

## CAROTENOID INTAKE, VEGETABLES, AND THE RISK OF LUNG CANCER AMONG WHITE MEN IN NEW JERSEY

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A population-based incident case-control study of lung cancer in white males was conducted during 1980-1981 in six high-risk areas in New Jersey. Interviews were completed for 763 cases and 900 controls. To assess whether dietary intake of carotenoids, preformed retinol, or total vitamin A influences the risk of lung cancer, the authors asked the respondents about the usual frequency of consumption, approximately four years earlier, of 44 food items which provide 83% of the vitamin A in the US diet and about the use of vitamin supplements. The men in the lowest quartile of carotenoid intake had a relative risk of 1.3 compared with those in the highest quartile after adjusting for smoking. No increase in risk was associated with low consumption of retinol or total vitamin A. Intake of vegetables, dark green vegetables, and dark yellow-orange vegetables showed stronger associations than did the carotenoid index; the smoking-adjusted risks of those in the lowest quartiles of consumption of these food groups reached relative risks of 1.4-1.5 compared with the risks of those in the highest quartiles. The protective effect of vegetables was limited to current and recent cigarette smokers; the smoking-adjusted relative risks for low consumers reached 1.7, 1.8, and 2.2 compared with the risks for high consumers for vegetables, dark green vegetables, and dark yellow-orange vegetables, respectively. The reduction in risk with vegetable intake was most apparent for squamous cell carcinomas, but it extended to adenocarcinomas and most other cell types when only current and recent smokers were analyzed. This protection among current and recent smokers is consistent with the model that vegetable intake prevents a late-stage event of carcinogenesis. Consumption of dark yellow-orange vegetables was consistently more predictive of reduced risk than consumption of any other food group or the total carotenoid index, possibly because of the high content of  $\beta$ -carotene relative to other carotenoids in this particular food group.

carotene; carotenoids; diet; lung neoplasms; smoking; vegetables; vitamin A

Both  $\beta$ -carotene and vitamin A have been proposed to reduce the risk of cancer in general and of epithelial and lung cancers in particular.  $\beta$ -carotene is one of sev-

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eral carotenoids that occur in plants and can be metabolized to vitamin A by humans. Vitamin A activity in humans is also obtained from retinol, an active form of vitamin A which occurs in foods of animal origin. Humans can convert  $\beta$ -carotene into retinol, but not the reverse.

The vitamin A hypothesis evolved first. An acknowledged physiologic role for vitamin A is the regulation of cell differentiation. Since the mid-1960s, animal experiments have demonstrated that pharmacologic doses of retinol and retinoids (synthetic analogs of retinol) can retard or prevent the growth of tumors induced by various agents at a number of different sites (1). In 1981, Peto et al. (2) suggested that the intake of  $\beta$ -carotene might lower the risk of cancer. One mechanism might be that  $\beta$ -carotene captures free radicals, as it does in photosynthesis, and thus protects lipids and/or DNA from oxidative degradation (3, 4).

In 1980-1981, we designed a large case-control study of lung cancer in high-risk areas in New Jersey to assess the roles of smoking, occupation, and other potential risk factors. Several epidemiologic studies (5-8) had reported inverse relationships between consumption of vitamin A sources and risk of lung cancer, yet none had evaluated separately the contributions of vitamin A and carotenoids to the association. Therefore, our interview included questions about most of the major sources of carotenoids and retinol in order to distinguish between the two hypotheses.

#### MATERIALS AND METHODS

A population-based incident case-control study of lung cancer in males was imple-

mented in New Jersey in six high-risk areas, composed of municipalities with unusually high lung cancer mortality rates for white males during 1967-1976. Cases were all men, aged 25-89 years, diagnosed between September 1, 1980 and October 31, 1981 with primary cancer of the trachea, bronchus, or lung (code 162, International Classification of Diseases, 9th Revision (9)) and residing in these six high-risk areas of New Jersey. Cases were ascertained through a rapid reporting system which the New Jersey State Health Department had established with local hospitals and by periodic review of hospital pathology records. Additional cases were identified from New Jersey cancer registry and death certificate files. Pathology reports and other medical records as necessary were reviewed by Health Department physicians to verify the diagnoses. Only histologically confirmed cases of primary lung cancer were included in the study. The histologic type was based on the pathology reports.

An approximately equivalent number of controls were selected in one of two ways. For those cases directly interviewed, controls were randomly selected from New Jersey licensed drivers and frequency matched to cases within strata of age (five-year intervals), race, and high-risk area of residence. For those cases for whom surrogates had to be interviewed, either because the case had died or was incapacitated, controls were selected from the New Jersey mortality files and individually matched to cases by age, race, high-risk area of residence, and closest date of death. Potential controls were excluded if lung cancer or any other respiratory disease was listed on the death certificate.

