Increased green and yellow vegetable intake and lowered cancer deaths in an elderly population[1–4]

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ABSTRACT In a prospective cohort study of 1271 Massachusetts residents 66 years of age or older, we examined the association between consumption of carotene-containing vegetables and subsequent five year mortality. Dietary information was obtained by food frequency questionnaire in 1976. The relative risk of cancer mortality was examined within quintiles of green and yellow vegetable score (calculated from intake of carrots or squash, tomatoes, salads or leafy vegetables, dried fruits, fresh strawberries or fresh melon, and broccoli or brussel sprouts). After controlling for age and smoking behavior, those in the highest quintile of intake of these carotene-containing vegetables had a risk of cancer mortality which was 0.3 (95% confidence limits 0.10–0.96) that of those in the lowest quintile. The trend of decreased cancer risk with increasing intake of carotene containing vegetables was significant (p = .026). This relationship is consistent with the hypothesis that carotene may act as an inhibitor of carcinogenesis. *Am J Clin Nutr* 1985;41:32–36.

KEY WORDS Carotene, cancer mortality, diet, elderly, prospective cohort, vitamin A

Introduction

Numerous epidemiologic studies have shown that cancer risk is inversely related to the consumption of green and yellow vegetables (1, 2). Retrospective studies of green and yellow vegetables and risk of lung (3), gastrointestinal (4), bladder (5) and colon cancers (6) have found inverse relationships. Other investigations have revealed similar associations, though the measures of vitamin A intake have included milk in addition to carrots and green vegetables (7–10). The majority of such studies have been case-control in design.

Prospective dietary data from a study in Japan (11) show significant inverse relations of vegetable consumption with lung, stomach, and prostate cancer. Another prospective study of Norwegian men and women (12) followed over $11\frac{1}{2}$ years shows a similar significant inverse association between a 'vitamin A index' which was composed chiefly of carrots and green vegetables, and risk of lung cancer. Other studies have failed to show this inverse relation, or have shown positive associations between vitamin A index and cancer. (13, 14). Although some of the more recent studies have yielded unpromising results, some have been reasonably promising. A retrospective study of cancer of the cervix found rates to be significantly inversely correlated with measures of carotene intake (15). A case-control study of lung cancer organized

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by the Italian National Cancer Institute has found a large and highly significant inverse association between carotene intake and lung cancer which persisted at each level of smoking (16).

One possible explanation for the observed inverse relationship of cancer risk with green and yellow vegetable intake involves their carotene or provitamin A content. However, green and yellow vegetables contain other micronutrients and individuals with high vegetable consumption may have decreased intake of other nutrients from sources such as animal products.

The possible mechanisms by which carotenoids may act to prevent cancer have been extensively reviewed (17). Briefly, beta-carotene may deactivate certain reactive molecular species, thereby preventing cellular damage and breaking the chain of events leading to the development of cancer. A recent report that a threefold decrease in oral chromosome breakage rates (as assessed by the prevalence of micronucleated cells) can be achieved by supplementing the diet of Filipino betel nut chewers with capsules of retinol and carotene offers one possible mechanism (18).

The postulated inhibitory effects of carotene-containing vegetables may act during the later stages of carcinogenesis. Since 50% of malignancies reported in the Third National Cancer Survey were among individuals 65 years or older (19), we examined this relationship specifically among an elderly cohort. Using prospectively collected dietary data obtained from non-institutionalized residents who were followed over five years, we evaluated the hypothesis that greater intake of green and yellow vegetables reduces risk of death from cancer.

Subjects and methods

In 1976, dietary information was obtained by personal interview, from a cohort of 1271 residents 66 years of age or older, who were free from cancer, and who had previously been identified from a statewide area probability sample within Massachusetts (20). Follow-up of these participants in the Massachusetts Health Care Panel Study was conducted with annual mailings and a further interview in the last quarter of 1980. After 4.75 years, follow-up information was obtained on 1226 subjects (96% of the cohort). Among this group there were 317 reported deaths. The median age of this cohort at the time the dietary information was obtained was 72 years, with 38% of the cohort male and 62% female (**Table 1**). The age and sex distribution of the cohort are consistent with census data from Massachusetts.

Deaths were confirmed by searching the Massachusetts vital statistics register for 1976 through 1980. There were 292 deaths confirmed by certificate and the cause coded by trained nosologists according to the International Classification of Disease. Seven people were reported to have died out of state and 18 reported Massachusetts deaths could not be confirmed by death certificate. We excluded from the analyses the 40 subjects who died in 1976 since early symptoms of disease may have influenced their dietary intakes. This left 252 confirmed deaths within the cohort, of which 42 were due to cancer.

