



Dietary Vitamin C Intake and Lung Function in Rural China

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The relation between dietary vitamin C intake and pulmonary function was investigated in a cross-sectional study carried out in 69 counties in rural China in 1989. Within each of the 69 counties, 120 subjects aged 35–64 years were identified using a three-stage random clustering procedure. Each subject underwent pulmonary function testing, completed a detailed questionnaire, and provided a blood sample. Dietary vitamin C intakes were estimated among half of the subjects using a 3-day weighed record of household food intake. Plasma vitamin C was measured in sex-specific blood pools created from individual samples in each geographic area. Among the 3,085 subjects for whom there were complete data, dietary intake of vitamin C (151 mg/day (standard deviation, 111)) was significantly related to forced expiratory volume in the first second (FEV₁) and forced vital capacity after adjustment for sex, age, height, weight, total caloric intake, tobacco smoking, and education. An increase of 100 mg/day in vitamin C intake was associated with an increase of 21.6 ml (95% confidence interval –0.4 to 43.5) in FEV₁ and an increase of 24.9 ml (95% confidence interval 0.2 to 49.6) in forced vital capacity. No significant interaction with smoking status was observed. A significant positive association was also observed at the geographic level, between county-pooled plasma vitamin C and mean FEV₁. These data support the hypothesis that dietary vitamin C may protect against the loss of pulmonary function. *Am J Epidemiol* 1998;148:594–9.

antioxidants; lung function; vitamin C

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability among adults in the United States (1), as well as throughout the world (2). Cigarette smoking is a principal risk factor for COPD; however, only 15 percent of smokers develop COPD, which suggests that other factors may contribute to susceptibility among smokers. Searching for these factors is important both for public health and prevention of COPD and for adding to knowledge of the etiology of COPD.

Recent suggestions that the balance of oxidants and antioxidants may be important in the pathophysiology of COPD have raised interest in the relation of nutrition to lung function and to COPD risk. One possibility is that COPD may result partly from a derangement in the balance between proteases and antiproteases in the lung (3). Because antiproteases have a high sensi-

tivity to oxidative damage, exposure to oxidants from either an exogenous source such as smoking or an endogenous source such as oxidants released from macrophages may tip the balance (4). Thus, a logical question is whether dietary intake, which is a major source of nonenzymatic antioxidants, including vitamin C, plays a role in the risk of COPD. Since most mammals are capable of synthesizing vitamin C and have a high tissue concentration of the vitamin, it is difficult to study this question in an animal model. Thus, epidemiologic studies in human populations are needed.

The present study was carried out to investigate the relation of dietary vitamin C intake to lung function in a general population sample from rural China.

MATERIALS AND METHODS

The data were collected in 1989 in 69 rural counties chosen from approximately 2,300 counties in China. Following procedures devised for an earlier study (5), a three-stage random clustering procedure was used to identify study participants. A selection of two *xiangs* (a *xiang* is an administrative subunit of a county) was made in each county, and in each *xiang*, one village was selected. Two production teams were chosen within each village, and 30 households were randomly selected from an official registry of households in each

Received for publication July 16, 1997, and accepted for publication February 27, 1998.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second.

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production team. From each household, one male or female aged 35–64 years was selected and invited to participate. These procedures yielded a total study sample of 8,280 individuals (120 subjects in each county (60 of each sex)) equally distributed across the three 10-year age categories of 35–44, 45–54, and 55–64 years.

By design, dietary intake was assessed among half of the selected households using a 3-day weighed household food record (5). Briefly, all raw and processed foods present before initiation of the survey were weighed and recorded, and all daily purchases of food during the 3-day survey period were quantitatively recorded. At the end of the 3 days, all remaining foods were again weighed and recorded. Household food intake was then adjusted by the number of persons present for each meal and each person's age, sex, and physical activity level to compute the reference-man intake or standardized household intake of various macro- and micronutrients (5–7). Dietary vitamin C intake was calculated using the food composition tables developed by the Institute of Nutrition and Food Hygiene, Chinese Academy of Preventive Medicine (8).

