Original Article

Intake of vitamin A-rich foods and lung cancer risk in Taiwan: with special reference to garland chrysanthemum and sweet potato leaf consumption

Yi-Ru Jin MS[1, 2], Meei-Shyuan Lee DrPH[3], Jang-Hwa Lee MD[1], Hon-Ki Hsu MD[4], Jau-Yeong Lu MD[5], Shin-Shin Chao MS[6], Kow-Tong Chen MD, PhD[7], Saou-Hsing Liou MD, PhD[3, 8] and Luo-Ping Ger MPH[2, 6, 9]

[1]*Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[2]*Department of Biological Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan*
[3]*School of Public Health, National Defense Medical Center, Taipei, Taiwan*
[4]*Division of Thoracic Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[5]*Division of Chest Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[6]*Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[7]*Department of Public Health College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[8]*Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Kaoshiung, Taiwan*
[9]*Institute of Biomedical Science, National Sun Yat-Sen University, Kaohsiung, Taiwan*

A case-control study was conducted to investigate the association between the consumption of local common foods that are rich in vitamin A and the risk of lung cancer in Taiwan. A total of 301 incident lung cancer cases, 602 hospital controls, and 602 neighborhood controls were recruited. The consumption of 13 food items and vitamin supplements was estimated by use of a food frequency questionnaire. The conditional logistic regression models were used to estimate the adjusted odds ratios (AOR) and 95% confidence intervals (CI) for lung cancer risk with each control group as reference by adjustment of covariates. A reduced risk for lung cancer was found to be associated with increased intakes of vitamin A, α-carotene, and β-carotene from 13 food items. More servings of vegetables (AOR for the highest versus the lowest quartile = 0.67-0.70, 95% CI = 0.42-1.08, $p_{linear\ trend}$ = 0.04), garland chrysanthemum (AOR for the highest versus the lowest tertile = 0.58-0.74, 95% CI = 0.37-1.14, $p_{linear\ trend} \leq 0.04$) and sweet potato leaves (AOR for the highest versus the lowest tertile = 0.43-0.65, 95% CI = 0.28-0.96, $p_{linear\ trend} \leq 0.03$) were associated with the reduced risk for lung cancer. In conclusion, higher consumption of vitamin A-rich vegetables, especially garland chrysanthemum and sweet potato leaves might provide potential protection from lung cancer.

Key Words: lung cancer, case-control study, vitamin A, garland chrysanthemum, and sweet potato leaves

INTRODUCTION

Since 1983, cancer has become the leading cause of death in Taiwan. Lung cancer is ranked as the second leading cause of cancer death in 2003, accounting for approximately 20% of all cancer deaths annually. The mortality rate of this disease is still increasing although the rate of increase has slowed considerably over the past decade.[1] Cigarette smoking is well recognized as the primary etiologic factor for lung cancer. However, the epidemiological characteristics of lung cancer in Taiwan cannot be fully explained by smoking alone.[2] Accordingly, it may be of interest to target other exposures that are associated with lung cancer so as to reduce the incidence of the disease. One such exposure is vitamin A, a central physiologic role in regulation of cell differentiation.[3, 4]

Previous experimental[5-7] and epidemiological[8-17] studies consistently demonstrated the protective effects of dietary intake of vitamin A, vegetables and fruits in lung cancer. However, recent studies reported the lack of associations between vegetable or fruit intake and the development of lung cancer.[18, 19] Moreover, three large clinical intervention trials[20] have failed to demonstrate any observable reduction

Corresponding Author: Professor Luo-Ping Ger, Department of Medical Education and Research, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Rd., Kaohsiung, Taiwan.
Tel.: 011-886-7-346-8356; Fax: 011-886-7-3468056
Email: lpger@vghks.gov.tw
Manuscript received 18 August 2006. Initial review completed 3 October 2006. Revision accepted 14 November 2006.

in lung cancer risk from supplements of β-carotene/vitamin A. Therefore, the preventive effect of vitamin A-rich foods and supplements for lung cancer are still controversial.

To date, few studies have evaluated the association between lung cancer and dietary factors in Asian region. There were only five published studies in China,[21-25] two in Singapore,[26, 27] two in Japan[14, 28] and two in Taiwan.[2, 29] These studies demonstrate protective effects of vegetable, fruit, fish, or milk intake against lung cancer. However, relatively little attention has been given to the preventive effect of common vitamin A-rich foods. Therefore, we carried out this case-control study to assess the risk of lung cancer and the intakes of vitamin A, α-carotene, β-carotene, retinol, vitamin A-rich foods, and vitamin A supplements in Taiwan.

MATERIALS AND METHODS

Case definition and identification

The total eligible cases (≤80 yrs) were 333 patients newly diagnosed with histopathologically confirmed primary lung cancer. They were inpatients in the Tri-Service General Hospital between 1990 and 1994 and the Kaohsiung Veterans General Hospital between 1997 and 1998. Of the 333 eligible cases, 27 (8%) patients had been discharged when the interviewer visited them in the ward. These patients or their relatives refused to be interviewed either in hospital or at home. Another five (2%) patients refused to be interviewed during hospitalization. Therefore, a total of 301 lung cancer cases were successfully interviewed, a response rate of 90%. They were classified by cell type as follows, 143 (48%) adenocarcinoma, 81 (27%) squamous cell carcinoma, 36 (12%) small cell carcinoma, 16 (5%) bronchioloalveolar adenocarcinoma, 14 (5%) unclassified carcinoma, 4 (1%) large cell carcinoma, 3 (1%) adenosequamous carcinoma, 2 (1%) undifferentiated carcinoma, 1 (<1%) papillary adenocarcinoma and 1 (<1%) mucinous adenocarcinoma.

Control definition

Two different control groups were recruited. The first group of 602 hospital controls two-to-one matched with each case on sex, date of birth (± 5 years), hospital, date of interview (± 4 weeks) and insurance status were selected from Ophthalmology Department. The second group of 602 neighborhood controls two-to-one matched with each case on age, sex and residence where the case lived at the date of diagnosis were randomly selected from those eligible neighbors.

Interviews and data collection

The cases and hospital controls were interviewed in the ward and the neighborhood controls were interviewed at home. All of them signed an informed consent before they were interviewed by use of a structured questionnaire that elicited detailed information on personal smoking habits, exposure to passive smoking, incense burning, mosquito repellant coil burning, type of cooking, the use of coals as cooking fuel, past history of lung disease, and intake of vitamin A-rich foods. We also obtained a lifetime history of all jobs held with a duration of at least 3 months (job title, activities and exposure). Each interview took about 40 minutes to complete. The interviewers were aware of whether the interview was a case or a control. The supervisor checked all questionnaires on the day following the interview. If the questionnaire was not completed, additional information was obtained either by personal interview or by telephone interview. In addition, a random sample of 5 percent of the subjects were reinterviewed by the supervisor, either on exposure history or on dietary intake.

Smokers were defined as those who have smoked one cigarette or more per day (or 30 mg of tobacco a month) for at least one year. For each smoker a detailed smoking history was obtained including the type of tobacco product (cigarettes, cigars and pipes), daily consumption quantity, intensity of inhalation, age at which regular smoking started and age at any major change of smoking habits. The childhood exposure to passive smoke was obtained by asking subjects whether, as a child, they had lived with their father or mother who was a smoker during that time. Those who answered yes were asked the number of years their parents smoked in their presence. The adult exposure to passive smoke at home was defined as having a spouse or children who smoked for a year or more in their presence during a period of more than five hours per day. The exposure to passive smoke at work was defined as having colleagues who smoked in their presence for more than five hours per day for a period of more than one year. The adult exposure to passive smoke from friends was defined as having friends who smoked in their presence indoors for one or more hours per day for a period of more than one year.

