

Season-specific Correlation between Dietary Intake of Fruits and Vegetables and Levels of Serum Biomarkers among Chinese Tin Miners at High Risk for Lung Cancer

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INTRODUCTION

Tin miners have been at an increased risk of lung cancer by virtue of their occupational exposures to arsenic and radon.^{1,2,35} In the early 1990s, the lung cancer mortality rate among Yunnan Tin Corporation (YTC) miners in southern China was 487/100,000 compared with a rate of 30/100,00 in Chinese men.³ In an incident case-control study of the YTC miners, dietary intakes of specific fruits and vegetables were inversely associated with the odds ratio of lung cancer, after adjustment for occupational and smoking histories.⁴

High intakes of fruits and vegetables and elevated blood levels of β -carotene have been consistently associated with a reduced risk of lung cancer.^{5,6} Dietary intake of fruits and vegetables has been positively correlated with blood levels of carotenoids and vitamin C as well as urinary flavonoid metabolites.⁷⁻¹⁰ The magnitude of these correlations varied by gender, age, and season.¹⁰⁻¹² Smoking status, alcohol intake, body weight, and intakes of fat and fiber have confounded the diet-biochemical correlation.¹¹⁻¹⁶

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between Dietary Intakes and Levels of Vitamin C in Chinese Tin Miners

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As part of a large-scale prospective cohort study of lung cancer among the YTC miners, a diet-biochemical validation study (DBVS) was conducted in 1995 and 1996. The objective of this paper is to examine the season-specific correlation between intakes of fruits and vegetables and serum biomarker levels, before and after adjustment for covariates.

MATERIAL AND METHODS

Study Population

Over 7,000 miners, who were aged ≥ 40 y, had ≥ 10 y of underground mining experience, and who were free of all cancer except nonmelanoma skin cancer, were enrolled prospectively as the high-risk cohort for lung cancer beginning in 1992 and followed annually to the present.¹ The DBVS miners ($N = 128$) were randomly selected from workers in four mine units who were similar by demographic and occupational characteristics to all YTC miners. Fifteen of the 128 were excluded from analysis because of incomplete dietary data or a diagnosis of a chronic disease in 1995–1996.

Dietary Data

Seven consecutive days of 24-hour food recalls were collected once during each of four seasons, beginning in the spring of 1995 and ending in the winter of 1996, for a total of 28 days of food recalls in one year. Trained interviewers administered food recalls at the same time daily in the miner's home. The interviewer asked about intake of each food item in a mixed dish or eaten individually by time of day, food preparation technique, gram amount, and place of consumption.¹⁷

Blood Sample Collection

In the morning of food recall day seven in the spring, blood was drawn from each miner after 12 hours in the fasting state. Because of cultural taboos about blood, subsequent blood collection was limited. One third of the DBVS sample was randomly selected for a blood drawing on food recall day seven during one of the remaining three seasons, for a total of two blood drawings from each participant.

Blood to measure red blood cell (RBC) folate; vitamins A, E, and C; as well as the carotenoids was collected in 6-mL serum separator tubes (SST®) and 3-mL K₃EDTA Vacutainers® (Becton-Dickenson, Franklin Lakes, NJ), protected from light by aluminum foil wrapping, and kept in ice until delivery to the clinic. Blood was centrifuged for 15 minutes at 2400–2500 rpm ($1500 \times g$). A 250 μ L of serum was placed into a cryovial (Nalge, Rochester, NY) with 1.0 mL of 6 g/dL metaphosphoric acid preservative added for the vitamin C sample; 0.5 mL of the EDTA tube for the carotenoids was removed for hematocrit measurement, and 100 μ L of the whole blood was added to 1.0 mL of 1 g/dL ascorbic acid to preserve the RBC folate sample. All samples were stored at -70°C until shipment to the Centers for Disease Control and Prevention for laboratory analysis.