The present analysis was restricted to white males, including Hispanics, because black males are still being interviewed to obtain larger numbers and will be reported on later. Of the 1,084 cases and 1,415 controls identified for the study, interviews were successfully completed for 763 (70 per cent) and 900 (64 per cent), respectively. For the cases, reasons for not successfully

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completing an interview included respondent refusal (11 per cent of the cases ascertained), late ascertainment (7 per cent), physician refusal (4 per cent), untraceability of respondent (4 per cent), insufficient time to allow for the state-mandated waiting period before contacting next of kin (2 per cent), and poor interview (1 per cent). For the controls, reasons for not successfully completing an interview included respondent refusal (25 per cent), untraceability of respondent (9 per cent), and poor interview (3 per cent).

The interview included questions about tobacco use, diet, occupational history, exposure to certain potentially high-risk materials, residential history, medical history, and demographic characteristics. Diet was assessed by asking about the usual frequency of consumption, approximately four years earlier, of 44 food items listed in the Appendix table. The major sources of preformed retinol (dairy products, eggs, liver, and fortified cereals) and carotenoids (selected fruits, vegetables, and juices) were included. Certain food items, such as hot red chili peppers and guacamole, were incorporated because a parallel case-control study of lung cancer along the Texas Gulf Coast (10) utilized the same questionnaire. For fruits and vegetables that the respondent said were eaten primarily in certain seasons, frequency of consumption both in and out of season and the length of season were obtained. Vitamin A supplementation was assessed by asking about the types of vitamins used since age 25 years and the duration and usual frequency of use.

The average frequency of consumption over an entire year was calculated for each food item. Food group consumption was calculated as the unweighted sum of the yearly frequencies of consumption of the food items that comprised the food group. A total of 23 food groups were formed, based on nutritional and botanical similarities; however, a number of the food groups were highly correlated with each other and differed only in terms of a few food items. Nutrient intake was calculated as the weighted sum of the yearly frequencies of

consumption of the food items that contained that nutrient, where the weights were the nutrient contents of typical portions of the food items (11, 12); vitamin supplements were not included. Age-specific portion sizes for white adult males were approximated on the basis of two recent national nutrition surveys (13, 14). Because of the food items included in the questionnaire, only the intake of carotenoids, preformed retinol, and total vitamin A could be reliably calculated. The intake of  $\beta$ -carotene could not be calculated since  $\beta$ -carotene content has not been determined for most food items. Low, moderate, and high levels of consumption of each food group and nutrient were defined by splitting the frequency distribution of the control population at the 25th and 75th percentiles.

Total vitamin A intake was calculated from the intake of retinol and carotenoids in two ways. The first way was according to the older international units convention (15), which assumed that retinol was twice as active as an equivalent weight of carotenoids because of inefficient metabolic conversion of carotenoids to retinol in humans. The second way was according to the retinol equivalents convention (16), adopted by the National Academy of Sciences in 1980, which assumed that retinol was six times as active as an equivalent weight of carotenoids because of inefficient conversion and because of animal experiments which indicated that carotenoids were less well absorbed through the intestines than had previously been thought. The international units convention is adopted in the commonly used 1963 US Department of Agriculture food composition data (11), which are only now being revised (12).

Occasionally, respondents would not know if a food item was eaten, or, if eaten, how often it was eaten or details of the seasonality of consumption. The 13 cases and 12 controls (1.5 per cent of study subjects) who gave these types of nonquantitative responses for five or more food items were eliminated from the dietary analysis. For the 1,638 study subjects remaining (750

cases and 888 controls), 99.8 per cent of the food items had quantitative responses. When we calculated food group and nutrient intake, we substituted appropriate medians for any nonquantitative responses. For example, the median level of consumption of a food item within the entire population was introduced when it had not been ascertained if the food item was eaten. The median level of consumption among those who actually ate the food was introduced when it was known that the food was eaten, but not how often.

Of the 1,638 study subjects, 990 (57 per cent of the cases and 63 per cent of the controls) were directly interviewed. The 648 surrogate interviews were with wives (67 per cent), children (21 per cent), siblings (9 per cent), or other relatives (4 per cent).

The association of diet with lung cancer risk was measured by maximum likelihood estimates of the relative risk, adjusted as necessary for confounding by stratification into multiple contingency tables (17). Effect modification was assessed by the systematic examination of stratum-specific relative risks. Ninety-five per cent confidence intervals were calculated according to Gart (18). Mantel's extension procedure (19) was used to test the progressive dependence (trend) of the relative risk on decreasing levels of food group or nutrient intake. Multivariate logistic regression with prospective and retrospective models (20, 21) was used to confirm the results derived by stratified analysis. Population-attributable risk per cent was calculated according to Cole and MacMahon (22).

Potential confounders and effect modifiers assessed were smoking, education, exposure to high-risk occupations or materials, mode of interview (with subject or surrogate), age, and high-risk area of residence in New Jersey. Whenever possible, these variables were divided so that each stratum contained an equivalent number of the controls in the study population. High-risk occupations and materials were empirically defined as those for which the smoking-adjusted relative risk (RR) was  $\geq 1.5$  in

this study population. (A more comprehensive analysis of occupation and lung cancer risk has been carried out by Schoenberg et al. (23).)