Dietary assessment

To assess intake of vitamin A-rich food, we designed a food frequency questionnaire (FFQ) based on 13 foods which account for 73.5% of total vitamin A intake and explain 96% of the vitamin A intake variation in Taiwan[30]. It is a structured and open-ended FFQ, which includes 3 fruits (liu-ting, mango and papaya), 6 vegetables (spinach, pak choy, garland chrysanthemum, water convolvulus, sweet potato leaves and carrot), two livers (pork and chicken) as well as eggs and milk. For each item, subjects were asked to report their frequencies and portion sizes of consumption over the preceding year prior to the diagnosis of the lung cancer (for cases) or the interview (for controls). The frequency of consumption was asked as times of intake per day, week, month or year, according to an appropriate timeframe. To help the subjects in estimating the portion sizes of consumption, we displayed two-dimensional colored photographs of each food during interview. In addition, subjects were also asked to report their use of vitamin supplements, such as dose (capsule or tablet), frequency of use, brand, and type of supplements. Less than 20 subjects ever regularly took vitamin A supplements (greater than or equal to 1capsules or tablets per day). Therefore, only vitamin A (not α-carotene, β-carotene and retinol) intakes from supplements were calculated. The vitamin A intake from supplements was calculated by multiplying the frequency and dose, which were based on the brand label from the drug store survey. Additionally, the nutrient intake from foods was calculated by multiplying the frequency and

consumption size of each food item by the corresponding nutrient content[1] based on the Database of Nutrients in Foods of Taiwan. Then, the daily nutrient intake from all 13 items was calculated. For various forms of vitamin A, we quantified the intakes of α-carotene, β-carotene and retinol from specific food items. The foods or various forms of vitamin A intakes were further classified into three groups; one was from animal sources (liver, eggs and milk), another was from plant sources (vegetables and fruits), and the other was from vitamin supplements.

A random sample of 40 (2.65%) subjects were reinterviewed by the supervisor the next day. The Spearman correlation coefficient was used to assess the test-retest reliability for each food item and vitamin A supplement. The 13 food items showed acceptable reliability with Spearman correlation coefficients of 0.43 for Garlan chrysanthemum and up to 0.80 for Mango (mean coefficient: 0.62). Quartiles or tertiles of consumption were determined separately on the basis of the intake patterns of the hospital controls or the neighborhood controls, respectively.

Statistical analysis

The distribution of demographic and food intake characteristics between cases and two various control groups were evaluated by t-test, chi-square test, or Mann-Whitney U test. The adjusted odds ratios (AORs) and 95% confidence intervals (95% CIs) were estimated for each quartile (or tertile) of intake relative to the reference level (quartile 1 or tertile 1) by multiple conditional logistic regression models[31] with adjustment for relevant covariates. The relevant covariates were selected by the multiple conditional logistic regression models with a step-up procedure in which significant variables were

Table 1. Number and percent distribution of cases and matched hospital/neighborhood controls according to socio-demographic characteristics

Characteristics	Cases	Controls		*p* value†	
	(n = 301)	Hospital (n = 602)	Neighborhood (n = 602)	Cases vs. Hospital Controls	Cases vs. Neighborhood Controls
Age (yr) mean ± SD	62.0 ± 11.2	62.2± 11.4	61.9 ± 11.3		
≤55	74 (24.6)	146 (24.2)	146 (24.2)		
56-65	84 (27.9)	163 (27.1)	186 (30.9)		
>65	143 (47.5)	293 (48.7)	270 (44.9)	$p = 0.79$	$p = 0.88$
Sex					
Male	187 (62.1)	374 (62.1)	374 (62.1)		
Female	114 (37.9)	228 (37.9)	228 (37.9)	$p = 1.00$	$p = 1.00$
Hospital					
TSGH	141 (46.8)	282 (46.8)	282 (46. 8)		
VGHKS	160 (53.2)	320 (53.2)	320 (53.2)	$p = 1.00$	$p = 1.00$
Medical insurance status					
Civilians	56 (18.6)	107 (17.8)	170 (28.2)		
Officers and relatives	78 (25.9)	149 (24.7)	105 (17.4)		
Labors	56 (18.6)	133 (22.1)	154 (25.6)		
Farmers	32 (10.6)	79 (13.1)	80 (13.3)		
Army, veterans and their relatives	79 (26.3)	134 (22.3)	93 (15.5)	$p = 0.45$	$p < 0.01$
Education (yr)					
0	48 (15.9)	126 (20.9)	117 (19.5)		
1-6	124 (41.2)	212 (35.2)	238 (39.5)		
7-9	38 (12.6)	68 (11.3)	69 (11.5)		
10-12	43 (14.3)	87 (14.5)	111 (18.4)		
>12	48 (16.0)	109 (18.1)	67 (11.1)	$p = 0.25$	$p = 0.12$
Religion					
None	71 (23.6)	152 (25.3)	128 (21.2)		
Buddhists	192 (63.8)	403 (66.9)	417 (69.3)		
Protestants	22 (7.3)	25 (4.1)	39 (6.5)		
Catholics and others	16 (5.3)	22 (3.7)	18 (3.0)	$p = 0.13$	$p = 0.22$
Smoking status					
Never	122 (40.5)	301 (50.0)	307 (51.0)		
Ex-	28 (9.3)	90 (15.0)	67 (11.1)		
Current (cigarettes/day)					
≤ 40	80 (26.6)	150 (24.9)	157 (26.1)		
> 40	71 (23.6)	61 (10.1)	71 (11.8)	$p < 0.01$	$p < 0.01$
Passive smoking					
No	67 (22.3)	193 (32.1)	215 (35.7)		
Yes	234 (77.7)	409 (67.9)	387 (64.3)	$p < 0.01$	$p < 0.01$
Occupational exposure					
No	258 (85.7)	553 (91.9)	561 (93.2)		
Yes	43 (14.3)	49 (8.1)	41 (6.8)	$p < 0.01$	$p < 0.01$

† *p*-value derived from t-test (continuous variables) or chi-square test (categorical variables) for significant differences between cases and two control groups.

added one at a time to assess their effect on the fit of the model. Finally, only the statistically significant confounders were chosen as covariates in the regression model for each food (or food group) to estimate AORs. Two sets of covariates were used in the regression models for each food, food group, or nutrient. One set included the covariates of pack-years of cigarette smoking (3 dichotomous dummy variables; >40.0 pack-yrs, 20.1-40.0 pack-yrs, 0.1-20 pack-yrs vs. 0 pack-yr), occupational exposure (a dichotomous dummy variable; yes vs. no), passive smoking exposure from mother (a dichotomous dummy variable; yes vs. no) or friends (a dichotomous dummy variable; yes vs. no) in the models for cases and hospital controls. The other set included above covariates as well as medical insurance status (a dichotomous dummy variable; army, veterans, or relatives vs. others) and education levels (a dichotomous dummy variable; >12 yrs vs. <=12 yrs) for cases and neighborhood controls. In addition, adjustment for smoking was best accomplished in our data when we included three 3 dichotomous dummy variables for smoking pack-years in the model. We tried other methods of smoking adjustment for the regression model (e.g. treating pack-years as continuous variable, adding age started as a covariate, replacing pack-years by smoking duration and number of cigarettes per day). However, none of the best alternatives yield meaningful differences in the odds ratio estimates. Tests for linear trend across quartiles (or tertiles) of intake were carried out by taking the median values of each quartile (or tertile) and entering the variable as continuous in the regression models. This method seemed appropriate since distributions of vitamin A-rich food intakes were typically highly skewed in this study. All analyses were performed with SAS system. A *p*-value of 0.05 was considered statistically significant in all analyses.[31]

RESULTS

The distributions of cases and controls by socio-demographic variables and environmental exposure are shown in table 1. The cases and two control groups showed similar distribution for age, sex, hospital, education, and religion. However, the cases had higher percentage of medical insurance of army, veteran and their relatives ($p<0.01$) than the neighborhood controls. As expected, the cases contained a far greater proportion of heavy smokers that consumed more than 40 cigarettes per day compared with controls ($p<0.01$). Furthermore, greater proportions of passive smoking and occupational exposure were observed for cases than the two control groups ($p<0.01$).