Serum levels of vitamin C (ascorbic acid), vitamin A (retinol), vitamin E (α -tocopherol), retinyl esters, and five carotenoid peaks (α - and β -carotene, β -cryptoxan-

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thin, lutein/zeaxanthin (referred to as lutein), and lycopene) were measured by C-18 reverse-phase column using high-performance liquid chromatography (HPLC).^{18,19} Quantitation was by peak height and based on a standard curve generated from external standards as part of the NIST Round Robin Program. RBC folate was measured using the Bio-Rad Laboratories Quantaphase II¹²⁵I/⁵⁷Co radioassay (Hercules, CA).²⁰

Body mass index (BMI) was calculated from weight measured to the nearest kilogram in 1995 and from height measured to the nearest centimeter at the baseline exam in 1992.

Statistical Analysis

The statistical analysis involved two phases. In phase one, 223 foods, that were coded from the food recalls, were classified into food groups, including fruits and vegetables. The total gram intake of each food was calculated from its intake over the seven days in each season, followed by a calculation of the percentage that the food contributed to the food group intake in each season. The seasons were defined: spring (March–May), summer (June–August), fall (September–November), and winter (December–February). To test for seasonal differences in dietary intake of fruits and vegetables and for seasonal differences in biochemical levels, analysis of variance (ANOVA) was performed, with statistical significance set at a two-tailed *p* value of ≤ 0.05 .

In phase two, season-specific Spearman Rank partial correlation coefficients were calculated between intakes of all fruits, of all vegetables, and of all fruits and vegetables and serum biomarker levels. Alcohol intake (g/d), smoking (number of cigarettes/d), BMI (kg/m^2), age, and income were adjusted in the ANOVA and in the correlation analyses, because each variable met one or both of two conditions. Notably, age, income, alcohol intake, and smoking were statistically significantly related to the mean serum levels in the ANOVAs in phase one, and/or they were recognized confounding factors of the diet-biochemical relationship in earlier studies.^{10-12,15,21,22}

RESULTS

Total fruit intake was higher in the spring and summer than in the fall and winter; whereas total vegetable intake was higher in the summer than in the spring (TABLE 1). Over 70% of the miners smoked cigarettes, and 60% drank alcohol (grain liquor) in fairly heavy amounts daily. Serum α -carotene levels were higher in the fall than in the spring and summer. β -carotene levels were higher in the winter than in all other seasons and also were higher in the spring and fall than in the summer. Lutein levels were lower in the summer than in the spring and winter. Serum lycopene and RBC folate levels were higher in the spring than in any other season. From 3 to 13% of the miners were folate deficient (RBC folate < 85 ng/mL) in one of the seasons. Serum vitamin C levels were lower in the spring and summer than in the fall and winter. The seasonal peaks of fruit and vegetable intake and of serum biomarker levels remained after adjustment for smoking, alcohol intake, BMI, age, and income.

and lycopene) were measured by C-18 liquid chromatography (HPLC).^{18,19} A standard curve generated from ex-hobbin Program. RBC folate was measured by a standard curve generated from ex-hobbin Program. RBC folate was measured by a standard curve generated from ex-hobbin Program. RBC folate was measured by a standard curve generated from ex-hobbin Program.

Weight was measured to the nearest kilogram and height to the nearest centimeter at the baseline.

Analysis

In phase one, 223 foods, that were grouped into food groups, including fruits and vegetables, were calculated from its intake over the study period. The calculation of the percentage that the intake of each food group was calculated from its intake over the study period. The seasons were defined: spring (March–May), fall (September–November), and winter (December–February). Seasonal differences in dietary intake of fruits and vegetables, and seasonal differences in biochemical levels, analysis of variance for statistical significance set at a two-tailed $p < 0.05$.

Rank partial correlation coefficients were calculated for all vegetables, and of all fruits and alcohol intake (g/d), smoking (number of cigarettes per day) were adjusted in the ANOVA and in the regression analysis for one or both of two conditions. No significant differences were statistically significantly related to season in phase one, and/or they were not statistically significant in the diet-biochemical relationship in earlier studies.