Only smoking and education confounded any of the relationships between diet and lung cancer risk, and adjustment for smoking eliminated the confounding by education. Unless otherwise stated, smoking was controlled by adjusting over six strata: non-smokers; pipe and cigar smokers only; and cigarette smokers of low intensity (<25 cigarettes per day) and low duration ( $\leq 40$  years), low intensity/high duration, high intensity/low duration, and high intensity/high duration. No additional reductions in relative risks were noted when three cigarette intensity strata were interfaced with three cigarette duration strata, when the cigarette smokers were divided into six duration strata, or when pack-years (intensity times duration integrated over all smoking intervals) were employed. When smoking was controlled by adjusting over these six strata, nine cases and 20 controls with unclear intensity or duration variables were excluded from the analysis.

## RESULTS

The smoking-adjusted relative risks of lung cancer for decreasing intake of various nutrients and food groups are given in table 1. Among the nutrients, only carotenoids showed an increase in risk with decreased intake; those in the lowest quartile of consumption had a relative risk of 1.3 (95 per cent confidence interval (CI) = 0.9-1.8) compared with the risk of those in the highest quartile. No inverse association was detected for intake of retinol or total vitamin A. In addition, vegetables, dark green vegetables, dark yellow-orange vegetables, and vegetables and fruit, all of which are partially correlated with each other and with carotenoids, showed an increase in risk with decreased intake. The inverse associations with these food groups were somewhat stronger than that with carotenoids, and the trends were statistically significant. For example, those in the lowest quartile of vegetable consumption had a

TABLE 1  
*Smoking-adjusted\* relative risks of lung cancer for nutrient and food group intake: 25- to 89-year-old white males in six high-risk areas in New Jersey who were diagnosed between September 1, 1980 and October 31, 1981*

Nutrient or food group	Level of consumption			p for trend
	Upper 25%	Middle 50%	Lower 25%	
Retinol	1.0	1.0	0.8	0.07
Carotenoids	1.0	1.2	1.3	0.10
Vitamin A (international units)	1.0	0.8	1.0	0.45
Vitamin A (retinol equivalents)	1.0	0.9	0.9	0.20
Dairy products (2-7)†	1.0	0.8	1.3	0.14
Vegetables and fruit (14-17, 19-43)	1.0	1.4	1.3	0.04
Fruit (14-16, 19, 28, 35-41)	1.0	1.2	1.0	0.35
Vegetables (20-27, 29-34, 42, 43)	1.0	1.3	1.4	0.01
Dark green vegetables (22, 25, 26, 30/2,‡ 33, 34, 42)	1.0	1.5	1.5	0.02
Dark yellow-orange vegetables (23, 24, 31, 32, 43)	1.0	1.5	1.5	0.004

\* Adjusted over 14 strata: nonsmokers; pipe and cigar smokers only; and cigarette smokers categorized simultaneously by intensity (<25 or ≥25 cigarettes per day), duration (≤40 or >40 years), and time since smoking ceased (0-1, 2-9, or ≥10 years).

† Numbers in parentheses refer to the Appendix and identify food items comprising the food group.

‡ The frequency of consumption of summer squash was multiplied by one-half on the assumption that one-half of the summer squash eaten was green zucchini and one-half was yellow crookneck.

relative risk of 1.4 (95 per cent CI = 1.0-2.0) compared with those in the highest quartile. No inverse association between intake of dairy products or fruit and lung cancer risk could be detected. Further adjustment for education and other potential confounders did not alter the smoking-adjusted relative risks presented in table 1.

Although statistically significant trends in the risk of lung cancer were noted for vegetables, dark green vegetables, dark yellow-orange vegetables, and vegetables and fruit, low and moderate consumers seemed to share a similar elevation in risk when compared with high consumers. When we compared the extremes, the lowest and highest deciles of consumers of these food groups, they did not yield larger smoking-adjusted relative risks than when we compared the lowest and highest quartiles.

Duration of cigarette smoking, time since smoking ceased, and intensity of cigarette smoking, in that order, confounded the associations between diet and risk of lung cancer. For example, 29 per cent of the nonsmokers were in the highest quartile of

vegetable consumption while 25, 23, and 22 per cent of the cigarette smokers of short (0-30 years), moderate (31-45 years), and long (>45 years) duration, respectively, were in the highest vegetable quartile. Of the current and recent cigarette smokers (subjects who quit 0-5 years before diagnosis), 21 per cent were in the highest vegetable quartile; and of the ex-cigarette smokers (subjects who quit >5 years before diagnosis), 26 per cent were in the highest vegetable quartile. Of those who only smoked pipes or cigars, 20 per cent were high vegetable consumers. Intensity of cigarette smoking was not consistently correlated with vegetable consumption.

For food groups, the following levels of intake in servings per day were found for those in the highest and lowest quartiles of consumption: vegetable consumption, >2.4 versus ≤1.1; vegetable and fruit consumption, ≥4.2 versus ≤2.0; dark green vegetable consumption, >1.0 versus ≤0.4; and dark yellow-orange vegetable consumption, ≥0.5 versus ≤0.1. For nutrients, the following levels of intake in retinol equivalents per

day were found for those in the highest and lowest quartiles of consumption: carotenoid consumption,  $\geq 800$  versus  $\leq 350$ ; total vitamin A consumption,  $> 2,500$  versus  $< 1,000$ . The Recommended Dietary Allowance for adult males for vitamin A from all sources is 1,000 retinol equivalents (16).