Dietary information was obtained for each of 41 items of a food frequency questionnaire, using the following scale: more than once a day, daily, not every day but more than once a week, once a week, less than once a week, never. This was then converted to a daily intake scale ranging from 1 for daily intake through 1/7 for once a week, to 0 for never.

The food items included in the 1976 questionnaire were selected without regard to testing hypotheses relating to retinol, carotene, or other micronutrients, and the wide range of carotene content in foods within some categories (eg carrots or squash) prevented a quantitative estimate of intake. We therefore calculated a green and yellow vegetable score, using the total number of servings per day of any of the following items: carrots or squash, tomatoes, salads or leafy green vegetables (like spinach or greens), dried fruits (like apricots, prunes or raisins), fresh strawberries or fresh melon, and broccoli or brussel sprouts. This simple summation across the six food items gave an equal weighting to each component of the green and yellow vegetable score. The total food intake was defined as the sum of daily frequency of intake for all items on the questionnaire other than the components of the green and yellow vegetable score.

Each of the fruit and vegetable items in the food frequency questionnaire was analyzed comparing the level of intake for those living at the end of follow-up with the corresponding level of intake among those who died during follow-up. For each item the cohort was divided at the median intake among survivors and the risk of death over five years of follow-up was compared for those above and below the median intake. The cohort

TABLE 1
Age and sex distribution of cohort

Age	Female (%)	Male (%)	Total (%)
65–69	262 (36)	175 (39)	437 (37)
70–74	211 (29)	114 (25)	325 (27)
75–79	132 (18)	100 (22)	232 (20)
80–84	85 (11)	40 (9)	125 (11)
85–89	31 (4)	17 (4)	48 (4)
90+	12 (2)	5 (1)	17 (1)
Total	733 (62)	451 (38)	1184*

* The 40 subjects who died in the first year of follow-up and were excluded from the analysis and the two subjects with missing gender information are excluded from this table.

was divided into quintiles based on the green and yellow vegetable score calculated for each individual, and the risk of cancer death across the quintiles was analysed. Age-adjusted relative risks were calculated using the following age intervals: 65–69, 70–75, 76+. Chi-square tests for association and trend were used to estimate the effect of these dietary intakes (21). All p-values are two sided.

Since 25% of the cohort died during follow-up and the number of cancer deaths was relatively small, a proportional hazards model (22) was fitted to the data to control for multiple risk factors simultaneously. Age (five-year categories), sex, total food intake, and smoking behavior (current smoker, ex-smoker or never smoked) were included in this model in addition to the green and yellow vegetable score. The multivariate analysis used categories of green and yellow vegetable intake defined by increments of half a serving per day. The PHGLM procedure available on SAS was used for these analyses (23).

TABLE 3
Cancer deaths by vegetable score

Vegetable score quintile	Living	All cause mortality	Cancer deaths*	Relative risk†
1 (lowest intake)‡	150	68	11	1.0
2	169	51	9	0.8
3	180	56	13	0.9
4	190	39	5	0.4
5 (highest intake)	215	37	4	0.3

$\chi_{\text{mantel extension}}$, test for trend: $\chi = -2.57$, $p = 0.01$

* Cancer deaths were coded as due to breast (6), lung (10), intestine (4), other (22).

† Relative risk of cancer death adjusted for age.

‡ Quintiles 1 to 5 correspond to the following number of servings of green and yellow vegetables per day: <0.7, 0.7–1.0, 1.1–1.5, 1.6–2.1, ≥2.2.

Results

The frequency of intake of each fruit and vegetable item was analysed, comparing those still living in 1980 with the 42 subjects who had died from cancer during the follow-up period. The relative risk of death from cancer for those in the higher intake group compared with those with lower intake is set out in **Table 2** for each of the six items used to calculate the green and yellow vegetable score. Carrots or squash, and salads both showed no association with risk of cancer mortality, while the other items all had an association of decreased risk of mortality with higher intakes.

Green and yellow vegetable score

After dividing the cohort into quintiles according to green and yellow vegetable score, the analysis of cancer deaths compared to living cohort members shows that the age adjusted risk of cancer death in the highest intake group was only 0.3 (95% confidence limits 0.10–0.96) that of the lowest intake group. Analysis for trend in proportions controlling for age shows a significant inverse trend with higher vegetable intake (χ mantel extension = −2.57, p = 0.01). Adjustment for smoking status or sex did not alter these results. (See **Table 3**).