Results

Mean age was higher in the summer than in the fall and winter; BMI was higher in the summer than in the spring (TABLE 1). Mean income was higher in the summer than in the fall and winter; 60% drank alcohol (grain liquor) in the summer. Serum lycopene levels were higher in the fall than in the spring and winter; serum lycopene levels were higher in the winter than in all other seasons. Lutein levels were higher in the fall than in the summer. Lutein levels were higher in the winter than in all other seasons. Serum lycopene and lutein levels were higher in the winter than in any other season. From 3 to 13% of subjects had serum lycopene levels < 85 ng/mL in one of the seasons. Mean alcohol intake and of serum biomarker levels were higher in the summer than in the fall and winter; BMI, age, and income.

TABLE 1. Mean (\pm SD) demographic characteristics; dietary intake of fruits, vegetables, and alcohol; and mean (\pm SE) serum biomarker levels by season: DBVS

Characteristic	Spring (n = 113)	Summer (n = 35)	Fall (n=31)	Winter (n = 32)
Age at interview (yr)	52 (9)	52 (9)	50 (9)	51 (8)
BMI	23 (3)	22 (3)	23 (3)	22 (3)
Income (Yuan/mo)	554 (552)	535 (195)	598 (195)	565 (223)
Education	5 (4)	6 (4)	6 (3)	6 (5)
Percent Current Smokers	75	77	72	74
Alcohol (g/d)	104 (115)	81 (117)	68 (100)	66 (105)
Fruit Intake (g/d)	56 (10.1) ^{b,#,c,*}	53 (4.7) ^{d,e,*}	32 (5.5)	23 (9.9)
Vegetable Intake (g/d)	263 (10.2) ^{a,#}	296 (12.3)	275 (10.7)	281 (11.4)
Serum (mg/dL)				
α -carotene	3 (0.2)	2 (0.2)	4 (0.3) ^{b,#,d,*}	3 (0.3)
β -carotene	23 (1.3) ^{a,+}	15 (0.9)	22 (1.5) ^{d,+}	31 (2.0) ^{c,#,e,+f,*}
Lutein/Zeaxanthin	66 (2.5)	57 (2.3) ^{a,+e,*}	59 (2.2)	68 (2.1)
Lycopene	8 (0.5) ^{a,+b,+c,+}	2 (0.2) ^{e,+}	2 (0.2) ^{f,*}	1 (0.1)
RBC Folate (ng/mL)	165 (5.5) ^{a,+b,#,c,*}	149 (5.7)	130 (4.1)	153 (5.0)
Vitamin C	0.6 (0.03) ^{b,#,c,+}	0.7 (0.03) ^{d,e,*}	0.8 (0.04)	0.8 (0.03)

^aSpring vs. Summer. ^bSpring vs. Fall. ^cSpring vs. Winter. ^dSummer vs. Fall. ^eSummer vs. Winter. ^fFall vs. Winter.

* $p < 0.05$. # $p < 0.01$. + $p < 0.001$.

Seasonal patterns of the major contributors (by at least 1%) to fruit intake included watermelon, bananas, and peaches in the spring; and bananas, peaches, pomegranates, pears, and apples in the summer (FIG. 1). By fall, apples as well as oranges and tangerines were the highest contributors, with bananas, pineapples, and persimmons adding another 6% each. Finally, in the winter, oranges and tangerines, apples, and bananas were the major contributors to fruit intake. Seasonal patterns of the major contributors to vegetable intake included a variety of fresh and pickled/salty green vegetables, scallions and leeks, white vegetables such as potato and radish root, and occasionally tomatoes (FIG. 2).

The significant diet-biochemical associations were positively correlated (TABLE 2). Serum α -carotene levels were correlated with fruit intake in the spring. During the summer, levels of α -carotene, lycopene, and RBC folate were correlated with fruit intake; serum lutein and vitamin C levels were correlated with vegetable intake; and RBC folate, serum α -carotene, lutein, and vitamin C levels were correlated with fruit and vegetable intake. During the fall, RBC folate was correlated with fruit intake; levels of α - and β -carotene, lutein, and vitamin C were correlated with vegetable intake; whereas α - and β -carotene, lutein, vitamin C, and RBC folate levels were correlated with fruit and vegetable intake. During the winter, vitamin C levels were correlated with vegetable intake and both fruit and vegetable intake.

