DIETARY VITAMIN A, BETA-CAROTENE AND RISK OF EPIDERMOID LUNG CANCER AMONG CHINESE MALES

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SYNOPSIS

A study of 50 pairs of Chinese male epidermoid lung cancer patients and controls matched on age, sex and ethnicity revealed an inverse dose-response relationship between beta-carotene intake and lung cancer risk. A comparison of the lowest and highest quartiles of intake gave an odds ratio of 3.8 and a 95% confidence limit of 1.0 - 15.2. The relationship is stronger among the age group 60 and above (O.R. = 8.7; 95% C.L. = 1.3 - 66.5). Similar analyses showed no significant association between total dietary vitamin A intake and lung cancer risk. Little correlation is found between smoking and vitamin A intake (r = 0.04) or between smoking and beta-carotene intake (r = -0.121).

SING MED J. 1988; 29:213–218

INTRODUCTION

Lung cancer is a leading cause of cancer death in many populations. In the United States and many other developed as well as developing countries, lung cancer ranks top among all cancer deaths(1). Lung cancer has a high mortality. The five year survival rate of epidermoid cancer, the most common type of lung cancer, is only about 9%.

In Hong Kong, in 1983, lung cancer gave the highest cancer mortality rates for both males and females. The rates were 50 and 25 per 100,000 respectively. From 1974 to 1983, lung cancer mortality rate in males increased from 30.7 to 49.6 per 100,000. The incidence rates for both sexes increased sharply from age 55 and peaked at 70-79(2).

Postulated aetiological factors of lung cancer include smoking, occupational exposure to radioactive materials in mines(3), asbestos(4), nickel, coal, mustard gas, arsenic, beryllium, iron, and chromates, and also air pollution(5). Among these, smoking is agreed to be the principal cause. Case control studies of bronchogenic carcinoma carried out as early as the 1950s(6) show a strong statistical association between cigarette smoking and lung cancer. The association was confirmed by other case control studies and cohort studies conducted later(7,8). In addition, the cancer risk was found to be reduced among ex-smokers, and the death rate was reduced with increasing duration of giving up smoking.

Besides aetiological factors, substances which may be protective against lung cancer have been investigated. A number of case- control studies on the relationship between vitamin A intake and lung cancer show an odds ratio of around 2 between studied subjects with low vitamin A and high vitamin A intakes (9-12).

A cohort study by Bjelke(13) of 8278 men in Norway found that the (smoking adjusted) risk in a lower vitamin A intake group was 2.6 times higher than in a higher intake group. Another cohort study by Shekelle et al.(14) showed a relative risk of 7 among men in the lowest quartile of carotene intake compared to men in the highest quartile. Two other cohort studies also showed an inverse relationship between serum vitamin A and the subsequent development of lung cancer(15,16).

Studies have also shown a sex and histological difference in the risk of lung cancer with decreased vitamin A intake(11,12,16,17). While an association was found among males, it was not so apparent in females. It has also been suggested that vitamin A and carotene are primarily protective against epidermoid lung cancer rather than against adenocarcinoma(13).

The protective effect of vitamin A is not confined to lung cancer only. Over the past decade, accumulating evidence, both experimental and epidemiological, has suggested that other cancer risks including stomach, bladder, larynx, and esophagus may also be reduced by dietary intake of vitamin A and carotene(18-21).

The objective of this paper is to report a study of the relationship between dietary vitamin A and beta-carotene intake with epidermoid lung cancer in Chinese male patients. The study was confined to male patients as previous studies have failed to show any relationship of these dietary variables among females; and to squamous cell lung carcinoma because of the more apparent relationship with this histological type.

The common dietary methods for estimating food intake in epidemiological studies include 24-hour recall, diet diary and dietary history directed to a certain period of time. The dietary history was preferred for this study as current food intake might be influenced by the disease process(22-24). Russell-Briefel, Caggiula & Kuller(25) compared and evaluated the measurement of vitamin A intake using three dietary methods directed to a time interval one year ago. The results showed that the food frequency questionnaire was less costly, less time-consuming, and much easier to administer and analyze. The food frequency questionnaire was recommended as the preferable method for the estimation of vitamin A intake of individuals. The reliability of food frequency questionnaire was also found to be high with 80% or greater agreement of responses. The method has been found to be of acceptable

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validity(12,26,27). Thus, a semi-quantitative food frequency method was adopted in this study.

METHODS

The study included all surviving Chinese male patients with the diagnosis of primary squamous carcinoma of lung managed in the Clinical Oncology Department of the Prince of Wales Hospital, one of the 2 teaching hospitals in Hong Kong. All diagnoses were confirmed by bronchoscopic biopsies.

