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REVIEW

Diet and Oral, Pharyngeal, and Esophageal Cancer

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Abstract: *Cancers of the upper digestive tract, including those arising in the oral cavity, pharynx, and esophagus, present a significant public health problem worldwide. These cancers are associated with high morbidity and mortality, and identification of protective factors is very important. A number of epidemiological studies have examined the association between vegetables, fruits, carotene, vitamin A, vitamin C, and vitamin E and oral, pharyngeal, and esophageal cancers. The results of 35 epidemiological studies, including one prospective cohort study, one nested case-control study, two randomized controlled trials, nine population-based case-control studies, and 22 hospital-based case-control studies, in addition to in vitro and animal studies, were examined to determine whether the criteria for causal assumption were satisfied for a protective role of these dietary components against development of oral, pharyngeal, and esophageal cancers. There is enough evidence to point to a preventive role of vegetable intake, including green vegetables, cruciferous vegetables, and yellow vegetables, total fruit intake, and citrus fruit intake. Yellow fruits are likely to be protective. Carotene, vitamin C, and vitamin E are protective, most likely in combination with each other and other micronutrients. The role of vitamin A is not clear because of conflicting findings in the studies reviewed.*

Introduction

In the United States, there are ~30,100 new oral and pharyngeal cancer cases and 13,200 new esophageal cancer cases each year. The number of deaths attributed to these conditions per year in the United States is ~7,800 for oral and pharyngeal cancer and 12,500 for esophageal cancer (1). The morbidity of those who survive can be extremely high, inasmuch as these cancers often require aggressive treatment, including radiation and chemotherapy, as well as surgery, which can be disfiguring and disabling, affecting speech, mastication, and swallowing. The values for incidence and mortality are far higher in many developing countries, and treatment is accessible to few. Countries with high incidence of upper digestive tract cancers include India, China, South Africa (Transkei region), northern France, and northern Iran, a few areas of central and eastern Europe, and South America (2,3). These cancers present a significant public health problem worldwide, and prevention is very important. Identification of protective factors can play a key role in prevention of these cancers.

The etiologic factors that have been identified in squamous cell carcinomas of the upper digestive tract (oral cavity, pharynx, and esophagus) are similar. The etiology of these cancers is multifactorial. It involves the interplay of genetic factors, exposure to risk factors, and exposure to protective factors. Host susceptibility includes genetic factors, which are inherited. However, susceptibility of the host is influenced by environmental factors; for example, mutagen sensitivity (which is a measure of an individual's intrinsic capacity to repair DNA damage, e.g., the damage caused by free radicals) has been demonstrated to be influenced by the presence of antioxidant vitamins such as A, C, and E (62).

The known risk factors for oral, pharyngeal, and esophageal (OPE) squamous cell carcinomas are exposure to tobacco, alcohol, and betel nut (2–4). The factors that have been studied for a possible protective role include dietary components, such as fruits, vegetables, meat, dairy products, and soy (17). A number of micronutrients, such as β-carotene, vitamin A, vitamin C, vitamin E, iron, copper, and zinc, have also been studied for their role as protective factors (11,17).

The objective of this article is to review the findings of studies that have examined the association between cancers of the upper digestive tract and intake of vegetables [total, cruciferous (e.g., kale, cabbage, cauliflower, and broccoli), green (e.g., spinach, beans, and green bell peppers), and yellow-orange (e.g., yellow-orange bell peppers, carrots, and sweet potatoes)] and fruits [total, citrus (e.g., oranges, tangerines, lemons, limes, and grapefruit), and yellow (e.g.,

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mangoes, peaches, apricots, and cantaloupe)] and to examine the association of these cancers with intake of the micronutrients vitamin A, carotene, vitamin C, and vitamin E, to determine whether these factors are protective.

Methods

All papers with the keywords "cancer" and "nutrition" published in the English language were identified through Medline (from 1966 to February 2002). Articles on studies of oral/pharyngeal/esophageal cancer and diet were reviewed. Other relevant articles were identified from the bibliography of these articles and included in the review. The selection of the specific dietary components to be evaluated in this review was based on the availability of a sufficient number of studies in the literature that have examined the association of these dietary components with oral/pharyngeal/esophageal cancer. The studies are described in Table 1.