Of the other food groups examined and not presented in table 1, including vitamin C-containing foods and vegetables in the Cruciferae family, none had smoking-adjusted associations with risk of lung cancer that were distinctly stronger than those for the four vegetable-containing food groups presented in the table.

The increase in risk of lung cancer associated with decreased vegetable intake was seen both in cigarette smokers and in pipe and cigar smokers who reported no cigarette use. There was no evidence for a vegetable-related increase in risk among non-smokers, but the number of cases was small (13 cases and 140 controls). The crude relative risks for vegetable intake among non-smokers and pipe and cigar smokers are shown in table 2. The increase in risk of lung cancer with decreased vegetable intake was evident in those who had smoked  $< 20$ , 20–29, or  $\geq 30$  cigarettes per day and in those who had smoked for 31–45 years or  $> 45$  years. However, the inverse association with vegetable intake was not noted in smokers of  $\leq 30$  years duration.

To further explore the lack of an effect

among short-term smokers, we calculated the smoking-adjusted relative risks of lung cancer for current smokers, including those who had quit smoking within one year of diagnosis, and for smokers who had quit 2–5, 6–9, or  $\geq 10$  years prior to diagnosis. Results are shown in table 2. Among the current smokers, the relative risk of lung cancer for those in the lowest quartile of vegetable consumption reached 1.8 compared with those in the highest quartile, and the trend was statistically significant. Among recent smokers, those who had quit 2–5 years prior to diagnosis, risk also increased with decreased vegetable intake. However, no such vegetable-related effect was seen among ex-smokers who had quit 6–9 or  $\geq 10$  years prior to diagnosis.

In this population, current and recent smokers were generally those men who had smoked for many years. Among the current and recent smokers, 52 per cent had smoked for  $> 45$  years, 42 per cent had smoked for 31–45 years, and only 6 per cent had smoked for  $\leq 30$  years. In this last category, current and recent smokers who had smoked for relatively few years, lung cancer risk did not seem to be inversely related to vegetable intake, although the numbers were small (22 cases and 27 controls).

Duration of cigarette smoking and years since quitting were the only consistent effect modifiers of the relationship between

TABLE 2

*Relative risks\* of lung cancer for vegetable intake by cigarette smoking and years since quitting: 25- to 89-year-old white males in six high-risk areas in New Jersey who were diagnosed between September 1, 1980 and October 31, 1981*

Cigarette smoking	No. of cases, controls	Level of consumption			p for trend
		Upper 25%	Middle 50%	Lower 25%	
Noncigarette smokers					
Nonsmokers	13, 140	1.0	1.2	0.3	0.20
Pipes and cigars only	21, 81	1.0	1.5	1.8	0.22
Cigarette smokers (years since quitting)					
0–1	465, 303	1.0	1.3	1.8	0.004
2–5	59, 51	1.0	2.2	1.9	0.19
6–9	49, 38	1.0	0.8	0.5	0.25
10+	134, 255	1.0	1.4	1.2	0.30

\* The relative risks among the cigarette smokers are adjusted for smoking as described in Materials and Methods. Crude relative risks are shown for the noncigarette smokers.

lung cancer risk and vegetable consumption. In general, after adjusting for smoking, inverse associations between lung cancer risk and vegetable intake were seen in study subjects of different educational levels and ages and in subjects exposed to high-risk occupations or materials and those who were not exposed.

The smoking-adjusted relative risks of lung cancer among current and recent cigarette smokers according to the intake of various nutrients and food groups are presented in table 3. Further adjustment for education and other potential confounders did not alter the relative risks shown. Results were similar to those for all study subjects, but the inverse associations were stronger, and dose-response relationships were apparent. Among the nutrients, carotenoids, but not retinol, showed an increased risk with decreased intake; subjects in the lowest quartile of carotenoid consumption had a relative risk of 1.7 (95 per cent CI = 1.1-2.6) compared with those in the highest quartile. This inverse association with carotenoid intake appeared to be reflected in a weak inverse association of lung cancer with vitamin A intake if calculated by the international unit convention. Furthermore, certain food groups also showed an increase in risk with decreased intake: veg-

etables, dark green vegetables, dark yellow-orange vegetables, and vegetables and fruit. As noted for all study subjects, the inverse associations with these food groups among current and recent smokers were, in general, stronger than those with carotenoids. For example, subjects in the lowest quartile of vegetable consumption had a relative risk of 1.7 (95 per cent CI = 1.1-2.7) compared with those in the highest quartile, and those in the lowest quartiles of dark green and dark yellow-orange vegetable intake had relative risks of 1.8 (95 per cent CI = 1.2-2.8) and 2.2 (95 per cent CI = 1.4-3.3) compared with those in the highest quartiles. Among the current and recent smokers, clear gradients in lung cancer risk with decreasing intake were noted for the four vegetable-containing food groups and carotenoids, and the trends were statistically significant. However, comparison of extremes, the lowest and highest deciles of consumers of these food groups, did not enhance the gradients noted when we compared the lowest and highest quartiles.