To control for multiple risk factors of cancer simultaneously, a multivariate analysis was performed using a proportional hazards regression model. Age, sex, smoking behavior and total food intake were included in the model in addition to the green and yellow vegetable score. Sex, smoking and total food intake were not significant predictors of cancer death (**Table 4**). The odds ratio for each increase of half a serving per day of green and yellow vegetables was 0.78 when all other factors are controlled (p = 0.026). The results for smoking status, however, are based on small numbers; 12 current cigarette smokers and 10 ex-smokers were cases in this multivariate analysis.

TABLE 2
Relative risk of cancer death for each component of green and yellow vegetable score*

Vegetable	Median # servings	RR†	CL‡
Strawberries	less than 1/week	0.3	(0.1–0.7)
Tomatoes	1/week	0.5	(0.3–0.8)
Dried fruits	1/week	0.6	(0.3–1.4)
Broccoli	less than 1/week	0.8	(0.4–1.6)
Carrots or squash	1/week	1.0	(0.5–1.8)
Salads	1/week	1.1	(0.5–1.9)

* High intake vs. low intake using median cut.

† Relative risk, age-adjusted.

‡ 95% confidence limits.

Discussion

This prospective study among an elderly cohort demonstrates an inverse relation of green and yellow vegetable intake with subsequent risk of cancer death. The statistically significant inverse relation between cancer mortality and higher green and yellow vegetable intake persisted even after adjustment for smoking habits, age, sex and total food intake in a multivariate analysis. Those deaths occurring within the first year of follow-up were excluded to minimize the possibility that preclinical manifestations of the disease had affected dietary intake.

The six items which constitute the green and yellow vegetable score were chosen *a priori* from a food frequency questionnaire which was constructed in 1976 to evaluate the Title VII nutrition program for older Americans (24). Those dying from cancer in this cohort had a significantly lower intake for strawberries and tomatoes. In contrast, carrots, the major source of beta-carotene in the United States, did not show any association with risk of cancer death when analyzed as the response to the food item for carrots and squash. The use of one combined item for both carrots and squash may, however, have diluted the effect of carrots. The possibility that lower overall intake of the items in the green and yellow vegetable score was due to lower total dietary intake was unlikely since the addition of a total food intake score to the proportional hazards model did not make a significant contribution nor did it materially alter the association between green and yellow vegetable intake and cancer death. The lack of significant association between current cigarette smoking and cancer mortality is based on a small number of cases (n = 12) and is consistent with the decrease in magnitude of relative risk for current smokers in older populations. Despite this decrease in relative risks, the rise in the rate of cancer with advancing age means that the attributable risk in older smokers remains substantial (25). Furthermore, two-thirds of the study population were female, and if smokers, would have smoked for shorter durations than those customarily experienced by males.

The findings of this study further support the hypothesis that a diet high in green and yellow vegetables may be protective against cancer. Due to the groupings of vegetables in the food frequency questionnaire used in this study, it is not possible to make a more quantitative estimate of carotene intake.

TABLE 4
Multivariate estimate for green and yellow vegetable intake and cancer deaths

	Beta	Standard error	p-value
Age	0.230	0.121	.06
Sex	0.058	0.356	.87
Current smoker	0.407	0.402	.31
Ex-smoker	−0.027	0.422	.95
Green and yellow vegetable intake*	−0.245	0.109	.03
Total food intake†	−0.028	0.065	.67

* Categories of green and yellow vegetable intake based on total daily intake for six items, categories of half a serving per day.

† Sum of daily frequency of intake for all items other than components of green and yellow vegetable intake.

However, the lack of any association between the item "carrots or squash" and risk of cancer death suggests that carotene may not be the micronutrient responsible for the association between green and yellow vegetable intake and cancer mortality. This is also consistent with the results from a small prospective study that showed no association between total serum carotene levels and cancer incidence (26). Thus it is possible that some factor, present in green and yellow vegetables, other than carotene, may be providing the protective effect which we and others have observed. Alternatively, it is possible that other nutrients or non-dietary risk factors are avoided by those with high vegetable intakes.