Limitations

This review is limited to published English language articles; therefore, unpublished data and non-English language articles were excluded. This could lead to a biased view if the excluded studies had results systematically different from those reviewed; for example, if negative results were more likely to remain unpublished. However, considering that most studies addressing this question are likely to be quite expensive, not only in terms of money, but also the expertise and time required to conduct such studies, it is unlikely that the results would remain unpublished. Although non-English language articles were excluded, the studies included in the review were conducted in various parts of the world.

In addition, there are some general limitations of the epidemiological research in this area. Most studies have measured dietary intake using questionnaires or interviews conducted at one point in time, that is, before or after the outcome of interest; in other words, they have not used a prospective method of collecting dietary data, for example, having the subjects keep diaries of daily consumption of food. This is due to logistic reasons and the likelihood of low compliance by healthy subjects. However, this can introduce bias, because many individuals have significant variability in their diet. This ranges from day-to-day variability, to seasonal variability, to variability at different points in the life of the individual. Therefore, there is a strong likelihood of some inaccuracy, with subjects not accurately remembering their dietary intake in the past. As long as cases and controls report with the same degree of inaccuracy, this would result in a bias toward the null. This situation is more likely in the prospective studies; however, in the retrospective studies, it is quite possible that the patients afflicted with cancers may respond with a degree of inaccuracy that is different from that of the controls (63). This is particularly true for oral, pharyngeal, and esophageal cancers, inasmuch as the treatment of these cancers may cause major alterations in the diet in the short term (due to mucositis caused by radiation and chemotherapy) and in the long term (if surgery affecting masticatory function is required). Also, diet may be affected long before diagnosis of the cancer as a result of symptoms from the cancer or precancerous lesions, which can interfere with eating. This type of differential bias could result in an unpredictable outcome for the effect measure, biasing it toward or away from the null.

All these factors make it difficult to measure intake of specific dietary components accurately. It is even more difficult to determine the intake of the amount of different micronutrients on the basis of these surveys. The amount of nutrient actually ingested may be affected not only by the amount of food ingested, but also by the freshness of the food, cooking procedure, cooking time and temperature, and storage time of cooked food (64). Thus this assessment can be far from exact. However, because in this case the errors are likely to be nondifferential, it would likely bias the estimate toward the null.

Once the data are collected, it can be very difficult, if not impossible, to control for the effects of other known (and as yet unknown) micronutrients. Most foods contain not just one micronutrient, but a large number of different micronutrients, which may be associated, resulting in multicollinearity. This also results in a large number of potential confounders and effect modifiers, which can be difficult (with each additional variable included in the models, larger and larger sample sizes are needed) or even impossible (in the case of nutrients that have not been identified) to control for. This problem also occurs in the intervention trials, where combinations of different micronutrients are used, and it is difficult to ascribe the treatment effect to any one of those. Also, in most studies of this nature, a large number of comparisons increase the likelihood of obtaining a significant result by chance.

Most publications divide the study subjects into subgroups (e.g., quantiles and quintiles), according to intake level of the nutrient of interest for the analysis, but do not report the average amount of a nutrient ingested in these subgroups. This makes it difficult to compare results from studies done in different populations that have very different diets.

Many studies do not identify the histological type of the cancer at a particular anatomic site. Over 90% of cancers arising in the oral cavity and pharynx are squamous cell carcinomas. Of cancers arising in the esophagus, the most common histological type in most parts of the world is squamous cell carcinoma, followed by adenocarcinoma. Adenocarcinomas are believed to have etiologic factors different from those of squamous cell carcinomas. In the United States, the most common type of esophageal cancer until the 1970s was squamous cell carcinoma; however, in the last two decades, the incidence of adenocarcinoma has been increasing, and ~50% of esophageal cancers in the United States now are adenocarcinomas. Among whites in the United States, the majority of esophageal cancers are adenocarcinomas; among

Table 1. Description of Studies Reviewed[a]