The mean and median intake of vitamin A, food group, individual food item, and vitamin A supplements between cases and two control groups are presented in table 2. The mean rank of vitamin A, α-carotene, β-carotene, vegetables, garland chrysanthemum, sweet potato leaves and carrots intakes by cases were significantly lower than that by two control groups.

Table 3 shows the associations (AOR and 95% CI) of various vitamin A intakes from specific food items and supplements with lung cancer risk among cases and two control groups. We found that the decreased adjusted odds ratios (AORs) were significantly associated with higher intakes of vitamin A, α-carotene and β-carotene between cases and two control groups. In the comparison of cases and hospital controls, the AORs for the highest *versus* the lowest quartile of intakes were 0.60 (95% CI = 0.39-0.92) for vitamin A, 0.64 (95% CI = 0.42-0.98) for α-carotene, 0.52 (95% CI = 0.34-0.80) for β-carotene, The corresponding AORs for the comparison of cases and neighborhood controls were 0.59 (95% CI = 0.37-0.94), 0.62 (95% CI = 0.39-0.97), 0.52 (95% C = 0.32-0.83), respectively. There were linear trends for above three nutrients in cases compared with two control groups, except α-carotene in cases compared with hospital controls. However, no significant association was observed for the intakes of retinol and vitamin A supplements in cases comparing with two control groups.

Table 4 shows the AORs of developing lung cancer according to servings per week of food groups, individual item, and vitamin supplements. The weekly consumption of various food groups was not significantly associated with lung cancer risk. In addition, there were no dose-response relationships in comparison with the two control groups, except for vegetables. The weekly consumption of various food items was not correlated with the risk of lung cancer in cases compared with two control groups, except garland chrysanthemum and sweet potato leaves. Although the highest tertile consumption of garland chrysanthemum was not significantly associated with the reduced risk of lung cancer in cases compared with hospital controls, there were significant dose-response relationships in cases compared with both control groups. Therefore, the higher consumption of garland chrysanthemum was inversely associated with lung cancer. Higher consumption of sweet potato leaves was also significantly associated with reduced risk of lung cancer in cases compared with both control groups, showing significant linear trends. Additionally, higher consumption of carrots was not significantly associated with reduced risk of lung caner in cases compared with the two control groups. There were significant dose-response relationships in cases compared with the hospital controls, but not with the neighborhood controls. Higher consumption of liu-ting was significantly associated with reduced risk of lung cancer with significant dose-response relationships only in cases compared with the neighborhood controls, but not with the hospital controls.

DISCUSSION

According to the results of the present study, a significantly lower risk of lung cancer was found to be associated with the higher intake of vitamin A, α-carotene, and β-carotene (but not retinal) from local common vitamin A-rich foods in Taiwan. In addition, higher consumption of vitamin A-rich vegetables, garland chrysanthemum, and sweet potato leaves were related with the reduced risk or lung cancer. However, we did not observe an inverse association between lung cancer development and intake of fruits or vitamin A supplements.

The connection between vitamin A and development of cancer was identified rather soon after the discovery of this vitamin and its chemical structure. Many animal studies show that the intake of vitamin A and its analogs

Table 2. The mean and median intake of vitamin A, food group, individual food item, and vitamin A supplements

Nutrients, Foods and supplements	Cases	Hospital control	Neighborhood control	*p* value†	
	Means ± SD (median, range)	Means ± SD (median, range)	Means ± SD (median, range)	Cases vs. Hos. Controls	Cases vs. Nei. Controls
Vitamin A (RE‡/day)	3289±5951 (1763, 38.0-64839)	3270±5015 (1937, 30.9-78835)	3451±4398 (1964, 13.4-39028)	0.05	0.01
α-carotene§	7002±16759 (2164, 0-197906)	7117±15240 (2834, 0-230433)	7193±11903 (2825, 0-98685)	<0.01	<0.01
β-carotene§	12641±24198 (5936, 6.7-289468)	13101±21691 (7440, 67.1-349039)	13499±17160 (7681, 0-136481)	<0.01	0.02
Retinol§	601±1469 (262, 0-18400)	495±808 (243, 0-9334)	604±1920 (242, 0-34595)	0.56	0.42
13 foods and vitamin supplements¶	25.8±19.6 (22.0, 0.8-177)	26.1±18.1 (22.1, 0.5-171)	26.3±17.2 (23.1, 0.3-108)	0.63	0.37
13 foods¶	24.6±19.2 (20.6, 0.8-177)	24.9±17.1 (21.0, 0.5-157)	25.0±16.4 (21.7, 0.3-108)	0.51	0.30
Animal foods¶	8.5±8.3 (7.2, 0-70.5)	8.1±7.5 (7.0, 0-58.2)	8.0±7.5 (7.1, 0-70.3)	0.77	0.69
Pork liver¶	0.3±2.0 (0, 0-28.1)	0.1±0.6 (0, 0-9.0)	0.2±2.6 (0, 0-52.6)	0.36	0.01
Chicken liver¶	0.1±0.3 (0, 0-4.0)	0.1±0.3 (0, 0-4.0)	0.1±0.4 (0, 0-10.0)	0.42	0.01
egg	3.5±3.4 (2.5, 0-28.1)	3.6±3.3 (3.0, 0-21.1)	3.5±4.2 (2.5, 0-63.2)	0.70	0.60
milk¶	4.7±6.6 (2.0, 0-63.2)	4.3±6.1 (2.0, 0-56.2)	4.2±5.2 (2.0, 0-42.1)	0.70	0.55
Plant foods¶	16.1±15.4 (12.1, 0.6-111)	16.8±14.1 (13.4, 0-157)	17.0±13.6 (13.7, 0-89.9)	0.12	0.07
Vegetables¶	8.6±9.6 (6.5, 0-96.7)	8.8±8.5 (7.2, 0-128)	9.6±8.4 (7.8, 0-63.7)	0.04	<0.01
Spinach¶	1.3±1.4 (0.7, 0-9.4)	1.5±3.2 (1.1, 0-65.5)	1.4±1.6 (0.7, 0-9.4)	0.35	0.64
Garland chrysanthemum¶	0.6±0.8 (0.3, 0-5.8)	0.6±0.9 (0.4, 0-11.7)	0.7±1.0 (0.4, 0-6.3)	0.02	<0.01
Water convolvulus¶	2.5±3.4 (2.0, 0-28.1)	2.3±2.6 (2.0, 0-28.1)	2.5±2.5 (2.0, 0-21.1)	0.92	0.23
Pak choy¶	1.5±2.3 (1.0, 0-17.5)	1.6±2.0 (1.0, 0-21.1)	1.9±2.3 (1.0, 0-21.1)	0.33	<0.01
Sweet potato leaves¶	1.1±2.6 (0.1, 0-28.1)	1.3±2.4 (0.2, 0-21.1)	1.5±2.6 (0.5, 0-24.6)	0.02	<0.01
Carrots¶	1.5±3.6 (0.4, 0-42.1)	1.5±3.3 (0.6, 0-49.1)	1.5±2.5 (0.6, 0-21.1)	0.01	<0.01
Fruits¶	7.5±10.5 (4.3, 0-99.5)	7.9±10.8 (4.5, 0-152)	7.4±9.1 (4.6, 0-88.6)	0.59	0.44
Liu-ting¶	4.2±8.0 (1.7, 0-93.5)	4.2±5.6 (2.5, 0-35.1)	4.2±5.3 (2.5, 0-43.8)	0.26	0.07
Mango¶	0.6±1.2 (0.1, 0-8.8)	0.7±1.7 (0.1, 0-15.6)	0.6±1.4 (0.1, 0-19.3)	0.91	0.05
Papaya¶	2.7±6.3 (0.9, 0-70.2)	3.0±8.1 (0.9, 0-147)	2.6±6.0 (0.8, 0-84.2)	0.83	0.75
Vitamin A supplements (RE/day)	8.6±9.6 (0, 0-243)	8.9±8.5 (0, 0-270)	9.6±8.4 (0, 0-225)	0.83	0.83

† *p*-value derived from Mann-Whitney test for significant differences between cases and two control groups. ‡ RE: Retinol Equivalent; One RE equals to 1 μg of retinol or 3.33 IU of vitamin A. § μg/day. ¶ Servings/week; one vitamin supplements equals 1 capsule or tablet; one serving of milk equals 35 gm full cream milk powder, 25 gm cream-free milk powder, or 250 ml milk; one serving of vegetables equals to 100 gm, one serving of fruits equals to 180 gm and one serving of liver equals to 30 gm.