In an analysis of fruit consumers ($n = 56$ in spring; $n = 24$ in summer; $n = 14$ in fall; $n = 11$ in winter), the following diet-biochemical correlations changed: fruit intake in spring and serum α -carotene ($r = 0.19$); fruit intake in summer and serum α -

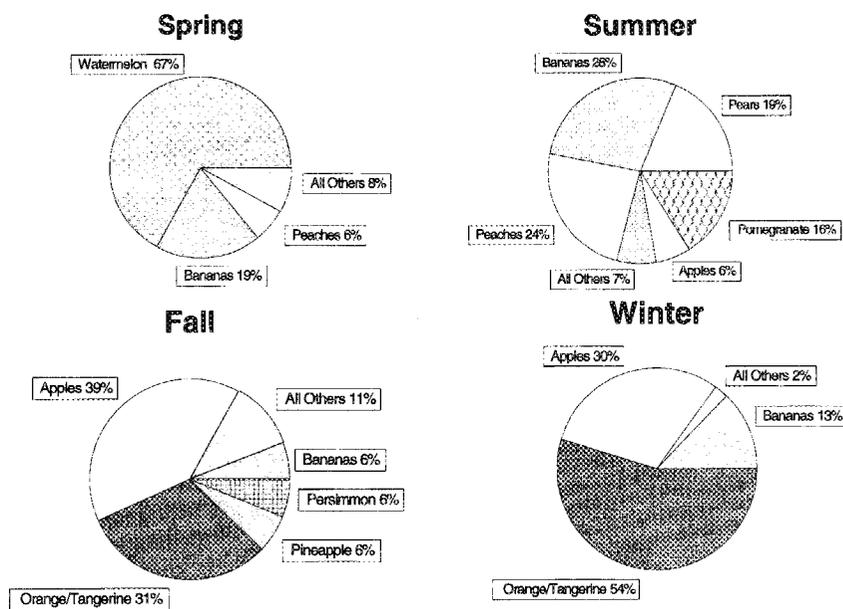


FIGURE 1. Percent contribution of individual fruits to fruit intake: DBVS.

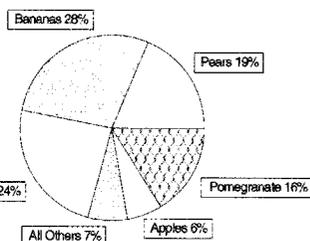
carotene ($r = 0.34$), β -carotene ($r = 0.46$, $p \leq 0.05$), and RBC folate ($r = 0.66$, $p \leq 0.01$); fruit intake in fall and RBC folate ($r = 0.74$, $p \leq 0.01$); fruit intake in winter and β -carotene ($r = 0.71$, $p \leq 0.01$). By and large, the correlation between the dietary intake of fruits and serum biomarker levels increased in the analysis of fruit consumers, with the exceptions of the relationship between fruit intake and serum α -carotene levels.

DISCUSSION

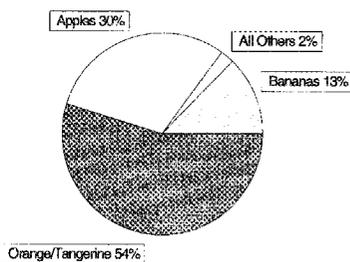
Based on seven days of food recalls and serum biomarker levels in each of four seasons of a year, miners experienced peak fruit intake in the spring; peak vegetable intake in the summer; and peak levels of α -carotene in the fall, β -carotene and lutein in the winter, lycopene and RBC folate in the spring, and higher vitamin C levels in the fall and winter than in the spring and summer. The magnitude of the correlation between fruit and vegetable intake and biomarker levels varied by season, with most significant correlations appearing in the summer and fall.

Individual foods contributing to fruit intake varied by season; only bananas were eaten in every season. Although bananas contain folate, only peaches are rich in β -carotene, and oranges and tangerines have β -cryptoxanthin. Likewise individual foods contributing to vegetable intake varied by season. Potatoes, Chinese cabbage, green beans, and scallions plus leeks were eaten in every season. Whereas all the fresh and pickled dark green vegetables are rich in folate and lutein and to some ex-

Summer



Winter



ual fruits to fruit intake: DBVS.