Blood was collected from each subject. After separation of the plasma and red blood cells, trichloroacetic acid-preserved plasma aliquots from individuals were combined to form sex- and xiang-specific plasma pools, and vitamin C was measured using colorimetric methods (9). For the purposes of this analysis, the two xiang values were averaged to obtain a single sex- and county-specific value.

Pulmonary function testing was carried out by a trained survey team using 8-liter, water-sealed Collins survey spirometers (Collins Company, Braintree, Massachusetts). The protocol used to measure pulmonary function followed techniques recommended by the American Thoracic Society for spirometry measurements in field studies (10). Five to eight maximal expiratory efforts were made by each subject, and all traces were read by two trained and supervised technicians for derivation of forced expiratory volume in the first second (FEV_1) and forced vital capacity. The highest test value attained was used, and test values were corrected for barometric pressure and temperature.

In assessing pulmonary function, several steps were taken for assurance of data quality. Ten percent of the traces were randomly chosen for blind rereading by the alternate technician, and 2.5 percent were blindly reread by one of the authors (G. H. or P. A. C.). Correlation coefficients for these reproducibility values ranged from 0.7 to 0.9. In 1993, a reliability study was conducted in 10 of the counties first surveyed in 1989. Both FEV_1 and forced vital capacity showed

excellent repeatability, with reliability coefficients of 0.79 and 0.73, respectively.

A questionnaire was administered to all study subjects by trained interviewers; it included questions on general characteristics (age, sex), education, symptoms of lung disease, and complete smoking history. Height and weight were assessed by physical examination. Additional information on county characteristics (for example, elevation and aridity) was obtained from the *Population Atlas of China* (11).

The data for this study were collected in a cluster fashion, with subjects sampled from 69 counties. Thus, data analysis considered both individual-level relations and geographic (between-county) relations. The cluster design of the study created a tendency for subjects at the same site to be more similar than random subjects in the population. Given that the variance of subjects within a county was correlated, regression methods that accounted for the correlation in the covariance (the PROC MIXED procedure in SAS, version 6.08 (SAS Institute, Cary, North Carolina)) were used to construct the final regression models for individual-level analyses. At the geographic level, the sex-specific mean lung function data were aggregated from individual-level data after age, height, and weight had been adjusted for, and they were then regressed against sex- and county-specific plasma vitamin values, adjusting for other covariates measured at the geographic level.

RESULTS

While the study protocol dictated that each subject complete pulmonary function testing and the questionnaire, data were incomplete for some subjects. By design, only half of the sample had dietary data. Thus, 7,404 subjects had spirometry and questionnaire data, and approximately half of them ($n = 3,085$) completed the 3-day household dietary survey. Subjects with complete data were not systematically different with regard to lung function measurements or important covariates than subjects without dietary data (table 1), with the exception that the proportion of males was higher among subjects with complete data (64 percent vs. 42 percent). Having a higher proportion of men in the final sample presents no particular selection bias. The overall mean dietary intake of vitamin C was 151.1 mg/day (standard deviation, 111.1), and the mean plasma vitamin C level was 1.09 mg/dl (standard deviation, 0.25). The values in these Chinese subjects were about 50 percent higher on average than comparable US values (12).

In baseline regression models, well-known determinants of lung function were examined. Regression coefficients for sex, age, and height all pointed in the

TABLE 1. General characteristics of subjects with complete data (pulmonary function, questionnaire, and dietary survey) compared with subjects without dietary data in a 1989 survey of 69 rural counties in the People's Republic of China

	Males		Females	
	Complete data	No dietary data	Complete data	No dietary data
No. (and %) of subjects	1,971 (64%)	1,810 (42%)	1,114 (36%)	2,509 (58%)
Smoking rate (%)	72.7	72.0	6.7	8.7
Age (years)	47.9 (8.8)*	48.3 (9.4)	47.5 (8.7)	47.5 (9.0)
Height (cm)	163.5 (6.4)	164.8 (6.4)	153.9 (5.9)	154.1 (6.1)
Weight (kg)	56.0 (7.9)	57.8 (8.2)	51.1 (8.3)	50.9 (8.7)
Education (%)				
No schooling	22.3	23.7	57.5	58.6
Primary school	51.4	46.5	32.0	29.5
More than primary school	26.3	29.8	10.5	11.9
FEV ₁ † (liters)	2.73 (0.77)	2.82 (0.76)	2.08 (0.55)	2.09 (0.57)
Forced vital capacity (liters)	3.72 (0.79)	3.77 (0.81)	2.69 (0.58)	2.67 (0.60)

* Standard deviations for continuous variables are given in parentheses.