Table 3. Adjusted odds ratios for lung cancer by various vitamin A intakes from foods and supplements

Nutrients intake	Cases vs. hospital controls		Cases vs. neighborhood controls	
	Quartile or tertile of intake	AOR† (95% CI)	Quartile or tertile of intake	AOR‡ (95% CI)
Foods				
Vitamin A§ (RE/day)	Q1 (≤ 947)	1.00	Q1 (≤ 1018)	1.00
	Q2 (947 - 1742)	0.73 (0.48-1.09)	Q2 (1018 - 1852)	0.78 (0.51-1.18)
	Q3 (1742 - 3630)	0.72 (0.48-1.07)	Q3 (1852 - 3728)	0.62 (0.41-0.95)*
	Q4 (≥ 3630)	0.60 (0.39-0.92)*	Q4 (≥ 3728)	0.59 (0.37-0.94)*
p for trend		*0.04*		*0.04*
α-carotene¶ (μg/day)	Q1 (≤ 723)	1.00	Q1 (≤ 693)	1.00
	Q2 (723 - 2834)	0.76 (0.51-1.13)	Q2 (693 - 2825)	0.88 (0.58-1.34)
	Q3 (2834 - 9377)	0.52 (0.34-0.80)**	Q3 (2825 - 9405)	0.68 (0.44-1.06)
	Q4 (≥ 9377)	0.64 (0.42-0.98)*	Q4 (≥ 9406)	0.62 (0.39-0.97)*
p for trend		*0.12*		*0.04*
β-carotene# (μg/day)	Q1 (≤ 3734)	1.00	Q1 (≤ 3714)	1.00
	Q2 (3735 - 7440)	0.60 (0.40-0.90)*	Q2 (3714- 7681)	0.74 (0.49-1.12)
	Q3 (7440-15363)	0.56 (0.37-0.84)*	Q3 (7681-16636)	0.69 (0.45-1.06)
	Q4 (≥15363)	0.52 (0.34-0.80)**	Q4 (≥ 16636)	0.52 (0.32-0.83)*
p for trend		*0.01*		*0.01*
Retinol§§ (μg/day)	Q1 (≤ 70.3)	1.00	Q1 (≤ 58 .7)	1.00
	Q2 (70.3 - 188)	0.94 (0.62-1.43)	Q2 (58.7 - 199)	1.10 (0.70-1.72)
	Q3 (188 - 397)	1.24 (0.83-1.87)	Q3 (199 - 390)	1.26 (0.81-1.97)
	Q4 (≥ 397)	1.10 (0.72-1.70)	Q4 (≥ 390)	1.08 (0.67-1.73)
p for trend		*0.43*		*0.82*
Supplements				
Vitamin A (μg/day)	Q1 (0)	1.00	Q1 (0)	1.00
	Q2 (>0)¶¶	0.88 (0.59-1.31)	Q2 (>0)¶¶	0.90 (0.60-1.35)

† Adjusted for pack-years of cigarette smoking, occupational exposure and passive smoking exposure from mother and friends. ‡ Adjusted for pack-years of cigarette smoking, occupational exposure, passive smoking exposure from mother and friends, medical insurance status and education levels. § Included 3 fruits (liu-ting, mango and papaya), 6 vegetables (spinach, garland chrysanthemum, water convolvulus, pak choy, sweet potato leaves and carrot), 2 livers (pork liver and chicken liver), eggs and milk. ¶ Included liu-ting, mango and papaya, water convolvulus, sweet potato leaves and carrot. # Included liu-ting, mango and papaya, spinach, garland chrysanthemum, water convolvulus, pak choy, sweet potato leaves and carrot. §§ Included pork liver, chicken liver, eggs and milk. ¶¶ only 47 (15.6%) cases, 97 (16.1%) hospital controls and 89 (14.8%) neighborhood controls in this groups. * $p < 0.05$. ** $p < 0.01$

decreases the incidence of cancer. In contrast, vitamin A deficiency causes an increase in the number of spontaneous and chemically induced tumors.[32, 33] In the present study, our results were consistent with previous epidemiological studies, which demonstrated the inverse association between vitamin A intake and lung cancer risk.[34-37]

In human diets, vitamin A is provided both by plant sources, which contain provitamin A (carotenoids), and by animal sources, which contain primary preformed vitamin A. α-carotene and β-carotene are the major carotenoids with vitamin A in human plasma. Liver, milk, eggs, carrots, dark green leafy vegetables and yellow-orange fruits are especially important sources of vitamin A.[38]

α-carotene is widely available but in smaller amounts than the beta form. It inhibited the growth of human cancer cell line in the laboratory.[39] α-carotene also drastically reduced the number of tumors and its fighting ability against cancer exceeded that of β-carotene in animal studies.[40] However, our results did not show that α-carotene was more potential protection than β-carotene. The results in this study were consistent with the previous studies that reported a significantly lower risk of lung cancer with higher intake of dietary α-carotene.[11, 41]

β-carotene could function as an antioxidant,[42] modulate cell-mediated immune responses[43] and stimulate gap junction communication between cells in vitro.[44] Our results on β-carotene were consistent with many previous epidemiological studies which support an association between lower lung cancer risk and higher β-carotene intake,[9-11, 45] especially in studies measuring serum concentrations of β-carotene.[8, 46] On the contrary, the supplemental β-carotene enhanced lung cancer incidence and mortality among smokers in intervention trials. The possible reasons were unsuitable dosages,[47] susceptible groups, β-carotene as a co-carcinogenic effect [48] or the modulation of apoptotic signaling.[49] Therefore, it would be interesting to clarify the protective effects of β-carotene by carrying out further research.

In animal models, the inhibitory effect is present when retinol is administered after the cancer has been induced on rat mammary carcinogenesis.[50] In early epidemiological studies, retinol intake from animal foods has been associated with a decreased risk of lung cancer.[51, 52] However, the recent data showed no significant risk reduction [17] and even increased risk associated with higher retinol intake.[15, 53] Similarly, our study showed that retinol intake from animal foods was not correlated with lung cancer.