Ref.	Study Location	Design	No. of Subjects	Population Characteristics	Exposure	Outcome	OR/RR Adjusted	Data Collection
5	USA[b] 1994	Population-based nested case-control study	1,090	Oral and pharyngeal cancer patients (4- to 5-yr follow-up)	Vegetables, fruits, retinol, carotene, vitamin C, vitamin C supplements, other	Development of 2nd primary cancer (any site)	Age, Quetelet index tumor stage, smoking, alcohol, calories	Interviews conducted at baseline and after 4–5 yr of follow up
6	Iowa (USA) 1995	Prospective cohort study	34,691 (33 cases)	Healthy women (7-yr follow-up)	Multivitamin and vitamin C and E supplements, fruits, vegetables, yellow-orange vegetables, other	OPE cancer	Age, smoking, total energy intake	Self-administered questionnaire
7	Linxian (China) 1993	Randomized, placebo-controlled intervention trial, not double-blinded	3,318	Persons with esophageal dysplasia (6-yr follow-up)	1) Multivitamin and multimineral supplementation and 2) placebo	Esophageal cancer	Age, gender, commune, initial grade of dysplasia	Assessment of compliance through pill counts
8	Linxian (China) 1994	Randomized, placebo-controlled intervention trial, not double-blinded	29,584	General population from area of high incidence of esophageal and stomach cancer; poor nutritional status (5.25-yr follow-up)	1) Retinol and zinc, 2) riboflavin and niacin, 3) vitamin C and molybdenum, 4) vitamin E, selenium and β-carotene; 5) placebo and blood levels of nutrients	Esophageal cancer	Age, gender, smoking, alcohol	Assessment of compliance through pill counts and biochemical analysis of blood
9	Washington, DC (USA) 1981	Population-based case-control study	370 (120 cases, 250 controls)	Cases were black men who died of primary esophageal cancer during 1975–1977; controls were black men of the same age as cases who died of other causes during the same time period	Vegetables, fruits, retinol, carotene, vitamin C	Esophageal cancer	Alcohol	Interviews with next of kin
10	Los Angeles, CA (USA) 1988	Population-based case-control study	550 (cases, 275 controls)	Esophageal carcinoma cases identified through population-based cancer registry; controls identified from the same neighborhood using a systematic sequence from case patient's house; they were matched on gender, year of birth, and race	Raw vegetables and fresh fruits	Esophageal cancer	Education, alcohol, tobacco, fried bacon/ham, bread preference, metal dust exposure	Interviews: direct or by proxy
11	Calvados (France) 1987	Case-control study	2,718 [743 cases (704 M + 39 F), 1,975 controls (922 M + 1,053 F)][c]	Not clear whether population- or hospital-based case-control study; procedure of ascertainment of cases and controls not explained; most analyses restricted to men	Vegetables, fruits, citrus fruits, dietary retinol, vitamin A, β-carotene, vitamins C and E	Esophageal cancer	Age, alcohol, tobacco, urban/rural residence	Interviews

12	Multicenter study in USA[b] 1988	Population-based case-control study	1,850 (871 cases, 979 controls)	White oral/pharyngeal cancer patients from cancer registeries; controls matched on age, gender, and race chosen randomly from the same geographic area by random-digit dialing and HCFA rosters	Vegetables, fruits (and their subgroups), retinol, carotene, vitamins C and E from dietary sources	Oral/pharyngeal cancer	Alcohol, smoking	Interviews
13	Washington, DC (USA) 1989	Population-based case-control study	713 (166 cases, 547 controls)	Pharyngeal cancer cases from cancer registry; controls identified through random-digit dialing; matched on age and gender	Dietary vitamin C, carotenoids, retinol, multivitamin, and vitamin C and A supplements	Pharyngeal cancer	Age, gender, alcohol, smoking	Telephone interviews
14	Uruguay 1990	Population-based case-control study	783 (261 cases, 522 controls)	Hospitalized esophageal cancer cases, controls were patients hospitalized with diseases unrelated to tobacco and alcohol and who had lived in the country for at least 5 yr; 2 controls/case were matched on gender and age	Raw vegetables and fruits	Esophageal cancer	Age, residence, smoking duration, type of tobacco, alcohol consumption	Interviews
15	USA[b] 1990	Population-based case-control study	391 (190 cases, 201 controls)	Black oral/pharyngeal cancer patients from cancer registeries; controls matched on age, gender, and race chosen randomly from the same geographic area by random-digit dialing and HCFA rosters	Vegetables, fruits (and their subgroups), retinol, carotene, vitamin C	Oral/pharyngeal cancer	Smoking, alcohol, calories	Interviews
16	USA[b] 1992	Population-based case-control study	2,382 (1,114 cases, 1,268 controls)	Oral/pharyngeal cancer cases from cancer registeries; controls chosen randomly from same geographic area by random-digit dialing	Vegetable, fruit, dietary vitamin C; multivitamin and vitamin C, A, and E supplements	Oral/pharyngeal cancer	Race, gender, tobacco, alcohol	Interviews
17	Shanghai (China) 1994	Population-based case-control study	2,454 (902 cases, 1,552 controls)	Esophageal cancer cases (Shanghai cancer registry); controls frequency matched on age and gender, randomly chosen (Shanghai Resident Registry)	Total vegetables, green leafy, dark orange, allium, and cruciferous vegetables, total fruits, citrus, other; retinol, carotene, vitamins C and E	Esophageal cancer	Age, education, birthplace, tea drinking, cigarette smoking, alcohol, total calories	Interviews
18	New York (USA) 1982	Hospital-based case-control study	1,013 (425 cases, 588 controls)	Hospitalized oral cancer cases; patients admitted for nonneoplastic diseases of sites other than upper GI tract randomly selected for control group	Vitamins A and C	Oral cancer	Age, smoking, alcohol intake	Interviews
19	North Carolina (USA) 1984	Hospital-based case-control study	632 [227 cases (156 hospital + 71 registry) 405 controls]	Hospitalized female oral/pharyngeal cancer cases and those identified through tumor registries; controls included hospital controls, residence controls, and death-certificate controls matched to cases on age, race , county of residence	Green vegetables, other vegetables, fruits	Oral/pharyngeal cancer	Unadjusted	Interviews: direct and next of kin