The controls were hospital patients in Orthopaedic, Surgical or Medical wards of the same hospital. They were not suffering from malignancy and represented patients with a wide spectrum of disease pattern. Each case was matched with a control patient by age, sex and ethnicity. The age difference between cases and controls was maximally 5 years. Data were collected by means of personal interview with a structured questionnaire. Interviewers were 4th year medical students who were undertaking a project in epidemiology in the Chinese University of Hong Kong.

Besides the dietary questionnaire, the interview covered medical history, family history of cancer, smoking habits and occupation. The presence of any of the following gastrointestinal problems in the medical history was noted. These were gastrectomy, chronic pancreatitis, chronic diarrhoea or gastrointestinal operations. Patients who had any of the above conditions before the appearance of symptoms of lung cancer or the present disease condition were excluded because such conditions might affect vitamin absorption. Altogether 50 cases and an equal number of controls were included in the study.

The intensity of smoking was quantified in terms of pack-years (the product of packs of cigarette consumed per day and years that the patient smoked). Occupations classified as high risk in our study were those with exposure of more than 1 year to radioactive ores, asbestos, certain chemicals like coal, mustard gas and certain metals like arsenic, chromates, and nickel.

A semi-quantitative food frequency method was used in this study. The cases were asked about the intake of certain food items directed to the one-month period three months before the appearance of any symptoms of their disease. A total of 58 food items which give the major contribution to vitamin A and beta- carotene in the Hong Kong Chinese diet were included in the questionnaire. The food items included vegetables, fruits, liver, poultry, eggs and milk products.

For each particular food item the subject reported his frequency of intake in one month and the usual amount consumed each time. The amount was quantified by the patient in terms of percentages of common household measures. For example, for a special food item, the subject may indicate 'a quarter of a medium-sized Chinese bowl once a week'. Vitamin supplements and tonics contributing to dietary vitamin A were also included. Dietary vitamin A intake (in terms of retinol equivalents) is the sum of preformed vitamin A in foods and supplements and that converted in vivo from the pro-vitamin A, beta-carotene. The relationship of beta-carotene with lung cancer was assessed separately.

Seasonal differences in dietary intake were taken into consideration by asking the matched control about the dietary habits for the same season and time period as for the case. Each interview lasted about 45 minutes.

RESULTS

The distribution of the controls were 24% from the medical, 30% from the surgical and 46% from the orthopaedic wards. The ages of the subjects ranged from 30 to 90 with a similar distribution among both cases and controls. The mode was at 60 to 70 with 34% of controls and 42% of cases falling into this group.

The occupational distribution was also quite similar between cases and controls. The group of "production worker, transport worker, mechanics and labourers" heads the list with 60% of the cases and 52% of the controls belonging to this group. Quite a few of the study subjects, 24% of the cases and 30% of the controls, were "service workers" and "fishermen and farmers". Only 10% of the cases and 12% of the controls were of the higher occupational groupings - "professionals", "administrative staff" and "secretaries and teachers". The occupational classifications show that our subjects largely came from the lower social classes.

The numbers of subjects with positive answers of family history of cancer and occupational risk exposure were small. Although the odds ratios were found to be 2 for these 2 risk factors, the McNemar test showed no statistical significant association between either of this and the risk of lung cancer at the 5% level of significance.

Table 1 shows the paired distribution of cases and controls according to their smoking status. The relative risk of smoking against non-smoking towards lung cancer risk is found to be 3.67 and the association of lung cancer with smoking is marginally significant with p = 0.06.

TABLE 1
PAIRED DISTRIBUTION OF CASES NAD CONTROL BY SMOKING STATUS

Case	Control		Total
	Smoker	Non-smoker	
Smoker	35	11	46
Non-smoker	3	1	4
Total	38	12	50

x^2 = 3.5
df = 1
p = 0.06

Odds Ratio 3.67 (95% confidence limit 0.8–23.9)

However, a chi-square test for trend (Table 2) with smoking categorised to different levels of pack-years showed a significant dose-response relationship (p=0.003) between smoking and risk of lung cancer. The risk of lung cancer increases correspondingly with the level of smoking. Those who smoked 60- 160 pack-years had a relative risk of 6.9 compared to the non- smokers.

The relationship of dietary vitamin A intake and lung cancer was assessed by calculating equivalents as well as carotene intake. The retinol equivalent was the sum of retinol contained in foods (from pre-formed vitamin A) and that converted in-vivo from pro- vitamin A (beta-carotene).

The levels of intake were divided into quartiles with as near as possible one quarter of the total cases and controls in each quartile. The distribution of the cases and controls is shown in Table 3. Except for the quartile of above 50,000 ug where more controls (30%) than cases

(18%) were observed, no specific trend could be seen. It seems that for any level of intake less than 50,000 ug per month the risk of lung cancer is higher, with a relative risk of about 2 compared to those who have vitamin A intake at the highest quartile. Adjustment for smoking and age (Table 4) also did not reveal any significant relationship although lung cancer risk seemed to be increased comparing the low and the high vitamin A intake among the age group at or above 60. No correlation was seen between smoking in terms of pack- years and vitamin A intake in terms of μg of retinol equivalents (r=0.04).