The intake of retinol through consumption of animal foods would increase the intake of some harmful components, such as heterocyclic amines [54] and fat,[9, 17, 55, 56] at the same time. Therefore, the protective effect of retinol

Table 4. Adjusted odds ratios of lung cancer for weekly consumption of various food groups, individual food item, and vitamin supplements

Food groups or items (servings[†]/week)	Cases vs. hospital controls		Cases vs. neighborhood controls	
	Quartiles or tertiles of intake	AOR[‡](95% CI)	Quartiles or tertiles of intake	AOR[§](95% CI)
13 foods and vitamin supplements	Q1 (≤ 14.1)	1.00	Q1 (≤ 14.3)	1.00
	Q2 (14.2 - 22.1)	1.06 (0.56-1.28)	Q2 (14.4 - 23.1)	0.85 (0.68-1.63)
	Q3 (22.2 - 33.0)	0.78 (0.51-1.18)	Q3 (23.2 - 33.6)	0.78 (0.49-1.24)
	Q4 (≥ 33.1)	0.85 (0.59-1.33)	Q4 (≥ 33.7)	0.89 (0.53-1.34)
p for trend		*0.51*		*0.30*
13 foods	Q1 (≤ 13.7)	1.00	Q1 (≤ 14.0)	1.00
	Q2 (13.8 - 21.0)	0.98 (0.52-1.22)	Q2 (14.1 - 21.7)	0.80 (0.63-1.52)
	Q3 (21.1 - 30.4)	0.86 (0.52-1.19)	Q3 (21.8 - 31.5)	0.79 (0.55-1.35)
	Q4 (≥ 30.5)	0.79 (0.56-1.29)	Q4 (≥ 31.6)	0.85 (0.50-1.25)
p for trend		*0.47*		*0.26*
Animal foods	Q1 (≤ 2.6)	1.00	Q1 (≤ 2.5)	1.00
	Q2 (2.7 - 7.0)	0.70 (0.37-0.87)	Q2 (2.6 - 7.1)	0.57 (0.45-1.10)
	Q3 (7.1 - 11.0)	0.96 (0.68-1.55)	Q3 (7.2 - 11.2)	1.03 (0.62-1.48)
	Q4 (≥ 11.1)	0.79 (0.59-1.38)	Q4 (≥ 11.3)	0.90 (0.51-1.23)
p for trend		*0.73*		*0.51*
Pork liver				
No	Q1 (< 1)	1.00	Q1 (< 1)	1.00
Yes	Q2 (≥ 1)[¶]	0.52 (0.18-1.05)	Q2 (≥ 1)[¶]	0.93 (0.29-3.04)
Chicken liver				
No	Q1 (< 1)	1.00	Q1 (< 1)	1.00
Yes	Q2 (≥ 1)[#]	0.46 (0.08-2.65)	Q2 (≥ 1)[#]	0.41 (0.07-2.30)
Egg	Q1 (≤ 1.5)	1.00	Q1 (≤ 1.5)	1.00
	Q2 (1.6 - 4.4)	0.97 (0.68-1.40)	Q2 (1.6 - 4.0)	1.11 (0.75-1.65)
	Q3 (≥ 4.5)	0.78 (0.52-1.18)	Q3 (≥ 4.1)	1.03 (0.69-1.56)
p for trend		*0.19*		*0.95*
Milk	Q1 (0)	1.00	Q1 (0)	1.00
	Q2 (< 7)	0.90 (0.61-1.33)	Q2 (< 7)	1.41 (0.91-2.19)
	Q3 (≥ 7)	1.07 (0.75-1.52)	Q3 (≥ 7)	0.99 (0.69-1.43)
p for trend		*0.59*		*0.73*
[4] Plant foods	Q1 (≤ 7.7)	1.00	Q1 (≤ 8.0)	1.00
	Q2 (7.8 - 13.4)	1.08 (0.72-1.62)	Q2 (8.1 - 13.7)	1.17 (0.76-1.79)
	Q3 (13.5 - 21.5)	0.84 (0.54-1.29)	Q3 (13.8 - 21.6)	0.85 (0.53-1.34)
	Q4 (≥ 21.6)	0.77 (0.50-1.18)	Q4 (≥ 21.7)	0.87 (0.55-1.36)
p for trend		*0.14*		*0.29*
Vegetables	Q1 (≤ 4.0)	1.00	Q1 (≤ 4.1)	1.00
	Q2 (4.1 - 7.2)	0.81 (0.55-1.20)	Q2 (4.2 - 7.8)	1.15 (0.76-1.75)
	Q3 (7.3 - 11.1)	0.53 (0.34-0.83)*	Q3 (7.9 - 11.7)	0.75 (0.48-1.18)
	Q4 (≥ 11.2)	0.70 (0.46-1.06)	Q4 (≥ 11.8)	0.67 (0.42-1.08)
p for trend		*0.04*		*0.04*
Spinach	Q1 (≤ 0.6)	1.00	Q1 (≤ 0.5)	1.00
	Q2 (0.7 - 1.3)	0.76 (0.54-1.07)	Q2 (0.6 - 1.3)	1.02 (0.72-1.45)
	Q3 (≥ 1.4)	0.73 (0.50-1.07)	Q3 (≥ 1.4)	0.88 (0.59-1.34)
p for trend		*0.09*		*0.60*
Garland chrysanthemum	Q1 (≤ 0.2)	1.00	Q1 (≤ 0.2)	1.00
	Q2 (0.3 - 0.8)	0.65 (0.46-0.91)*	Q2 (0.3 - 0.8)	0.73 (0.51-1.03)
p for trend	Q3 (≥ 0.9)	0.74 (0.48-1.14)	Q3 (≥ 0.9)	0.58 (0.37-0.93)*
		0.04		*0.01*
Water convolvulus	Q1 (≤ 1.0)	1.00	Q1 (≤ 1.0)	1.00
	Q2 (1.1 - 3.0)	0.85 (0.60-1.21)	Q2 (1.1 - 3.0)	1.01 (0.70-1.46)
	Q3 (≥ 3.1)	0.93 (0.63-1.37)	Q3 (≥ 3.1)	1.06 (0.69-1.61)
p for trend		*0.64*		*0.81*
Pak choy	Q1 (≤ 0.5)	1.00	Q1 (≤ 0.6)	1.00
	Q2 (0.6 - 2.0)	1.00 (0.72-1.39)	Q2 (0.7 - 2.0)	0.79 (0.56-1.12)
	Q3 (≥ 2.1)	0.80 (0.53-1.21)	Q3 (≥ 2.1)	0.67 (0.42-1.05)
p for trend		*0.35*		*0.06*
Sweet potato leaves	Q1 (0)	1.00	Q1 (0)	1.00
	Q2 (≤ 1.0)	0.97 (0.68-1.38)	Q2 (≤ 1.2)	0.66 (0.45-0.97)*
	Q3 (≥ 1.1)	0.65 (0.45-0.96)*	Q3 (≥ 1.3)	0.43 (0.28-0.66)**
p for trend		*0.03*		*<0.01*

Table 4. (continous)