(continued)

Table 1. *(Continued)*

Ref.	Study Location	Design	No. of Subjects	Population Characteristics	Exposure	Outcome	OR/RR Adjusted	Data Collection
20	Italy 1987	Hospital-based case-control study	453 (105 cases, 348 controls)	Hospitalized esophageal cancer cases; controls hospitalized for surgery, trauma, and orthopedic, ENT, skin, and dental disorders	Green vegetables, fresh fruit, carotene, retinol	Esophageal cancer	Age, gender, education, social class, BMI, alcohol, tobacco	Interview
21	Mumbai (India) 1987	Hospital-based case-control study	1,211 [819 cases (278 oral + 225 pharynx + 236 esophagus), 392 controls = 392 (215 hospital + 177 population)]	Hospitalized male cancer cases from Maharashtrian Hindus; hospital controls were those presenting to cancer center but not diagnosed with cancer; population controls were identified from electoral rolls from areas of comparable socioeconomic status	Vegetables, fruits	OPE cancer	Age, tobacco habits	Interview
22	Brazil 1989	Hospital-based case-control study	696 (232 cases, 464 controls)	Hospitalized oral cancer cases; controls admitted to same or neighboring hospitals and matched (2/case) on gender, 5-yr age group, and trimester of hospital admission	Carotene-rich foods, green vegetables, citrus fruits	Oral cancer	Age, gender, study site, admission period, alcohol, smoking	Interview
23	Northeast Italy 1991	Hospital-based case-control study	1,001 (302 cases, 699 controls)	Hospitalized oral/pharyngeal cancer cases; controls admitted to hospitals in the same catchment areas as cases with acute nonneoplastic conditions unrelated to smoking, alcohol, and long-term dietary changes	Vegetables, fresh fruits, citrus fruits	Oral/pharyngeal cancer	Age, gender, occupation, smoking and drinking habits	Interview
24	Northern Italy 1991	Hospital-based case-control study	1,274 [105 cases (35 oral + 70 oropharynx), 1,169 controls]	Hospitalized oral cancer cases; controls included patients admitted to the same network of hospitals for acute, nonneoplastic or digestive diseases unrelated to alcohol or tobacco consumption	Green vegetables, fruits	Oral/pharyngeal cancer	Age, gender, smoking, residence, education, social class, milk, meat, cheese, carrots, green vegetables, fruit, alcohol	Interview
25	Italy 1991	Hospital-based case-control study	6,560 [413 cases (119 oral/pharyngeal + 294 esophageal) 6,147 controls]	Oral/pharyngeal, esophageal cancer cases; controls admitted to the same network of hospitals with acute, nonneoplastic, nondigestive conditions unrelated to smoking, alcohol, and long-term dietary changes	Green vegetables and fruits	OPE cancer	Age, gender, education, area of residence; tobacco, alcohol, vegetable, and fruit consumption	Interviews
26	Uruguay 1991	Hospital-based case-control study	410 (57 cases, 353 controls)	Hospitalized male tongue cancer (squamous cell carcinoma) cases; controls were patients admitted to the same hospital for diseases believed to be unrelated to tobacco and/or alcohol exposure	Vegetables and fruits	Oral cancer	Age, county, type of tobacco, smoking intensity; alcohol, meat, vegetables, fruits, mate	Interviews