Previous studies of diet as a source of carotene have on the whole considered people in younger age groups. Despite the limitations of our dietary data, they do offer some indication that even in old age, higher intakes of green and yellow vegetables are still associated with lowered risks of cancer death. Despite the similar associations that have been found in many other observational studies (1), it is still not known whether the protective relationship with such vegetables is truly one of cause and effect, and still less is known concerning which (if any) components of such vegetables are chiefly involved. The results from randomized trials are necessary to determine whether dietary beta-carotene reduces risk of human cancer.

References

1. Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? Nature 1981;290:201–8.
2. Hennekens CH, Lipnick RJ, Mayrent SL, Willett W. Vitamin A and risk of cancer. J Nutr Educ 1982;14:135–6.
3. MacLennan R, DeCosta J, Day NE, Law CH, Ng YK, Shanmugaratnam K. Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. Int J Cancer 1977;20:854–60.
4. Modan B, Cuckle H, Lubin F. A note on the role of dietary retinol and carotene in human gastrointestinal cancer. Int J Cancer 1981;28:421–4.
5. Mettlin C, Graham S. Dietary risk factors in human bladder cancer. Am J Epidemiol 1979;110:255–63.
6. Graham S, Dayal H, Swanson M, Mittelman A, Wilkinson G. Diet in the epidemiology of cancer of the colon and rectum. J Natl Cancer Inst 1978;61:709–14.
7. Mettlin C, Graham S, Swanson M. Vitamin A and lung cancer. J Natl Cancer Inst 1979;62:1435–8.
8. Shekelle RB, Lepper M, Lini S. Dietary vitamin A and risk of cancer in the Western Electric study. Lancet 1981;1:1185–90.
9. Graham S, Mettlin C, Marshall J, Priore R, Rzepka T, Shedd D. Dietary factors in the epidemiology of cancer of the larynx. Am J Epidemiol 1981;113:675–80.
10. 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;119:227–37.
11. Hirayama T. Diet and cancer. Nutr Cancer 1979;1:67–81.
12. Kvale G, Bjelke E, Gart JJ. Dietary habits and lung cancer risk. Int J Cancer 1983;31:397–405.
13. Graham S, Haughey B, Marshall J. Diet in epidemiology of carcinoma of the prostate gland. J Natl Cancer Inst 1983;70:687–92.
14. Kolonel L, Hankin J, Lee J. Diet and prostate cancer (abstract). Am J Epidemiol 1983;118:454.
15. Marshall JR, Graham S, Byers T, Swanson M, Brasure J. Diet and smoking in the epidemiology of cancer of the cervix. J Natl Cancer Inst 1983;70:847–51.
16. Pastorino U, Berrino F, Gervasio A, Pesenti V, Riboli E, Crosignani P. Proportion of lung cancers due to occupational exposure. Int J Cancer 1984;33:231–7.
17. Peto R. The marked differences between carotenoids and retinoids: methodological implications for biochemical epidemiology. Cancer Surveys 1983;2:327–40.
18. Stich HF, Rosin MP, Vallejera MO. Reduction with vitamin A and beta-carotene administration of the proportion of micronucleated buccal mucosal cells in asian betal nut and tobacco chewers. Lancet 1984;1:1204–6.
19. Scotto J, Chiazze L. Third National Cancer Survey. Hospitalizations and payments to hospitals. Part A Summary. Washington, DC: DHEW Pub No (NIH) 76-1094, 1977.
20. Branch L. Vulnerable Elders, Gerontological Society of America. Monograph #6, 1980; Washington D.C.
21. Mantel N. Chi-square tests with one degree of freedom: extension of the Mantel-Haenzel procedure. J Am Stat Assoc 1963;59:690–700.
22. Cox DR. Regression models and life tables. J Roy Stat Soc 1972; Series B 34:187–220.
23. Harrell F. The PHGLM procedure. In: SAS Supplemental Library User's Guide. Cary, NC: SAS Institute Inc, 1980:119–32.
24. Posner, BM. Evaluation of Title VII Nutrition Program for older Americans: Implications for intervention design. Doctoral Dissertation. Harvard University School of Public Health. Boston, Massachusetts 1978.
25. Hennekens CH, Buring JE, Mayrent SL. Smoking and aging in coronary heart disease. In Bosse R, Rose CL (eds). Smoking and Aging. Lexington, MA: Lexington Books, 1984:95–115.
26. Willett C, Polk BF, Underwood BA, Stampfer MS, Pressel S, Rosner B, Taylor JO, Schneider K, Hames CG. Relation of serum vitamins A and E and carotenoids to the risk of cancer. N Engl J Med 1984;310:430–4.