05), and RBC folate ($r = 0.66, p \leq 0.05$); fruit intake in winter ($r = 0.74, p \leq 0.01$); the correlation between the dietary intake of fruit and vegetable consumed in the analysis of fruit consumption and serum α -carotene and RBC folate and to some ex-

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um biomarker levels in each of four seasons: peak fruit intake in the spring; peak vegetable intake in the fall; β -carotene and lutein levels in the spring, and higher vitamin C levels in the winter. The magnitude of the correlation between fruit intake and serum biomarker levels varied by season, with most correlations being significant in the spring and fall.

varied by season; only bananas were a source of folate, only peaches are rich in β -carotene, and only pomegranate is rich in lutein. Likewise individual fruit types were consumed in every season. Whereas all the fruits were consumed in folate and lutein and to some ex-

TABLE 2. Spearman correlations^a between dietary fruit and/or vegetable intake and serum biomarkers by season: DBVS, YTC

Season	Biomarkers					
	α -Carotene	β -Carotene	Lutein	Lycopene	RBC Folate	Vitamin C
Spring						
Fruit	0.32*	0.14	0.08	0.19	0.08	0.13
Vegetables	0.07	0.12	0.07	0.01	0.02	0.05
Fruits and Vegetables	0.19	0.11	0.09	0.05	0.03	0.07
Summer						
Fruit	0.47 [#]	0.27	0.18	0.38*	0.46*	0.35
Vegetables	0.33	0.27	0.45*	0.16	0.23	0.44*
Fruits and Vegetables	0.41*	0.33	0.46*	0.24	0.39*	0.51 [#]
Fall						
Fruit	0.01	0.07	0.04	0.12	0.71 ⁺	0.28
Vegetables	0.51*	0.62 [#]	0.52*	0.23	0.34	0.58 [#]
Fruits and Vegetables	0.45*	0.61 [#]	0.55 [#]	0.21	0.61 [#]	0.74 ⁺
Winter						
Fruit	-0.10	-0.03	-0.22	0.33	0.05	-0.10
Vegetable	0.08	0.33	0.32	0.20	-0.06	0.48*
Fruits and Vegetables	0.11	0.29	0.20	0.35	-0.03	0.47*

^a With adjustment for age, income, alcohol, smoking, and body mass index.

* $p < 0.05$. [#] $p < 0.01$. ⁺ $p < 0.001$.

tent β -carotene, raw tomatoes provide lower levels of lycopene than tomato products. Among the vegetables in the "other" category, limited orange and yellow vegetables were eaten to add to α -carotene and β -carotene intake.

The range in fruit intake over the four seasons of the DBVS was from one tenth of a cup to a little over one quarter of a cup each day, when one half a cup of raw fruit per day is equivalent to a serving based on the National Cancer Institute's (NCI) 5-A-Day Program. The range in vegetable intake was from one and one quarter cup to one and one half cup a day over the year, when one cup of leafy green vegetables or one half a cup of raw vegetables is equivalent to a serving in the NCI 5-A-Day Program. Therefore fruits and vegetables were consumed in very small amounts daily, with a minimal range in intake from the lowest to the peak seasons.

The seasonal peak of fruit and vegetable intake did not correspond with the biochemical peaks of the serum markers because the major contributors to fruit intake did not frequently have high concentrations of the same micronutrients as the serum markers. The amount of fruit and vegetable intake across the seasons did not vary appreciably, even though the seasonal differences in intake were statistically significant (see above). Fat intake was in the form of lard used in food preparation (13g/d),