27	USA[b] 1992	Hospital-based case-control study	1,269 [423 cases (290 oral + 133 esophageal), 846 controls]	Hospitalized oral cancer cases; controls with nonneoplastic diseases, benign neoplasms, and cancers believed to be unrelated to tobacco and alcohol use matched for age, gender, race, hospital, and time of admission	Multivitamin, vitamin C and E supplement use	Oral/esophageal cancer	Smoking, drinking, Quetelet index, years of education, race, meat and vegetable intake, intake of multivitamin and vitamin B, C, and E supplements	Interviews
28	New York (USA) 1992	Hospital-based case-control study	580 (290 cases, 290 controls)	Hospital pathology records used to identify oral cancer cases; controls matched on neighborhood, age, and gender	Retinol, carotene, vitamin C	Oral cancer	Age, gender, neighborhood, alcohol, smoking, total calories, Quetelet index, teeth lost but not replaced	Interviews
29	Beijing (China) 1993	Hospital-based case-control study	808 (404 cases, 404 controls)	Hospitalized oral cancer cases; controls hospitalized for minor surgery, ophthalmic and ear conditions, low back pain, and UTIs matched for age, gender, and referral pattern	Individual vegetables, fruits; vitamins A and C, carotene	Oral cancer	Tobacco, alcohol, inadequate dentition, Quetelet index, total energy intake, years of education, gender, age	Questionnaires
30	Northeast China 1994	Hospital-based case-control study	588 (196 cases, 392 controls)	Hospitalized esophageal cancer cases; controls were patients hospitalized with nonneoplastic, nonesophageal diseases; 2 controls/case, matched on gender, age, and area of residence	Vegetables, fruits, retinol, β-carotene, vitamin C	Esophageal cancer	Alcohol, smoking, income, occupation	Interviews
31	Japan 1996	Hospital-based nested case-control study	36,793 (266 cases, 36,527 controls)	Patients presenting to the hospital and diagnosed within 1 yr with oral/pharyngeal cancer; controls included patients confirmed to be cancer free between 1988 and 1993	Green-yellow vegetables, raw vegetables, fruits	Oral/pharyngeal cancer	Age, gender, smoking, drinking, year of visit	Self-administered questionnaire
32	Switzerland 1998	Hospital-based case-control study	440 (156 cases, 284 controls)	Hospitalized oral and pharyngeal cancer cases; controls admitted for trauma, other orthopedic conditions, acute surgical diseases, and other nonneoplastic conditions believed to be unrelated to tobacco, alcohol, and long-term modification of diet	Cooked and raw vegetables, citrus fruits	Oral/pharyngeal cancer	Age, gender, education, alcohol, smoking, nonalcohol total energy	Interviews
33	Uruguay 1999	Hospital-based case-control study	492 [99 cases (33 oral/pharyngeal + 66 esophageal cancer), 393 controls]	Hospitalized oral, pharyngeal, and esophageal cancer cases; controls, admitted for trauma, eye diseases, abdominal hernia, acute appendicitis, varicose veins, and skin diseases, were frequency matched to cases on 10-yr age group, gender, residence, urban/rural status	Vegetables, fruits	OPE cancer	Age, gender, BMI, residence, urban/rural, education, alcohol, smoking, total energy intake	Interviews

(continued)