† FEV₁, forced expiratory volume in the first second.

expected direction and had absolute values in the expected range (data not shown). Smoking had little or no association with FEV₁ in these data; findings relative to smoking are presented elsewhere (P. Cassano et al., Cornell University, unpublished manuscript). In examining the relation of vitamin C to lung function, the salient procedure is to fully adjust for the effects of smoking and to consider the possibility that nutritional effects on lung function might differ among smokers and nonsmokers.

Dietary vitamin C intake was positively associated with both FEV₁ and forced vital capacity (table 2) after adjustment for covariates, including sex, age, height, weight, education, and smoking. When total caloric intake was added to the regression model, there was little or no change in the coefficients for vitamin C. Thus, an increase of 100 mg/day in household vitamin C intake was associated with an increase of

about 22 ml (95 percent confidence interval -0.4 to 43.5 ml) in FEV₁ and an increase of about 25 ml (95 percent confidence interval 0.2 to 49.6 ml) in forced vital capacity. The magnitude of the point estimate of both effects is equivalent to approximately 1 year of age-related decline in lung function during adult life (although opposite in direction).

As a way of examining the form of the relation of vitamin C to lung function, vitamin C intakes were grouped into quartiles. The adjusted FEV₁ and forced vital capacity increased by 61 ml and 56 ml, respectively, from the lowest quartile of vitamin C intake to the highest (quartile mean values for vitamin C intake were 42, 99, 159, and 285 mg/day). There was a graded increase in FEV₁ across quartiles (quartile values were 2,700, 2,711, 2,752, and 2,761 ml), suggesting a monotonic dose-response relationship, but the pattern of increase for forced vital capacity was less clear (quartile values were 3,350, 3,323, 3,408, and 3,406 ml).

The interaction between dietary vitamin C intake and smoking was explored. The effect of vitamin C did not differ by smoking category (ever smoker vs. never smoker) or by cumulative smoking dose among smokers. When the analysis was limited to nonsmokers, there was little or no change in the regression coefficient for vitamin C intake (table 2). Similarly, there was no significant interaction between vitamin C and sex, although the proportion of smokers differed markedly by sex.

At the geographic or ecologic level, county mean vitamin C status, represented by plasma vitamin C assayed in the pooled samples, was examined in relation to mean lung function in each county after adjustment for other determinants. The geographic-level

TABLE 2. Linear regression of dietary vitamin C intake on FEV₁* and forced vital capacity at the individual level in a 1989 survey of 69 rural counties in the People's Republic of China (n = 3,085)†

	FEV ₁ (ml)			Forced vital capacity (ml)		
	β‡	SE*	p	β‡	SE	p
Model 1: overall effect	21.6	11.2	0.05	24.9	12.6	0.05
Model 2: stratified by smoking status						
Nonsmokers	21.2	15.1	0.16	27.8	16.8	0.10
Ever smokers	22.0	14.6	0.13	22.5	16.5	0.17

* FEV₁, forced expiratory volume in the first second; SE, standard error.

† Covariates included in the models were age, height, weight, sex, education, smoking (all measured in individuals) and aridity and elevation (both measured in counties).

‡ Coefficient is for an increase of 100 mg/day in vitamin C intake.

analysis among counties comprised approximately 138 sex- and county-specific data points. Use of pooled samples assumes that the subjects within a pool are relatively homogeneous, while greater variation exists between the pools. This is likely to be true for the plasma vitamin C values, because the within-county correlation was 0.61 ($p < 0.001$) between male and female pools and 0.50 ($p < 0.001$) between the two xiang pools across the 69 counties. Mean plasma vitamin C level was significantly and positively associated with mean FEV₁ (table 3). The regression coefficient for forced vital capacity pointed in the same direction, although it was not statistically significant.