The smoking-adjusted relative risks of lung cancer by histologic type were calculated for decreasing levels of vegetable intake for all study subjects. For squamous cell carcinoma, which comprised 49 per cent of the cases, a statistically significant

TABLE 3

*Smoking-adjusted relative risks of lung cancer for nutrient and food group intake among current and recent cigarette smokers\*: 25- to 89-year-old white males in six high-risk areas in New Jersey who were diagnosed between September 1, 1980 and October 31, 1981*

Nutrient or food group	Level of consumption			p for trend
	Upper 25%	Middle 50%	Lower 25%	
Retinol	1.0	1.1	1.0	0.48
Carotenoids	1.0	1.5	1.7	0.02
Vitamin A (international units)	1.0	1.0	1.5	0.02
Vitamin A (retinol equivalents)	1.0	1.2	1.2	0.26
Dairy products	1.0	0.8	0.9	0.26
Vegetables and fruit	1.0	1.7	1.8	0.005
Fruit	1.0	1.4	1.2	0.28
Vegetables	1.0	1.3	1.7	0.004
Dark green vegetables	1.0	1.4	1.8	0.002
Dark yellow-orange vegetables	1.0	1.6	2.2	<0.001

\* Current cigarette smokers are those who smoked at diagnosis and those who quit within 1 year of diagnosis. Recent smokers are those who quit 2-5 years prior to diagnosis. Included for analysis are 524 cases and 354 controls.

trend in risk was seen ( $p$  for trend = 0.004); the relative risks among subjects in the lowest 25 per cent and middle 50 per cent of vegetable consumption reached 1.7 and 1.5 compared with those in the highest 25 per cent. However, for adenocarcinoma, which comprised 16 per cent of the cases, there was no increase in risk ( $p$  for trend = 0.48); the corresponding relative risks were only 1.0 and 1.1, respectively. For small cell or oat cell carcinoma (15 per cent of the cases), other cell types combined (undifferentiated or anaplastic (8 per cent), large cell (3 per cent), and adenosquamous carcinomas (1 per cent)), and carcinoma not otherwise specified (8 per cent), risk was somewhat increased with decreased vegetable intake, but the trends were not significant.

Since the vegetable-related reduction in risk of lung cancer was concentrated among current and recent cigarette smokers and among subjects with squamous cell carcinoma, the independence of these two patterns was examined. Table 4 shows the smoking-adjusted relative risks of lung can-

cer for vegetable intake by both histologic type and years since quitting cigarette smoking (0-5 years vs. 6+ years). The patients with squamous cell carcinoma showed the sharpest vegetable-related reduction in risk among current and recent smokers and the most consistent trend ( $p$  for trend = 0.001). Patients with small cell carcinoma, adenocarcinoma, and carcinoma not otherwise specified also showed a slight vegetable-related reduction in risk among current and recent smokers, although the trends were not consistent or statistically significant. Among the ex-smokers, whenever there were adequate numbers to examine, vegetable intake was not related to a reduction in risk.

The results presented in table 4, as well as the effect modification noted for years since quitting smoking and for duration of smoking, were seen for the food groups vegetables and fruit, dark green vegetables, and dark yellow-orange vegetables and for the carotenoid index, as well as for vegetables.

Intakes of dark green and dark yellow-

TABLE 4

*Smoking-adjusted relative risks of lung cancer for vegetable intake by histologic type and years since quitting cigarette smoking: 25- to 89-year-old white males in six high-risk areas in New Jersey who were diagnosed between September 1, 1980 and October 31, 1981*

Cell type, years since quitting cigarette smoking	Level of consumption			$p$ for trend
	Upper 25%	Middle 50%	Lower 25%	
<b>Squamous</b>				
0-5	1.0 (38)*	1.7 (123)	2.2 (85)	0.001
6+	1.0 (26)	1.1 (53)	1.1 (22)	0.45
<b>Small cell</b>				
0-5	1.0 (19)	1.0 (36)	1.5 (27)	0.12
6+	1.0 (6)	1.4 (15)	1.0 (5)	0.48
<b>Adenocarcinoma</b>				
0-5	1.0 (20)	1.0 (39)	1.4 (26)	0.14
6+	1.0 (8)	1.2 (18)	0.3 (2)	0.12
<b>Other cell types†</b>				
0-5	1.0 (11)	1.4 (16)	1.0 (18)	0.50
6+	1.0 (2)	0.9 (8)	2.0 (5)	0.15
<b>Carcinoma not otherwise specified</b>				
0-5	1.0 (14)	0.7 (38)	1.6 (14)	0.10
6+	1.0 (3)	2.1 (5)	2.9 (5)	0.10

\* Numbers in parentheses are the numbers of cases. The numbers of controls in the upper 25%, middle 50%, and lower 25% of vegetable consumption are 86, 180, and 88 for cigarette smokers who quit 0-5 years before diagnosis and 79, 146, and 68 for those who quit 6 or more years before diagnosis, respectively.