Food groups or items (servings[†]/week)	Cases vs. hospital controls		Cases vs. neighborhood controls	
	Quartiles or tertiles of intake	AOR[‡](95% CI)	Quartiles or tertiles of intake	AOR[§](95% CI)
Carrots	Q1 (≤ 0.1)	1.00	Q1 (≤ 0.1)	1.00
	Q2 (0.2 - 0.6)	0.76 (0.51-1.12)	Q2 (0.2 - 0.6)	0.89 (0.59-1.33)
	Q3 (0.7 - 2.0)	0.57 (0.37-0.88)*	Q3 (0.7 - 2.0)	0.66 (0.42-1.03)
	Q4 (≥ 2.1)	0.65 (0.41-1.03)	Q4 (≥ 2.1)	0.68 (0.41-1.13)
p for trend		*0.02*		*0.05*
Fruits	Q1 (≤ 1.8)	1.00	Q1 (≤ 2.0)	1.00
	Q2 (1.9 - 4.6)	0.82 (0.55-1.23)	Q2 (2.1 - 4.6)	0.71 (0.45-1.12)
	Q3 (4.7 - 9.9)	0.72 (0.47-1.11)	Q3 (4.7 - 9.8)	0.72 (0.46-1.13)
	Q4 (≥ 10.0)	0.82 (0.54-1.25)	Q4 (≥ 9.9)	0.79 (0.51-1.22)
p for trend		*0.29*		*0.34*
Liu-ting	Q1 (≤ 0.6)	1.00	Q1 (≤ 0.6)	1.00
	Q2 (0.7 - 2.5)	0.74 (0.49-1.10)	Q2 (0.7 - 2.5)	0.76 (0.48-1.18)
	Q3 (2.6 - 5.8)	0.79 (0.53-1.19)	Q3 (2.6 - 5.8)	0.70 (0.43-1.13)
	Q4 (≥ 5.9)	0.73 (0.46-1.15)	Q4 (≥ 5.9)	0.57 (0.35-0.95)*
p for trend		*0.21*		*0.03*
Mango	Q1 (0)	1.00	Q1 (0)	1.00
	Q2 (≤ 0.1)	1.29 (0.86-1.93)	Q2 (≤ 0.1)	1.23 (0.78-1.92)
	Q3 (0.2 - 0.5)	1.10 (0.71-1.68)	Q3 (0.2 - 0.8)	0.76 (0.51-1.15)
	Q4 (≥ 0.6)	0.97 (0.65-1.43)	Q4 (≥ 0.9)	0.72 (0.47-1.12)
p for trend		*0.92*		*0.07*
Papaya	Q1 (≤ 0.1)	1.00	Q1 (≤ 0.2)	1.00
	Q2 (0.2 - 0.9)	0.98 (0.66-1.46)	Q2 (0.3 - 0.8)	0.83 (0.54-1.29)
	Q3 (1.0 - 3.0)	1.14 (0.74-1.75)	Q3 (0.9 - 3.0)	0.99 (0.66-1.49)
	Q4 (≥ 3.1)	0.92 (0.61-1.40)	Q4 (≥ 3.1)	1.22 (0.76-1.97)
p for trend		*0.88*		*0.38*
Vitamin supplements	Q1 (0)	1.00	Q1 (0)	1.00
	Q2 (≤7.0)	0.90 (0.56-1.31)	Q2 (≤7.0)	0.85 (0.55-1.45)
	Q3 (≥7.1)	0.59 (0.43-3.89)	Q3 (≥7.1)	1.29 (0.19-1.80)
p for trend		*0.75*		*0.36*

[†] One serving of vegetables equals to 100 gm, one serving of fruits equals to 180 gm and one serving of liver equals to 30 gm. [‡] Adjusted for pack-years of cigarette smoking, occupational exposure, and passive smoking exposure from mother and friends. [§]Adjusted for pack-years of cigarette smoking, occupational exposure, passive smoking exposure from mother and friends, medical insurance status and education levels. [¶] only 5 (1.7%) cases, 16 (2.7%) hospital controls and 11 (1.8%) neighborhood controls in this groups. [#] only 2 (0.7%) cases, 7 (1.2%) hospital controls and 7 (1.2%) neighborhood controls in this groups.* $p < 0.05$. ** $p < 0.01$

might be attenuated by other components in animal foods.

In numerous case-control and cohort studies over the last 10 years, inverse associations for both fruit and vegetable consumption were found in United State,[57] Sweden,[15] Netherlands,[13] Europe,[45] Germany,[58] Finland,[8] and Singapore.[26] On the contrary, a multicenter study in Canada found no effect of either fruit or vegetable consumption.[59] Additionally, one study has observed an inverse association for fruit but not for vegetables in Europe.[19] Two studies have observed a statistically significantly inverse relation for vegetable but not for fruit in Hawaii [36] and Taiwan.[2] Our results were consistent with theses two studies, particularly for the latter one carried out in Taiwan. We suspect that the conflicting results may be a result of different varieties of vegetables and fruits as well as various preparation methods among countries and study models. Additionally, the difficulty in assessing fruit and vegetable intakes, leading to misclassification, may be another reason for the discrepancy.

According to our results, increased consumption of carrots was associated with the reduced risk of lung cancer in cases compared with the hospital controls, but not in cases compared with the neighborhood controls. It might be affected by selection or recall bias of the hospital controls,[60] since most of them (about 80%) were cataract patients in matched ophthalmologic control groups. In Taiwan, there is a common belief that intake of more carrots can prevent the disease of cataract. Hence there may be a tendency to have higher consumption of carrots. Although case-control studies are often prone to several potential biases, our study also has strength. One of the principal strength is that the consistency of associations by comparing with two distinct characteristics of control groups in our study. Other strengths include the use of 2 two-dimensional colored photographs for quantification of intakes, the use of incident and histopathologically confirmed lung cancer cases and intensive interviewer training of impartial questioning techniques. So the biases should have been minimized by these strengths.

Of specific interest is the inverse relation with sweet potato leaves and garland chrysanthemum. Sweet potato (Ipomoea batatas L.) of the family Convolvulacease is tuberous-rooted perennial. Sweet potato leaves have been commonly consumed as a fresh vegetable all year around

in Taiwan. Edible Garland Chrysanthemum (Chrysanthemum coronarium) of the family Asteraceae, also called Shingiku in Japan, is an annual leafy plant. This vegetable grows very well in mild or slightly cold climate. It is popular in South China, Japan and South Asia. Young leaves and stems are widely used in oriental stir-fry, salad and soups, especially the latter. All five green leafy vegetables interviewed in our study are rich in vitamin A but the sweet potato leaves (1269.2 RE) contain about two to six times more vitamin A than the means of spinach (638.3 RE), water convolvulus (378.3 RE), pak choy (198.3 RE), and garland chrysanthemum (503.3 RE). In addition, garland chrysanthemum contains more vitamin A than the means of water convolvulus and pak choy.[1] However, it is not clear which specific micronutrients in garland chrysanthemum and sweet potato leaves might be responsible for the protective effect. One study in Taiwan found that sweet potato leaves had higher contents of flavonoids and antioxidative activities than other vegetables.[61] Two studies carried out in Japan found special micronutrients in sweet potato leaves. One investigation reported that sweet potato leaves contained mono-, di- and tri-caffeoylquinic acid derivatives that played a role in the antimutagenicity.[62] Another micronutrient that was identified and measured in sweet potato leaves was anthocyanin compound[63] that might be expected to protect human from various kinds of diseases or cancer.[64] Until now, no previous epidemiological studies were specifically designed to investigate the association of garland chrysanthemum and sweet potato leaves consumption with lung cancer risk. Therefore, the findings merit further studies to clarify the possibility that in addition to vitamin A some known or unknown but related micronutrients may account for this protective effect.

The limitation of the study is that the FFQ used in our study has not been validated by other methods of measuring dietary intake or biomarkers. The 13 food items chosen for the FFQ are from the food list of top 20 predictor foods of vitamin A which were validated by the 3-day food weighing technique in a national household nutritional survey in Taiwan.[65] Their study demonstrates that the 13 food items accounts for 73.5% of total vitamin A intake and explain 96% of the vitamin A intake variation in Taiwan.[30] The test-retest reliability estimated by Spearman correlation coefficients for the 13 food items in FFQ averaged 0.62 (range, 0.43 for Garlan chrysanthemum to 0.80 for Mango) in the study. In addition, a comprehensive FFQ using the similar reference and design concept got an acceptable validity and reliability in Taiwan.[65] However, the estimates of nutrient intakes from the FFQ might be not precise and the potential for measurement error should not be rule out in the study.

In conclusion, the intake of vitamin A, α-carotene and β-carotene rich food groups (but not fruits) provided potential protection against development of lung cancer. Additionally, our findings suggest that higher consumption of vegetables, particularly garland chrysanthemum and sweet potato leaves, might reduce the risk of lung cancer.

ACKOWLEDGEMENTS

This research was supported by a grant for Field Epidemiology Training Program from the National Institute of Preventive Medicine, Department of Health to Professor Luo-Ping Ger. In addition, it was supported by grant VGHKS87-51, VGHKS94-043, and VGHKS94G-43 from Kaohsiung Veterans General Hospital to Professor Luo-Ping Ger and Dr. Jang-Hwa Lee.