The relationship of carotene and lung cancer risk was similarly studied. An inverse relationship between the two variables was observed (Table 5). A chi-square test for trend showed a borderline p-value of 0.06. The relative risk of getting lung cancer was 3.8 for people who had carotene intake in the lowest quartile compared to those at the highest quartile. As smoking was a possible confounding variable, adjustment for smoking was carried out. The relative risk of lung cancer for smokers having beta-carotene intake at the lowest quartile was 3.3 compared with those having an intake at the highest quartile. As the number of non-smokers was small (4 i.e. 8% among the cases and 12 i.e. 24% among the controls), no specific trend was observed. Adjustment for smoking seemed to slightly decrease the odds ratio between the low and high intakes. However there was little correlation between smoking and beta-carotene intake (r=-0.121).

Adjustment for age showed a more pronounced effect of low carotene intake among the subjects aged 60 and above (Table 6). An odds ratio of 8.7 was observed between the low and high intakes and the 95% confidence limit did not cover 1.0. A stronger and more significant dose-response relationship was also apparent in this age group.

TABLE 2
DISTRIBUTION OF CASES AND CONTROLS ACCORDING TO LEVEL OF SMOKING

Smoking Level (pack)	Case	Control	O.R.	95% C.L.
0	4	12	1	
1–39	13	21	1.9	0.4–8.7
40–59	17	10	5.1	1.1–25.8
60–160	16	7	6.9	1.3–38.7
Chi-square test for trend x^2 = 9.1 df = 1 p = 0.003				

TABLE 3
RELATIONSHIP OF LUNG CANCER RISK AND VITAMIN A BY APPROXIMATE SUBJECT QUARTILES AMONG ALL SUBJECTS AND AMONG SMOKERS

Total Vitamin A (μg/month)	All Subjects				Smokers			
	Case	Control	O.R.	(95% C.L.)	Case	Control	O.R.	(95% C.L.)
2000–16000	13	12	1.8	(0.5–6.6)	13	8	1.6	(0.4–7.1)
16000–27000	14	12	1.9	(0.5–7.1)	13	10	1.3	(0.3–5.4)
27000–50000	14	11	2.1	(0.6–7.9)	11	11	1.0	(0.2–4.2)
Above 50000	9	15	1.0		9	9	1.0	
	x^2 = 1.3 df = 1 p = 0.25				x^2 = 0.24 df = 1 p = 6			

Paired analyses using the paired t-test revealed no significant difference between the pairs of cases and controls in terms of vitamin A intake, and a borderline level of significance for beta-carotene intake.

Another paired analysis using conditional multiple logistic regression revealed that, with adjustment for smoking, a decrease in 10,000 ug carotene intake gave a relative risk of 1.033 (logistic regression coefficient = -0.0328 and p = 0.09) of getting lung cancer. With an average difference between the lowest quartile and highest quartile of 400,000 ug per month, this gave a relative risk of 3.7 for the low intake group. The result was consistent with what we found comparing the lowest and highest quartiles of intake (O.R.=3.8). Similar analyses for vitamin A revealed a relative risk of 1.8 between the lowest and highest quartile (logistic regression coefficient = -0.0117 and p = 0.16).

DISCUSSION

Both family history of cancer and high risk occupation showed no significant association with lung cancer risk in

TABLE 4
RELATIONSHIP OF LUNG CANCER RISK AND VITAMIN A BY APPROXIMATE SUBJECT QUARTILES AND BY AGE GROUP

Total Vitamin A (μg/month)	Under 60				60 & above			
	Case	Control	O.R.	(95% C.L.)	Case	Control	O.R.	(95% C.L.)
2000–16000	3	6	0.5	(0.04–5.2)	10	6	3.7	(0.7–21.1)
16000–27000	6	2	3.0	(0.2–194.1)	8	10	1.8	(0.4–9.1)
27000–50000	6	8	0.8	(0.1–5.9)	8	3	5.9	(0.8–47.5)
Above 50000	4	4	1.0		5	11	1.0	
					x^2 = 1.83 df = 1 p = 0.18			

TABLE 5
RELATIONSHIP OF LUNG CANCER RISK AND BETA-CAROTENE INTAKE BY APPROXIMATE SUBJECT QUARTILES

Beta-carotene intake (μg/month)	All Subjects				Smokers			
	Case	Control	O.R.	(95% C.L.)	Case	Control	O.R.	(95% C.L.)
14000–70000	15	8	3.8	(1.0–15.2)	16	7	3.3	(0.7–15.2)
70000–120000	13	15	1.7	(0.5–6.3)	12	11	1.6	(0.4–6.2)
120000–220000	14	11	2.6	(0.6–9.6)	11	10	1.6	(0.4–7.0)
220000–900000	8	16	1.0		7	10	1.0	
	x^2 = 3.6 df = 1 p = 0.058				x^2 = 2.25 df = 1 p = 0.13			

this study. However, the number of persons with positive exposure to these two variables was few. The positive finding of cigarette smoking as a significant risk factor is in agreement with previous studies which confirmed the lung cancer risk of smoking (7,8).

