during the same period and from the same domain as the cases. They should thus provide valid estimates of folate intake. However, selection bias could not be denied because of their voluntary participation in the study. Information bias was unlikely, because the effect of folate was not established for COPD and all participants were blinded to the study hypothesis. Nevertheless, residual confounding might still present even though established confounders were controlled for in the logistic regression analyses.

In conclusion, an inverse association was found between dietary folate intake and the prevalence of breathlessness in Japanese adults, together with a significant dose-response relationship for COPD risk. Moreover, increasing folate intake may be beneficial to lung function. Further replications and prospective cohort studies are recommended to confirm the observed protective effects in other populations, and to determine whether increased intakes can improve the mortality rate due to COPD. The usage of folate supplements to improve lung function and treatment of COPD and breathlessness symptom should also be investigated in future clinical trials.

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AUTHOR DISCLOSURES

None declared for all authors.

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葉酸的攝取與肺功能、呼吸困難及慢性阻塞性肺部疾病的盛行率

在日本中部的一個病例對照研究，調查飲食攝取的葉酸與肺功能、呼吸困難及慢性阻塞性肺部疾病(COPD)之間的關聯。共有 278 位在過去 4 年內被檢測出罹患 COPD 的病人，男性 244 名與女性 34 名，年齡介於 50-75 歲；另外以 340 位同社區居民為對照組，男性 272 名與女性 68 名。評估所有對象是否有呼吸障礙，並以肺活量計測量其肺部功能。以面對面方式填寫結構型問卷，用來蒐集人口學、生活型態、日常的飲食攝取資料。使用日本食品成分表算出葉酸的攝取量。比起控制組的人(平均 261，標準差 110 μg /天)，COPD 病人日常的葉酸攝取(平均 231，標準差 90 μg /天)顯著的較低，$p<0.001$。肺部功能與飲食葉酸攝取量有正相關。葉酸攝取量的最高四分位比上最低四分位，其 COPD 盛行率與呼吸困難比例皆較低，校正過的勝算比分別為 0.74(95%CI 0.35-1.58)與 0.43(95%CI 0.21-0.91)。相對應的線性趨勢檢定亦為顯著的($p<0.05$)。結論是，在日本成人中，飲食葉酸攝取量和呼吸困難盛行率，呈現一個明顯的負相關，並且和慢性阻塞性肺部疾病風險有顯著的劑量效應關係。此外，增加葉酸的攝取可能對於肺功能是有益的。

關鍵字：呼吸困難、慢性阻塞性肺部疾病、葉酸、日本、肺功能