REFERENCES

1. Department of Health EY, Health and vital statistics, 2004.
2. Ko YC, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, Wang HZ, Chang PY. Risk factors for primary lung cancer among non-smoking women in Taiwan. Int J Epidemiol. 1997;26(1):24-31.
3. Wolbach SBPRH. Tissue changes following deprivation of fat-soluble A vitamin. J Exp Med. 1925;42:753-77.
4. De Luca L, Maestri N, Bonanni F, Nelson D. Maintenance of epithelial cell differentiation: the mode of action of vitamin A. Cancer. 1972;30(5):1326-31.
5. Epstein KR. The role of carotenoids on the risk of lung cancer. Semin Oncol. 2003;30(1):86-93.
6. De Flora S, Bagnasco M, Vainio H. Modulation of genotoxic and related effects by carotenoids and vitamin A in experimental models: mechanistic issues. Mutagenesis. 1999;14(2):153-72.
7. Lotan R. Retinoids in cancer chemoprevention. Faseb J. 1996;10(9):1031-9.
8. Holick CN, Michaud DS, Stolzenberg-Solomon R, Mayne ST, Pietinen P, Taylor PR, Virtamo J, Albanes D. Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study. Am J Epidemiol. 2002;156(6):536-47.
9. Ziegler RG, Mayne ST, Swanson CA. Nutrition and lung cancer. Cancer Causes Control. 1996;7(1):157-77.
10. van Poppel G, Goldbohm RA. Epidemiologic evidence for beta-carotene and cancer prevention. Am J Clin Nutr. 1995;62(6 Suppl):1393S-402S.
11. Michaud DS, Feskanich D, Rimm EB, Colditz GA, Speizer FE, Willett WC, Giovannucci E. Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. Am J Clin Nutr. 2000;72(4):990-7.
12. Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, Willett WC, Colditz GA. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. J Natl Cancer Inst. 2000; 92(22):1812-23.
13. Voorrips LE, Goldbohm RA, Verhoeven DT, van Poppel GA, Sturmans F, Hermus RJ, van den Brandt PA. Vegetable and fruit consumption and lung cancer risk in the Netherlands Cohort Study on diet and cancer. Cancer Causes Control. 2000;11(2):101-15.
14. Gao CM, Tajima K, Kuroishi T, Hirose K, Inoue M. Protective effects of raw vegetables and fruit against lung cancer among smokers and ex-smokers: a case-control study in the Tokai area of Japan. Jpn J Cancer Res. 1993;84(6):594-600.
15. Nyberg F, Agrenius V, Svartengren K, Svensson C, Pershagen G. Dietary factors and risk of lung cancer in never-smokers. Int J Cancer. 1998;78(4):430-6.
16. Ruano-Ravina A, Figueiras A, Barros-Dios JM. Diet and lung cancer: a new approach. Eur J Cancer Prev. 2000;9(6):395-400.

17. De Stefani E, Brennan P, Ronco A, Fierro L, Correa P, Boffetta P, Deneo-Pellegrini H, Barrios E. Food groups and risk of lung cancer in Uruguay. Lung Cancer. 2002;38(1):1-7.
18. Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. Cancer Causes Control. 2004;15(4):349-57.
19. Miller AB, Altenburg HP, Bueno-de-Mesquita B, Boshuizen HC, Agudo A, Berrino F, Gram IT, Janson L, Linseisen J, Overvad K, Rasmuson T, Vineis P, Lukanova A, Allen N, Amiano P, Barricarte A, Berglund G, Boeing H, Clavel-Chapelon F, Day NE, Hallmans G, Lund E, Martinez C, Navarro C, Palli D, Panico S, Peeters PH, Quiros JR, Tjonneland A, Tumino R, Trichopoulou A, Trichopoulos D, Slimani N, Riboli E. Fruits and vegetables and lung cancer: Findings from the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2004;108(2):269-76.
20. Patrick L. Beta-carotene: the controversy continues. Altern Med Rev. 2000;5(6):530-45.
21. Koo LC. Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. Nutr Cancer. 1988;11(3):155-72.
22. Forman MR, Yao SX, Graubard BI, Qiao YL, McAdams M, Mao BL, Taylor PR. The effect of dietary intake of fruits and vegetables on the odds ratio of lung cancer among Yunnan tin miners. Int J Epidemiol. 1992;21(3):437-41.
23. Swanson CA, Mao BL, Li JY, Lubin JH, Yao SX, Wang JZ, Cai SK, Hou Y, Luo QS, Blot WJ. Dietary determinants of lung-cancer risk: results from a case-control study in Yunnan Province, China. Int J Cancer. 1992;50(6):876-80.
24. Hu J, Johnson KC, Mao Y, Xu T, Lin Q, Wang C, Chen Y, Yang Y. A case-control study of diet and lung cancer in northeast China. Int J Cancer. 1997;71(6):924-31.
25. Zhong L, Goldberg MS, Gao YT, Jin F. A case-control study of lung cancer and environmental tobacco smoke among nonsmoking women living in Shanghai, China. Cancer Causes Control. 1999;10(6):607-16.
26. Seow A, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Chia KS, Yu MC, Lee HP. Diet, reproductive factors and lung cancer risk among Chinese women in Singapore: evidence for a protective effect of soy in nonsmokers. Int J Cancer. 2002;97 (3):365-71.
27. Yuan JM, Stram DO, Arakawa K, Lee HP, Yu MC. Dietary cryptoxanthin and reduced risk of lung cancer: the Singapore Chinese Health Study. Cancer Epidemiol Biomarkers Prev. 2003;12(9):890-8.
28. Takezaki T, Hirose K, Inoue M, Hamajima N, Yatabe Y, Mitsudomi T, Sugiura T, Kuroishi T, Tajima K. Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas. Br J Cancer. 2001;84(9):1199-206.
29. Ger LP, Hsu WL, Chen KT, Chen CJ. Risk factors of lung cancer by histological category in Taiwan. Anticancer Res. 1993;13(5A):1491-500.
30. Pan WH, Lee MM, Yu SL, Huang PC. Foods predictive of nutrient intake in Chinese diet in Taiwan: II. Vitamin A, vitamin B1, vitamin B2, vitamin C and calcium. Int J Epidemiol. 1992;21(5):929-34.
31. Le CT, Lindgren BL. Computational implementation of the conditional logistic regression model in the analysis of epidemiologic matched studies. Comput Biomed Res. 1988;21(1):48-52.
32. Sankaranarayanan R, Mathew B. Retinoids as cancer-preventive agents. IARC Sci Publ. 1996(139):47-59.
33. Verma AK. Retinoids in chemoprevention of cancer. J Biol Regul Homeost Agents. 2003;17(1):92-7.
34. Bjelke E. Dietary vitamin A and human lung cancer. Int J Cancer. 1975;15(4):561-5.
35. Hinds MW, Kolonel LN, Hankin JH, Lee J. Dietary vitamin A, carotene, vitamin C and risk of lung cancer in Hawaii. Am J Epidemiol. 1984;119(2):227-37.
36. Le Marchand L, Yoshizawa CN, Kolonel LN, Hankin JH, Goodman MT. Vegetable consumption and lung cancer risk: a population-based case-control study in Hawaii. J Natl Cancer Inst. 1989;81(15):1158-64.
37. Yong LC, Brown CC, Schatzkin A, Dresser CM, Slesinski MJ, Cox CS, Taylor PR. Intake of vitamins E, C, and A and risk of lung cancer. The NHANES I epidemiologic followup study. First National Health and Nutrition Examination Survey. Am J Epidemiol. 1997;146(3):231-43.
38. Friedrich W. Vitamin A and its provitamins. In: Vitamins. de Gruyter press, Berlin, 1988; 92-95
39. Murakoshi M, Takayasu J, Kimura O, Kohmura E, Nishino H, Iwashima A, Okuzumi J, Sakai T, Sugimoto T, Imanishi J. Inhibitory effects of alpha-carotene on proliferation of the human neuroblastoma cell line GOTO. J Natl Cancer Inst. 1989;81(21):1649-52.
40. Murakoshi M, Nishino H, Satomi Y, Takayasu J, Hasegawa T, Tokuda H, Iwashima A, Okuzumi J, Okabe H, Kitano H. Potent preventive action of alpha-carotene against carcinogenesis: spontaneous liver carcinogenesis and promoting stage of lung and skin carcinogenesis in mice are suppressed more effectively by alpha-carotene than by beta-carotene. Cancer Res. 1992;52(23):6583-7.
41. Knekt P, Jarvinen R, Teppo L, Aromaa A, Seppanen R. Role of various carotenoids in lung cancer prevention. J Natl Cancer Inst. 1999;91(2):182-4.
42. Bendich A, Olson JA. Biological actions of carotenoids. Faseb J. 1989;3(8):1927-32.
43. Hughes DA. Effects of carotenoids on human immune function. Proc Nutr Soc. 1999;58(3):713-8.
44. Sies H, Stahl W. Carotenoids and intercellular communication via gap junctions. Int J Vitam Nutr Res. 1997;67 (5):364-7.
45. Brennan P, Fortes C, Butler J, Agudo A, Benhamou S, Darby S, Gerken M, Jokel KH, Kreuzer M, Mallone S, Nyberg F, Pohlabeln H, Ferro G, Boffetta P. A multicenter case-control study of diet and lung cancer among nonsmokers. Cancer Causes Control. 2000;11(1):49-58.
46. Ito Y, Wakai K, Suzuki K, Tamakoshi A, Seki N, Ando M, Nishino Y, Kondo T, Watanabe Y, Ozasa K, Ohno Y. Serum carotenoids and mortality from lung cancer: a case-control study nested in the Japan Collaborative Cohort (JACC) study. Cancer Sci. 2003;94(1):57-63.
47. Albanes D. Beta-carotene and lung cancer: a case study. Am J Clin Nutr. 1999;69(6):1345S-50S.
48. Paolini M, Cantelli-Forti G, Perocco P, Pedulli GF, Abdel-Rahman SZ, Legator MS. Co-carcinogenic effect of beta-carotene. Nature. 1999;398(6730):760-1.
49. Palozza P, Serini S, Di Nicuolo F, Calviello G. Modulation of apoptotic signalling by carotenoids in cancer cells. Arch Biochem Biophys. 2004;430(1):104-9.
50. McCormick DL, Moon RC. Influence of delayed administration of retinyl acetate on mammary carcinogenesis. Cancer Res. 1982;42(7):2639-43.
51. Mettlin C, Graham S, Swanson M. Vitamin A and lung cancer. J Natl Cancer Inst. 1979;62(6):1435-8.
52. Kvale G, Bjelke E, Gart JJ. Dietary habits and lung cancer risk. Int J Cancer. 1983;31(4):397-405.