Table 1. *(Continued)*

Ref.	Study Location	Design	No. of Subjects	Population Characteristics	Exposure	Outcome	OR/RR Adjusted	Data Collection
34	Uruguay 1999	Hospital-based case-control study	492 [99 cases (33 oral/pharyngeal + 66 esophageal cancer), 393 controls]	Hospitalized oral, pharyngeal, and esophageal cancer cases; controls admitted for trauma, eye diseases, abdominal hernia, acute appendicitis, varicose veins, and skin diseases, were frequency matched to cases on 10-yr age group, gender, residence, urban/rural status	Retinol, β-carotene, vitamins C and E	OPE cancer	Age, gender, BMI, residence, urban/rural, education, alcohol, smoking, total energy intake	Interviews
35	Northern Italy 1999	Hospital-based case-control study	906 [42 cases (10 M + 32 F),864 controls (442 M + 422 F)]	Hospitalized nonsmoker oral cancer cases; nonsmoker controls admitted for trauma, nontraumatic orthopedic conditions, acute surgical diseases, other nonmalignant and nondigestive diseases believed to be unrelated to tobacco and alcohol use	Green vegetables, fresh fruits, citrus fruits, retinol, β-carotene	Oral/pharyngeal cancer	Age, gender, study center, education, and alcohol intake	Interviews
36	Northeast and central Italy 1999	Hospital-based case-control study	2089 [598 cases (271 oral + 327 pharynx), 1,491 controls]	Oral/pharyngeal cancer cases; controls admitted to hospitals in the same catchment areas as cases with acute nonneoplastic conditions unrelated to smoking, alcohol, and long-term dietary changes	Vegetables and fruits	Oral/pharyngeal cancer	Age, gender, education, center, total energy, tobacco, alcohol	Interviews
37	Italy and Switzerland 2000	Hospital-based case-control study	2,529 (754 cases, 1,775 controls)	Hospitalized oral cancer (344) and pharyngeal cancer (410) cases; controls admitted for trauma, other orthopedic conditions, acute surgical diseases, and other nonneoplastic conditions believed to be unrelated to tobacco, alcohol, and long-term dietary changes	Retinol, carotene, vitamins C and E from dietary sources	Oral/pharyngeal cancer	Age, gender, study center, education, occupation, BMI, alcohol, smoking, nonalcohol energy	Interviews
38	Cuba 2001	Hospital-based case-control study	400 [200 cases (143 M + 57 F), 200 controls (136 M + 64 F)]	Hospitalized oral and pharyngeal cancer cases; controls admitted for trauma or orthopedic conditions, acute surgical diseases, acute medical conditions, and skin, neoplastic, eye, and other miscellaneous diseases	Vegetables, cruciferae, fruits, citrus fruits	Oral/pharyngeal cancer	Age, gender, residence, education, smoking, alcohol intake	Interviews
39	Northeast Italy 2001	Hospital-based case-control study	280 (132 cases, 148 controls)	Hospitalized oral/pharyngeal cancer cases; controls admitted for trauma, nontraumatic orthopedic conditions, acute surgical diseases and skin, eye, and ear diseases	Green vegetables, total fruits, and citrus fruits	Oral/pharyngeal cancer	Age, gender, education, total no. of portions, tobacco, alcohol	Interviews

a: Abbreviations are as follows: OR, odds ratio; RR, relative risk; BMI, body mass index; OPE, oral/pharyngeal/esophageal; HCFA, Health Care Finance Administration (>65 yr of age); GI, gastrointestinal; ENT, ear, nose, and throat; M, male; F, female.

b: Multicenter study: New Jersey, Los Angeles and San Francisco, CA, and Atlanta, GA.

c: Note ratio of male to female cases and controls.

blacks, the majority of esophageal cancers remain squamous cell carcinomas (3). Therefore, not restricting or stratifying by the histological type of the cancer, especially for esophageal cancers, may result in a grouping together of distinct cancers having different etiologies and a resulting dilution of the strength of association with the risk factors being studied.

The Linxian intervention trials were not double-blinded (7,8). This can bring the validity of the results into question because of the serious biases that can occur in unblinded studies.

Results

Each micronutrient dietary component to be evaluated was examined to determine whether it satisfied the following criteria of causal assumption (40): temporal relationship, consistency of results, strength of association, dose response, and biological plausibility.

Carotene

Temporal Relationship

The two prospective cohort studies in Table 1 (5,6), where carotene intake had been assessed years before the outcome, found a decreased risk (not statistically significant) with higher intake of carotene. Also the intervention trials (7,8), where carotene plus other micronutrient supplementation was done before development of the cancers, found decreased risks of developing cancer in the supplemented groups.