DISCUSSION

Whether the relation of vitamin C to lung function was examined among individuals within a county or the relation of mean blood levels of vitamin C to mean lung function was examined among counties, the data were consistent in showing that vitamin C was independently associated with lung function. Given that FEV₁ is generally accepted to be an indicator of airways obstruction and ultimately of the risk of dying from COPD, there may be more interest in nutritional factors that are related to FEV₁. In these data, the results for FEV₁ were somewhat more consistent than the results for forced vital capacity: Dietary and plasma vitamin C were consistently associated with FEV₁, and there was a monotonic dose-response relationship between dietary vitamin C and FEV₁.

The present study was consistent with the findings of three previous studies carried out in Western populations (13–15), both in the direction and in the magnitude of the association of vitamin C with lung function. All three Western studies reported a positive association of dietary intake and/or plasma vitamin C with respiratory symptoms and/or results of pulmo-

nary function tests. The present study adds to current knowledge by considering the question of a link between nutritional factors and pulmonary function in a different sociocultural context. This is important for two reasons.

First, food sources of vitamin C in the diet of the rural Chinese population differ somewhat from food sources in Western populations. While fruits and vegetables together comprise approximately 73 percent of vitamin C intake in the typical US diet (12), 73 percent of household vitamin C intake in this rural Chinese population came from vegetables alone; 24 percent was from tubers, and 2 percent was from fruits. In approximately one fifth of the counties, more than 50 percent of dietary vitamin C was derived from sweet potatoes. In any nutritional epidemiologic study, one must consider whether an observed association is attributable to a single nutrient, given the well known covariance among nutrients. In these data from rural China, regardless of which other dietary intake variables were considered (vitamin E, carotenes, vitamin A), there was little or no change in the relation of vitamin C to pulmonary function. The consistency of findings across sociocultural settings with different food habits provides some support that the observed effect is more likely to be due to vitamin C per se. The geographic-level findings for plasma vitamin C, which are consistent with the dietary findings, suggest that the observed relations are attributable to vitamin C per se.

Second, past reports of a protective effect of vitamin C on lung function are subject to the concern that residual confounding, due to imperfect measurement of smoking, may explain the apparent effect of vitamin C. Smoking has been regarded as an important potentially confounding variable in assessment of the relation of vitamin C to lung function, because smokers tend to have lower dietary intakes of vitamin C-rich foods (16–18). In the present study, the lack of a main effect of smoking on FEV₁ means that the effect of vitamin C is not likely to be explained by residual confounding due to smoking.

Another consideration relative to smoking is its potential interaction with dietary vitamin C. One mechanism posited for vitamin C is that it protects the lung from smoking-induced damage. Thus, an interaction may exist such that the effect of vitamin C would be stronger in smokers. However, no interaction between smoking and vitamin C was observed in these data. Similarly, no interaction has been reported in past studies (16, 19).

Dietary information was collected at the household level rather than the individual level because of dietary habits in rural China: People within a household share

TABLE 3. Linear regression of plasma vitamin C (mg/dl) on FEV₁* and forced vital capacity at the ecologic level in a 1989 survey of 69 rural counties in the People's Republic of China (n = 138)†

	FEV ₁ ‡ (ml)			Forced vital capacity‡ (ml)		
	β§	SE*	p	β§	SE	p
Plasma vitamin C	143	46.9	0.003	94	65.5	0.15

* FEV₁, forced expiratory volume in the first second; SE, standard error.

† Covariates included in the model were sex, aridity, elevation, income, and education.

‡ The sex-specific county mean lung function data were aggregated from individual-level data after adjustment for age, height, and weight.

§ Coefficient is for an increase of 1 mg/dl in plasma vitamin C level.

the same dishes, and in fact eat from a "common" pot. The 3-day weighed household food record has been regarded as the most precise method for dietary surveys in China, and it has been used in all three national nutrition surveys in China (20, 21). This method yielded a daily intake of vitamin C for each household adjusted for differences in the age, sex, and physical activity of household members, providing information with which to rank order the households. The analysis assumes that subjects living in a household ranking high on vitamin C intake are likely to have ranked similarly had an individual-level assessment been feasible. Seasonal variation and uneven food distribution among family members within a household may introduce error. In the present study, this kind of measurement error is likely to have been nondifferential; thus, the true effect of vitamin C on lung function may be stronger than what was observed.