53. Axelsson G, Rylander R. Diet as risk for lung cancer: a Swedish case-control study. Nutr Cancer. 2002;44 (2):145-51.
54. Deneo-Pellegrini H, De Stefani E, Ronco A, Mendilaharsu M, Carzoglio JC. Meat consumption and risk of lung cancer; a case-control study from Uruguay. Lung Cancer. 1996;14(2-3):195-205.
55. Goodman MT, Hankin JH, Wilkens LR, Kolonel LN. High-fat foods and the risk of lung cancer. Epidemiology. 1992;3(4):288-99.
56. Veierod MB, Laake P, Thelle DS. Dietary fat intake and risk of lung cancer: a prospective study of 51,452 Norwegian men and women. Eur J Cancer Prev. 1997;6(6):540-9.
57. Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. Cancer Res. 1993;53(3):536-43.
58. Kreuzer M, Heinrich J, Kreienbrock L, Rosario AS, Gerken M, Wichmann HE. Risk factors for lung cancer among nonsmoking women. Int J Cancer. 2002;100 (6):706-13.
59. Hu J, Mao Y, Dryer D, White K. Risk factors for lung cancer among Canadian women who have never smoked. Cancer Detect Prev. 2002;26(2):129-38.
60. W. W. Nutritional epidemiology. New york: Oxford University press, 1998.
61. Hsu HF CC, Chu YH. Flavonoid contents and antioxidative activities of several vegetables. Taiwanese Journal of Argricultural Chemistry and Food Science. 2000;38 (5):377-87.
62. Yoshimoto M, Yahara S, Okuno S, Islam MS, Ishiguro K, Yamakawa O. Antimutagenicity of mono-, di-, and tricaffeoylquinic acid derivatives isolated from sweetpotato (Ipomoea batatas L.) leaf. Biosci Biotechnol Biochem. 2002;66(11):2336-41.
63. Islam MS, Yoshimoto M, Terahara N, Yamakawa O. Anthocyanin compositions in sweetpotato (Ipomoea batatas L.) leaves. Biosci Biotechnol Biochem. 2002;66 (11):2483-6.
64. Hou DX. Potential mechanisms of cancer chemoprevention by anthocyanins. Curr Mol Med. 2003;3(2):149-59.
65. Lee MS, Pan WH, Liu KL, Yu MS. Reproducibility and validity of a Chinese food frequency questionnaire used in Taiwan. Asia Pac J Clin Nutr. 2006;15(2):161-9.

Original Article

Intake of vitamin A-rich foods and lung cancer risk in Taiwan: with special reference to garland chrysanthemum and sweet potato leaf consumption

Yi-Ru Jin MS[1, 2], Meei-Shyuan Lee DrPH[3], Jang-Hwa Lee MD[1], Hon-Ki Hsu MD[4], Jau-Yeong Lu MD[5], Shin-Shin Chao MS[6], Kow-Tong Chen MD, PhD[7], Saou-Hsing Liou MD, PhD[3, 8] and Luo-Ping Ger MPH[2, 6, 9]

[1]*Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[2]*Department of Biological Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan*
[3]*School of Public Health, National Defense Medical Center, Taipei, Taiwan*
[4]*Division of Thoracic Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[5]*Division of Chest Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[6]*Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[7]*Department of Public Health College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[8]*Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Kaoshiung, Taiwan*
[9]*Institute of Biomedical Science, National Sun Yat-Sen University, Kaohsiung, Taiwan*

臺灣地區富含維生素 A 食物的攝取與罹患肺癌的風險：尤指茼蒿及地瓜葉的食用研究

我們利用病例對照研究法，探討攝食臺灣盛產且富含維生素 A 的食物與罹患肺癌危險性之關係。共收案 301 位原發肺癌新病人、602 位醫院對照病人和 602 位鄰居對照受試者，使用食物頻率問卷估量其 13 種食物和維他命補充劑之攝取量後，以條件式羅吉斯迴歸模式估算肺癌病人與每組對照組於共變數調整後勝算比(adjusted odds ratio: AOR)與其 95%信賴區間(95% CI)。結果發現從 13 種食物中攝食維生素 A、α 胡蘿蔔素和 β 胡蘿蔔素愈高者，其罹患肺癌的危險性愈低。而攝食較多份數的蔬菜（病例組與對照組之高 vs.低四分位之調整後勝算比為 0.67-0.70，95% CI 為 0.42-1.08，趨勢 *p* 值為 0.04)、茼蒿（高 vs.低三分位調整後勝算比分別為 0.58- 0.74，95% CI 為 0.37-1.14，趨勢 *p* 值≤0.04）或地瓜葉（高 vs.低三分位調整後勝算比分別為 0.43-0.65，95% CI 為 0.28-0.96，趨勢 *p* 值≤ 0.03）者，其罹患肺癌的危險性則較低。結論：攝食較多富含維生素 A 的蔬菜，特別是茼蒿和地瓜葉，提供了對肺癌保護的可能性。

關鍵字：肺癌、病例對照研究法、維生素 A、茼蒿、地瓜葉。