Consistency of Results

The odds ratio (OR)-and-relative risk (RR) sets from 18 different studies are summarized in Table 2. The total number of OR/RR sets is 32, with 26 showing a decreased risk (11 were statistically significant), 3 showing an increased risk (none were statistically significant), 1 reporting no change in risk with OR = 1, and 2 showing no clear trends with increasing intake of carotene. The number of OR/RR sets for esophageal cancer as outcome is 12, with 11 showing a decreased risk (4 were statistically significant) and 1 showing an increased risk (not statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is 12, with 8 showing a decreased risk (4 were statistically significant), 2 showing an increased risk (none were statistically significant), and 2 showing no clear trends with increasing intake of carotene. The number of OR/RR sets for pharyngeal cancer as outcome is one, which showed a decreased risk (not statistically significant). The number of OR/RR sets for oral cancer as outcome is five, with four showing a decreased risk (3 were statistically significant), none showing an increased risk, and one reporting no change in risk with OR = 1.

A number of basic science studies have also found a protective role of micronutrients in experimental models of carcinogenesis. Experiments done in hamsters, where epidermoid tumors were induced by local application of carcinogens on the buccal pouch, have demonstrated regression of the tumors by oral administration of combinations of β-carotene and α-tocopherol. Oral administration of β-carotene or α-tocopherol alone has not been effective in causing regression of the tumors (41). However, regression of the tumors has been demonstrated using local injections of β-carotene alone and α-tocopherol alone into the tumors (42,43).

Studies on blood levels of carotene have shown that high-risk populations, including those who live in areas of high incidence of OPE cancers, such as Linxian, China (44), Samarkand Oblsat of Uzbek SSR (45), and Transkei, South Africa (46), and those who have precancerous changes of the mucosa (47) have low serum levels of carotene and other micronutrients. OPE cancer patients have also been shown to have lower levels of carotene (48), although in patients who have already developed cancer, these lower levels may be a result of the cancer itself. All these studies found low levels of other micronutrients in addition to carotene.

A nested case-control study by Knekt et al. (61), where blood samples were collected before diagnosis of the cancer, found differences in blood levels of β-carotene between cases and controls that were not statistically significant. Mean levels were lower in the lip/oral/pharyngeal cancer group (n = 20) than in matched controls (n = 37), whereas mean levels were higher in the esophageal cancer group (n = 9) than in matched controls (n = 16). Controls were matched on gender, age, and municipality (which controlled for time of baseline examination and duration of storage of the serum samples).

Strength of Association

The OR/RRs from all listed studies range from 0.2 to 1.6; statistically significant OR/RRs range from 0.2 to 0.7. "Protective" values range from 0.2 to 0.94, with most being ≥0.5. For any individual nutrient, this may represent a strong association, because a number of different dietary components play important and possibly synergistic roles in control of carcinogenesis.

For studies with esophageal cancer as outcome, the OR/RRs range from 0.23 to 1.1; statistically significant OR/RRs range from 0.23 to 0.7. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.2 to 1.6; statistically significant OR/RRs range from 0.2 to 0.7.

For studies with oral cancer as outcome, the OR/RRs range from 0.41 to 1.0; statistically significant OR/RRs range from 0.41 to 0.54.

Dose Response

Different carotene intake levels were compared in 15 studies (5,6,9,11,12,13,15,17,20,22,28–30,35,37). A dose-response [with P (for trend) < 0.05] was seen in seven of these studies (11,12,15,17,20,29,37), all of which showed a decreasing risk with increasing intake of carotene. However, the criterion of dose response may not clearly apply in this

Table 2. Carotene[a]