The present study was cross-sectional, and the assessment of diet was carried out at a single point in time. The hypothesis posits a relation of long term vitamin C level to lung function, although the exact timing of dietary pattern in relation to lung function is not well specified. An advantage of this study is that current dietary vitamin C intake is likely to represent a usual long term average, since dietary patterns in China have been rather stable due to reliance on local agriculture for most foodstuffs.

Although a possible role of vitamin C in the pathogenesis of airways disease was first suggested as early as the last century, the mechanisms through which vitamin C may protect the airways are not well understood; at least four possible mechanisms have been suggested. First, as a major dietary antioxidant, vitamin C has the capacity to trap both exogenous (e.g., ozone and nitrogen dioxide) and endogenous (released from neutrophils) free radicals, thus preventing free radical-induced lipid peroxidation. Specifically, vitamin C could protect the α_1 -proteinase inhibitor from oxidative damage, and thus vitamin C may play a role in sustaining the balance of proteases and antiproteases. It has been reported that prior supplementation with vitamins C and E prevented both the oxidant gas-induced increase in lipid peroxidation and the associated decrease in elastase inhibitory capacity in the alveolar lining fluid of human subjects (22). Second, as a cofactor of the hydroxylation reaction, vitamin C may help repair lung tissue damage through the synthesis of collagen. This mechanism is widely regarded as the basis for the role of vitamin C in the prevention of scurvy. Third, vitamin C may directly modify prostaglandin production. Preadministration of ascorbic acid was reported to ameliorate methacholine-induced airways constriction among mildly asthmatic

subjects (23) and among healthy subjects (24). In both instances, the effect of ascorbic acid was blocked by administration of indomethacin, an antiinflammatory drug which is a cyclooxygenase inhibitor. Cyclooxygenase is an enzyme corresponding to a pathway of arachidonic acid metabolism that determines prostaglandin production and, ultimately, airways "tone." The interaction of vitamin C and indomethacin in both studies (23, 24) supported the possibility of a role for vitamin C through a mechanism involving prostaglandin production. Finally, there is some evidence that vitamin C may protect the airways through improved immune function (25). Supplemental vitamin C reportedly decreases the duration of colds and the severity of respiratory symptoms (26), but epidemiologic surveys have failed to establish a meaningful relation between vitamin C status and the improvement of immunity in healthy subjects (27). Data from the present study support a protective role of vitamin C on lung function, but do not allow any exploration of the possible mechanisms reviewed above.

The magnitude of the association between vitamin C intake and lung function in the present study is equivalent to approximately 1 year of age-related decline in lung function for every 100-mg/day decrease in vitamin C intake. Although this is clinically significant, the magnitude of this association may have been affected by measurement error in both vitamin C intake and lung function and by the potentially confounding effects of other unmeasured variables. The association appears robust in that it was observed for both individual-level and ecologic-level data, and for both dietary vitamin C and plasma vitamin C data. The findings are free of potential residual confounding due to smoking, and are consistent with the results of previous epidemiologic studies which studied Western populations with some differences in the food sources of vitamin C. Given the cross-sectional nature of this study, however, it is not possible to make inferences about the effect of vitamin C on age-related decline in pulmonary function. A longitudinal study is needed to gauge the effect of vitamin C over time and its role in protecting the lung against age-related changes in pulmonary function.

ACKNOWLEDGMENTS

This work was supported in part by grant 5R29HL45731 from the US National Heart, Lung, and Blood Institute.

The authors are indebted to the staff at the Chinese Academy of Preventive Medicine (Beijing, People's Republic of China) for their tireless efforts in carrying out the fieldwork for this study. The authors also thank Dr. F. E. Speizer for his help in identifying spirometers for the fieldwork early in the study. The authors acknowledge the gen-

erous help of the Warren E. Collins Company (Braintree, Massachusetts) in refurbishing the spirometers used in this study.

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