† Other cell types include undifferentiated and anaplastic, large cell, and adenosquamous carcinomas.

orange vegetables, with a correlation coefficient of 0.37, were each strongly associated with decreased risk of lung cancer among current and recent cigarette smokers. Low consumption of both food groups, compared with high consumption of both, gave a smoking-adjusted relative risk of 3.1 (table 5). This exceeds the smoking-adjusted risks for low, compared with high, intake of either dark yellow-orange vegetables (RR = 2.2) or dark green vegetables (RR = 1.8). In general, the reduction in risk with consumption of dark yellow-orange vegetables was seen at all intake levels of dark green vegetables, and vice versa (table 5).

For those cases who were interviewed directly, controls were randomly selected from the files of New Jersey licensed drivers. However, 14 per cent of these cases and 0.9 per cent of their controls did not have current New Jersey licenses at the time of interview. Exclusion of these study subjects did not markedly alter the smoking-adjusted relative risks of lung cancer associated with intake of vegetables, dark green vegetables, dark yellow-orange vegetables, vegetables and fruit, or carotenoids, either among all study subjects or among the current and recent cigarette smokers. In addition, similar smoking-adjusted associations were seen for those interviewed directly and those for whom surrogates were interviewed.

Many vitamin supplements such as multiple vitamins, therapeutic multiple vitamins, fish liver oils, and vitamin A capsules contain retinyl acetate or retinol, which are active forms of vitamin A. The relationship

of their use to the risk of lung cancer among white males in New Jersey was assessed, and the detailed results are presented by Albanes et al. (24). In summary, no reduction in risk was seen for those who took supplements which contained vitamin A compared with those who took supplements without vitamin A. Risk of lung cancer was not related to either years of use of vitamin A supplements or dosage of vitamin A activity in the supplements recently taken.

## DISCUSSION

The dietary component of this case-control study of lung cancer among New Jersey white men was designed to distinguish whether intake of carotenoids or total vitamin A modifies the risk of lung cancer. Food items included in the interview provide 83 per cent of the vitamin A in the US diet, based on the second Health and Nutrition Examination Study of the United States (1976-1980) (25). Carotenoid intake was inversely associated with overall risk of lung cancer, with the protection concentrated among current and recent smokers and smokers of moderate or long duration. However, there was no inverse association of total vitamin A with overall lung cancer risk, and among the current and recent smokers, total vitamin A seemed weakly protective only when calculated by the older international units convention. Among New Jersey white men, the contribution of carotenoid-containing foods to vitamin A intake was not substantial enough for the carotenoid-lung cancer association to be reflected in a clear vitamin

TABLE 5

*Smoking-adjusted relative risks of lung cancer for dark green and dark yellow-orange vegetable intake among current and recent cigarette smokers: 25- to 89-year-old white males in six high-risk areas in New Jersey who were diagnosed between September 1, 1980 and October 31, 1981*

Dark green vegetables (level of consumption)	Dark yellow-orange vegetables (level of consumption)		
	Upper 25%	Middle 50%	Lower 25%
Upper 25%	1.0* (37, 42)†	1.6 (47, 36)	1.6 (15, 12)
Middle 50%	1.3 (41, 36)	1.9 (161, 109)	2.4 (65, 37)
Lower 25%	1.0 (4, 6)	2.1 (70, 41)	3.1 (84, 35)

\* Referent group for all relative risks.

† Numbers in parentheses are the numbers of cases and controls.

A-lung cancer association, whether the carotenoid contribution to vitamin A activity was calculated by the international units convention or the less generous retinol equivalents convention. Based on the 1977-1978 US Department of Agriculture Nationwide Food Consumption Survey (26), the usual foods available to the US consumer provide 45 per cent of total vitamin A activity as carotenoids if the international units convention is applied and 21 per cent if the retinol equivalents convention is applied.

The inverse associations with lung cancer risk were more pronounced for intakes of vegetables, dark green vegetables, and dark yellow-orange vegetables than for carotenoid intake. One explanation is that the protective agent in vegetables may not be carotenoids; it could be vitamin C (27), indoles (28), plant phenols (4), or trace minerals such as selenium (29), all of which have been proposed to reduce the risk of cancer. However, this study did not reveal strong inverse associations with vitamin C-containing foods or cruciferous vegetables, which are rich in indoles. Another explanation stems from the nature of carotenoid determinations. Total carotenoid contents for vegetables and fruits are at the present time calculated from the vitamin A values in the US Department of Agriculture food composition tables (11, 12). These values were determined with different assay techniques performed by different laboratories in different decades and were sometimes imputed from results on similar foods. The assay method most often utilized detects not only  $\beta$ -carotene but also a number of other carotenoids, some with vitamin A activity and some without, and measures each carotenoid with a different efficiency unrelated to its potential efficacy in cancer prevention (30). Therefore, if the protective agent were  $\beta$ -carotene itself or some other chemically unique carotenoid, the estimate of total carotenoid intake might still be no more reliable a measure of exposure than is food group consumption.