The dietary questionnaire employed in the study contained food items with major dietary contributions of vitamin A and beta- carotene among the Hong Kong Chinese diet. Few studies have differentiated vitamin A from pro-vitamin A intake. A case control study by Hinds et al.(12) showed that lung cancer risk among males was affected by dietary vitamin A and carotene intake, but with a slightly stronger effect observed for carotene. On the other hand, Shekelle et al.(14) in his Western Electric Study of about 2,000 men found that the only dietary variable associated with lung cancer was beta-carotene. No relationship with retinol equivalents was found. Peto et al.(28) argued that dietary beta-carotene rather than retinol lowers the cancer risk in man. Our data seem to be more in support of Shekelle's finding and Peto's argument in that beta-carotene was found to have a strong inverse relationship with lung cancer while no significant relationship was found for retinol equivalents. Peto also pointed out that although the relative risk obtained from dietary questionnaire comparing low and high intake has been around 2 in many studies, the relative risk comparing true low with true high intake might be greater because most of these dietary questionnaires were designed for more

TABLE 6
RELATIONSHIP OF LUNG CANCER RISK AND BETA-CAROTENE INTAKE BY APPROXIMATE SUBJECT QUARTILES

Beta-carotene intake (μg/month)	Under 60				60 & above			
	Case	Control	O.R.	(95% C.L.)	Case	Control	O.R.	(95% C.L.)
14000–70000	2	3	0.8	(0.2–10.7)	13	5	8.7	(1.3–66.5)
70000–120000	7	5	1.7	(0.2–12.3)	6	10	2.0	(0.3–14.2)
120000–220000	5	6	1.0	(0.1–7.4)	9	5	6.0	(0.9–48.3)
220000–900000	5	6	1.0		3	10	1.0	
					x^2 = 5.11 df = 1 p = 0.024			

general purposes. The greater relative risks of low compared to high beta-carotene intakes (3.8 for all subjects and 8.7 among subjects 60 and above) found in this study are therefore not too surprising. First, only male epidermoid lung cancer patients for whom vitamin A has been shown to have a greater effect were included. Previous studies have showed that the dietary association was significant among male rather than female patients and among those with the histological type of squamous cell rather than adenocarcinoma. Secondly, the dietary questionnaire was designed specifically to assess vitamin A and beta-carotene intake. The total monthly intake thus obtained would probably represent a truer picture of intake compared to studies with a more general purpose.

Our data did not support the finding of Hinds and others of a more pronounced effect of vitamin A intake on lowering the lung cancer risk among smokers(10,12). Negative or very weak correlation of smoking with retinol and beta-carotene found in this study also indicated that smoking is not a strong confounding factor. Rather, the protective effect of high beta- carotene intake was noted to be much stronger among the older age group. This relationship has not been explored by other studies and deserves fuller investigation. Perhaps the effect of beta-carotene is of a long term accumulative effect and is more fully expressed in the older age group.

This is the first case-control study on Chinese male patients with epidermoid lung cancer specifically designed for the study of the relationship of vitamin A and beta-carotene intake with lung cancer risk. Our results support the carotene-lung cancer hypothesis in that carotene intake is associated with reduced relative risk of lung cancer and the effect is independent of smoking and vitamin A. That beta-carotene is an important risk factor is also in agreement with two other studies with large samples which suggested that the daily consumption of green- yellow vegetables (rich sources of beta-carotene) reduces lung cancer risk(9,29).

Our study suggests that carotene is an important independent dietary factor in modifying the expression of pulmonary carcinogens in older men. Various possible mechanisms have been postulated including quenching the energy of excited oxygen, trapping free radicals, or through some other unknown hormone- like mechanism. The protective effect of beta-carotene may also be due to some other products whose presence is closely related to that of beta-carotene(30).

ACKNOWLEDGEMENT

The authors thank Mr. Albert Cheung and Mr. Ben Cheung for their statistical assistance and Ms. Pamela Tang for typing this manuscript. The authors also thank Chan Siu Yuen, Cheung Kin Leung, Chiu Chi Suen, Chow Ki Yau, Fan Tak Chung, Ho Luen Cheung, Ho Ying Ho, Ko Tin Choi, Kwong Sui Wa and Lam Yan Kit for their participation in the study.

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