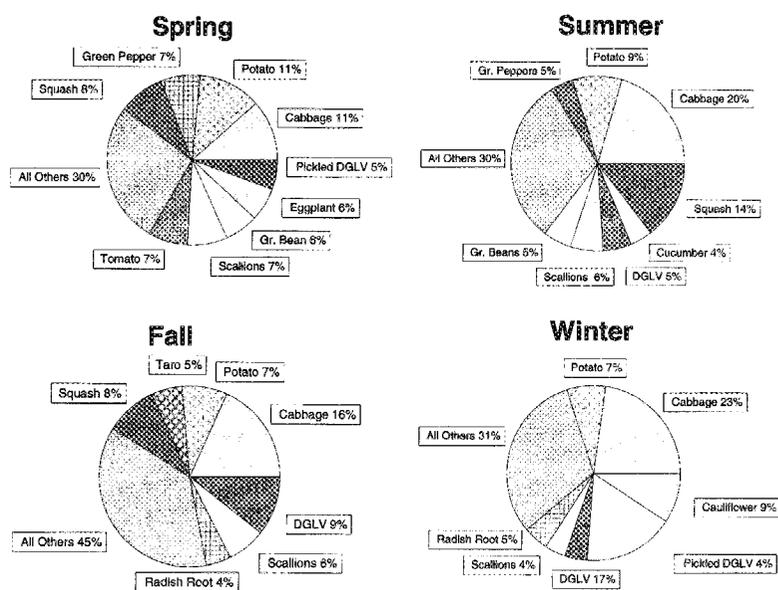


FIGURE 2. Percent contribution of individual foods to vegetable intake: DBVS.

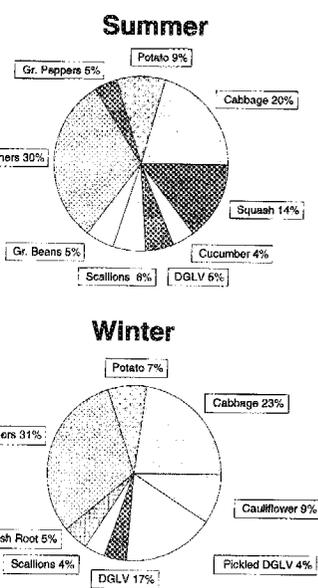
and therefore uptake of lipid soluble micronutrients might have been hindered by the low-fat intake. Finally, alcohol intake was high and altered levels of serum lipoproteins, which transport the carotenoids.

Seasonal differences in dietary intake of fruits and vegetables and in serum biomarker levels have been reported across cultures, including the northern province of Linxian, China,²³ the Gambia,²⁴ Spain,²⁵ Finland,²⁶ Britain,^{16,27} and Hawaii.²⁸ Seasonal patterns of fruit and vegetable intake might be due to market availability, cost, and accessibility as well as refrigeration, whereas seasonal variation in blood levels might be associated with the level of fruit and vegetable intake, underlying health status, and lifestyle characteristics.

Serum lycopene and α -carotene levels of the miners were lower than other populations, except for other Chinese.^{10,16,23,27,29} β -carotene levels were similar to²⁷ or were slightly higher than other male smokers^{10,29} and higher than other Chinese.²³ Vitamin C levels were comparable to other smoking populations,^{27,30} whereas lutein levels were much higher than others.²⁷

In the DBVS, the magnitude of the diet-biochemical correlation varied by season. The larger values and higher frequency of correlations typically appeared in the summer and fall, and the lower ones appeared in the spring and winter. Diet-lycopene levels were not significantly correlated in any season, except for one in summer that could be due to chance. Likewise, total fruit and vegetable intake among American women was the most significant determinant of each carotenoid except for lycopene.³¹

One factor that could potentially influence the magnitude of the diet-biochemical correlation was the number of food recall days that were averaged to reflect dietary



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intake. In this paper, seven consecutive days of food recalls were averaged because the blood was collected on day seven. Earlier clinical nutrition research in men has demonstrated that the carotenoids appeared in the blood from two to seven days after dietary intake.³²⁻³⁴ In a separate analysis, two days (food recall days 5 and 6) were averaged and then the diet-biochemical correlations were computed. No appreciable difference in the magnitude or the direction of these diet-biochemical correlations appeared using the two-day versus the seven-day averaged intakes. Our findings might not reflect earlier studies because of the differences in the diet and alcohol intakes as well as the smoking habits of the miners in contrast with healthy, nonsmoking male volunteers in the United States.

In summary, miners experienced peak seasons of fruit and vegetable intake and of serum biomarker levels. The magnitude of the diet-biochemical correlation varied by season with most correlations appearing in the summer and fall. Future research in the relationship between diet and/or biochemical parameters and lung cancer risk needs to take into account the seasonal patterns of diet and serum biochemical markers.

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