Although both vegetables and fruits con-

tain carotenoids, only vegetables seemed protective in this study. Dark yellow-orange and dark green vegetables, which are rich in  $\beta$ -carotene, seemed to account for most of the protection conferred by vegetable consumption; dark yellow-orange vegetables were the food group most strongly associated with reduced risk. Recent analysis by high-performance liquid chromatography of the various carotenoids in foods has demonstrated that dark yellow-orange vegetables, such as carrots, contain more  $\alpha$ - and  $\beta$ -carotene and less of other carotenoids than do dark green vegetables, such as broccoli and kale (31). Other high-performance liquid chromatography studies have suggested that certain fruits, such as oranges and tomatoes, may contain much less  $\beta$ -carotene than previously assumed on the basis of their total carotenoid content (32, 33).

The vegetable-related reduction in risk of lung cancer was concentrated among current and recent cigarette smokers and among cigarette smokers of moderate or long duration. Because in any age group the current smokers tend to have smoked for more years, it was not possible to separate these two factors. These findings suggest that vegetable intake prevents or retards a late stage event in lung cell carcinogenesis, perhaps involving promotion rather than initiation. In animal models, retinoids have been shown to block the promotion or progression of carcinogenesis when administered during the latent period after initiation (34). However, it is possible that the reduction in risk associated with high vegetable intake among current smokers was not detected among ex-smokers because fewer of their lung cancers were attributable to smoking or because of the smaller number of ex-smokers. It is also possible that failure to note a protective effect by vegetables among the nonsmokers was due to the very small number of nonsmoking cases.

The risk of squamous cell lung cancer was significantly associated with low vegetable consumption, but the risk of lung

adenocarcinoma seemed unaffected. This apparent relationship with histologic type is partially explained by the vegetable-related reduction in lung cancer risk that is concentrated among current and recent smokers. Cigarette smoking is a much stronger risk factor for squamous cell carcinoma than adenocarcinoma, with relative risks of 19 and 5, respectively, compared with lifelong nonsmokers in this study population. Among the relatively small number of current and recent cigarette smokers with adenocarcinoma, vegetable intake was slightly protective. For other cell types also, current and recent cigarette smokers experienced a reduction in risk with increased vegetable intake, although the effect was not as pronounced as for squamous cell carcinoma.

The influence of vegetable intake on the risk of lung cancer in the total study population, although statistically significant, was not strong; subjects in the lowest quartile of consumption had a relative risk of only 1.4 compared with those in the highest quartile. Even among current and recent cigarette smokers, the comparable relative risk for vegetable intake reached only 1.7. However, the influence of diet on the risk of lung cancer may be greater than it appears because of the imprecision involved in measuring the underlying exposure (35). It is difficult for people to recall precisely their usual frequency of consumption, several years earlier, of a number of food items. Questions on usual portion size were not asked; and typical portion sizes, derived from national surveys, were assumed for all individuals in the study. The imprecision of the carotenoid contents for the various food items has been mentioned above.

Even though the inverse association between vegetable consumption and lung cancer risk was not strong, the effect was consistent. It was noted among the subjects directly interviewed and those interviewed via surrogates, among subjects of different ages, and among subjects of different educational attainments. Clear dose-response relationships for vegetable intake also oc-

curred among the current and recent cigarette smokers. In addition, the association was specific; the intake of vegetables, but not that of dairy products, was related to risk of lung cancer.

Three explanations other than causality may account for statistical associations: confounding, bias, and chance. Smoking was a confounder of the lung cancer-vegetable relationship, but was controlled with increasingly fine stratifications of intensity, duration, and recency of use until there was no evidence of residual confounding; i.e., the relative risks no longer approached 1.0. None of the other potential risk factors were confounders. Even controlling for education, which may reflect other aspects of socioeconomic status and lifestyle correlated with diet, did not reduce the vegetable-lung cancer associations once they were adjusted for smoking.

Bias is always a concern in case-control studies of diet and cancer because the disease itself may affect dietary patterns prior to clinical onset or may alter recall of usual adult diet. Thus, respondents were asked to report diet four years earlier, ignoring any recent changes. The specificity of the associations with diet is perhaps the best argument against this type of bias. It is difficult to imagine a bias in recall of carotenoid-containing foods that does not also exist for retinol-containing foods. Similarly, it is unlikely that the dietary recall of current and recent smokers with lung cancer would be more biased than the recall of ex-smokers with lung cancer.

Four other case-control studies (7, 8, 36-38) and three cohort studies (5, 6, 39, 40) have also examined relationships between diet and risk of lung cancer. Only one of the studies (37) used an interview that included most of the foods that contain carotenoids and vitamin A; all the other interviews had been drafted before these two hypotheses were well-defined. Two of the studies (6, 7) did not form weighted nutrient indices and analyzed only food group consumption. To evaluate separately the relationship of carotenoids and total vi-

tamin A to the risk of lung cancer, indices of carotenoid and retinol intake must be formed and tested. This was done in only one analysis (39). However, the original dietary interviews for the cohort used in this study had been lost, and a series of approximations and assumptions were necessary to utilize the derived data still available.

The results of the seven studies are not consistent. Three of the studies (8, 36, 38, 40) showed a protective effect of vitamin A and included evidence to suggest that protection by carotenoids alone is not generating the appearance of protection by vitamin A. Two studies (6, 7) showed a protective effect of carotenoid-containing vegetables but did not assess vitamin A. Another study (39) revealed a protective effect of carotenoids and no protection by vitamin A. The last study (37) showed protection by both carotenoids and vitamin A but did not assess whether the apparent effect of vitamin A was due to carotenoids alone.

Two of the studies (38, 40) observed that the risk of squamous cell and small cell carcinomas of the lung was more strongly reduced by high vitamin A consumption than was the risk of lung adenocarcinoma. Another study (37) proposed that this type of histologic specificity would explain observation of a protective effect for carotenoids and vitamin A in men, but not in women. Only one study (40) has assessed interaction between diet and duration of cigarette smoking; protection by vitamin A was not more pronounced among current smokers than among ex-smokers. However, a detailed comparison of these findings with ours may be specious since the protective effect in these studies (38, 40) is attributed to total vitamin A, not carotenoids.

Four cohort studies have examined serum vitamin A levels in blood collected prior to diagnosis of lung cancer. Two (41, 42) failed to find any association between serum vitamin A and the subsequent risk of cancer in general or of lung cancer in particular. The third (43) found that serum

vitamin A was inversely related to lung cancer incidence, although not at a level of statistical significance, but was not associated with all cancer. The fourth (44) found that serum vitamin A was inversely related to incidence of all cancer, including lung cancer. These serologic studies are difficult to relate to studies of dietary vitamin A and cancer. In adequately nourished populations, serum vitamin A levels are maintained within a narrow range by liver stores and do not reflect recent dietary intake of vitamin A (45-47). However, the level of serum carotenoids is believed to reflect recent intake of carotenoids; this has been demonstrated for  $\beta$ -carotene supplementation at levels five times the Recommended Dietary Allowance for vitamin A (46) and for the day-to-day variation in carotenoid consumption characteristic of the US diet (47). The one published cohort study that had assayed carotenoids in stored sera (42) found no relationship to subsequent incidence of cancer in general or of lung cancer in particular. However, preliminary analyses of three other cohort studies which collected sera (48-50) have indicated that serum  $\beta$ -carotene, separated by high-performance liquid chromatography, was reduced among persons who ultimately developed lung cancer. If  $\beta$ -carotene is the protective agent, then consumption of a food group especially high in  $\beta$ -carotene, such as dark yellow-orange vegetables, might actually be a better measure of exposure than an index of total carotenoid consumption.

Although a number of studies have indicated that the consumption of either carotenoids or vitamin A is protective against lung cancer, on close examination the results of these studies are not entirely consistent. Our case-control study suggests that carotenoids rather than total vitamin A are associated with a lowered risk of lung cancer and that consumption of vegetables, especially dark yellow-orange and dark green vegetables, is even more predictive of reduced risk. The apparent protection by diet is most pronounced among current and

recent cigarette smokers and smokers of long duration. When all lung cancer is considered, the influence of vegetable intake on relative risk is not strong; after adjustment for smoking, those in the lowest 75 per cent of vegetable consumption have a relative risk of only 1.38 compared with those in the upper 25 per cent. However, since such a large percentage of the study population (75 per cent) consumes a diet that apparently elevates their lung cancer risk, the population-attributable risk is 22 per cent. This number represents the proportion of lung cancer cases among New Jersey white males that can be attributed to low vegetable intake, although diet is certainly not the sole cause of lung cancer in these individuals. More studies are needed to confirm the protection afforded by vegetable consumption in our study, quantify the effect, identify susceptible subgroups, and isolate the active agents.

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## APPENDIX TABLE

*Food items in questionnaire*

Sources of preformed retinol		Sources of carotenoids	
1. Eggs	14. Prunes or prune juice	30. Summer squash (s)	
2. Milk on cereal	15. Tomato or vegetable juice	31. Winter squash (s)	
3. Milk	16. Grapefruit juice	32. Sweet potato or pumpkin (s)	
4. Cottage cheese or yogurt	17. Cooked tomatoes or tomato sauce	33. Broccoli (s)	
5. Cheese	18. Corn tortillas, cornbread, grits	34. Greens, such as spinach, turnip greens, collards (s)	
6. Cheese in a combination dish such as lasagna, pizza	19. Fresh tomato (s)	35. Cantaloupe (s)	
7. Ice cream	20. Head lettuce (s)	36. Watermelon (s)	
8. Butter or margarine	21. Green cabbage or coleslaw (s)	37. Fresh peaches (s)	
9. Chicken liver	22. Leaf lettuce (s)	38. Canned peaches (s)	
10. Beef or calves liver	23. Carrots (s)	39. Nectarines (s)	
11. Cold cereal (s)*	24. Carrots in a salad or stew or mixed with other vegetables (s)	40. Apricots (s)	
12. Super-fortified cold cereal (s)	25. Green beans (s)	41. Pink grapefruit (s)	
13. Instant breakfast, breakfast squares, or toaster tarts (s)	26. Green peas (s)	42. Sweet green pepper (s)	
	27. Asparagus (s)	43. Sweet red pepper (s)	
	28. Avocado or guacamole (s)	44. Hot red chili peppers or hot pepper sauce (s)	
	29. Corn (s)		

\* (s), respondent was asked whether the food was eaten during the entire year, primarily in certain seasons, or not at all.