Ref.	OR/RR (95% CI)	Outcome	Risk With Higher Intake	Source
		Prospective studies		
5	1.0, 1.2, 0.7, 0.8 [*p* (for trend) = 0.24]	Development of 2nd primary cancer	Decreased	Carotenoids from diet (from data collected on development of 1st oral/pharyngeal cancer)
6	1.0, 1.1 (0.5,2.4), 0.7 (0.3–1.8) [*p* (for trend) = 0.44]	Incidence of OPE cancer	Decreased	Carotene: diet and supplements
		Intervention trials		
7	RR = 0.94 (0.73–1.20)	Esophageal cancer incidence	Decreased	Multivitamin/mineral supplements (β-carotene, 15 mg)
	RR = 0.84 (0.54–1.29)	Esophageal cancer mortality	Decreased	
8	RR = 0.58, (0.19–1.76)	Esophageal cancer	Decreased	β-carotene, selenium, α-tocopherol supplements (β-carotene, 15 mg)
	RR = 0.80, (0.40–1.57)	Esophageal dysplasia/cancer	Decreased	
		Case-control studies		
9	From high to low intake: 1.0, 1.3, 1.3 [*p* (for trend) > 0.1]	Esophageal cancer	Decreased	Dietary intake of carotene
11	1.0, 0.85, 1.0, 0.53 [*p* (for trend) = 0.026]*	Esophageal cancer	Decreased*	Dietary intake of carotene (men)
12	1.0, 1.0, 0.8, 0.8 [*p* (for trend) = 0.11]	Oral and pharyngeal cancer	Decreased	Total dietary intake of carotene (men)
	1.0, 0.9, 1.0, 0.8 [*p* (for trend) = 0.44]		No clear trend	Total dietary intake of carotene (women)
	1.0, 1.0, 1.0, 0.9 [*p* (for trend) = 0.47]		Decreased	Dietary intake of carotene from vegetables (men)
	1.0, 0.7, 1.0, 0.8, [*p* (for trend) = 0.71]		No clear trend	Dietary intake of carotene from vegetables (women)
	1.0, 0.7,* 0.7,* 0.4* [*p* (for trend) < 0.001]*		Decreased*	Dietary intake of carotene from fruits (men)
	1.0, 0.6,* 0.8, 0.4* [*p* (for trend) = 0.006]*		Decreased*	Dietary intake of carotene from fruits (women)
13	From high to low intake: 1.0, 0.8 (0.5–1.5), 1.1 (0.6–2.0), 1.3 (0.7–2.2) [*p* (for trend) = 0.295]	Pharyngeal cancer	Decreased	Dietary intake of carotenoids
15	1.0, 0.6, 0.6, 0.2* [*p* (for trend) = 0.001]*	Oral and pharyngeal Cancer	Decreased*	Dietary intake of carotene (men)
	1.0,1.6,1.4,1.5 [*p* (for trend) = 0.64]		Increased	Dietary intake of carotene (women)
17	1.0, 0.7,* 0.6,* 0.5* [*p* (for trend) < 0.001]*	Esophageal cancer	Decreased*	Dietary intake of carotene (men)
	1.0, 0.9, 0.8, 0.6 [*p* (for trend) = 0.09]		Decreased	Dietary intake of carotene (women)
20	1.0, 0.45 (0.23–0.93),* 0.23 (0.12–0.46)* [*p* (for trend) < 0.001]*	Esophageal cancer	Decreased*	Dietary intake of b-carotene
22	1.0, 0.8 (0.5–1.4), 0.4 (0.2–1.0) [*p* (for trend) = 0.06]	Oral cancer	Decreased	Dietary intake of carotene-rich foods (carrots, pumpkins and papayas)
28	1.0 (0.8–1.2) (1 unit = single SD increase in intake)	Oral cancer	No change	Dietary intake of carotene
29	1.0, 0.47 (0.28–0.81),* 0.64 (0.37–1.09), 0.51 (0.27–0.96)* [*p* (for trend) = 0.08]	Oral cancer	Decreased*	Total carotene from diet
	1.0, 0.41 (0.24–0.69),* 0.54 (0.32–0.93),* 0.52 (0.28–0.98)* [*p* (for trend) = 0.05]*		Decreased*	Carotene from vegetables
	1.0, 0.66 (0.40–1.10), 0.50 (0.29–0.86),* 0.52 (0.33–1.02) [*p* (for trend) = 0.27]		Decreased*	Carotene from fruits
30	1.0, 0.8 (0.5–1.4), 1.0 (0.6–1.7), 0.7 (0.4–1.4) [*p* (for trend) = 0.1]	Esophageal cancer	Decreased	Dietary intake of β-carotene
34	1.2 (0.7–2.1)	Oral and pharyngeal cancer	Increased	Dietary intake of β-carotene
	1.1 (0.8–1.5)	Esophageal cancer	Increased	
	0.7 (0.4–1.2)	Oral and pharyngeal cancer	Decreased	Dietary intake of α-carotene
	0.6 (0.4–0.9)*	Esophageal cancer	Decreased*	
35	1.0, 0.9 (0.4–2.0), 0.8 (0.3–1.8)	Oral and pharyngeal cancer	Decreased	Dietary intake of β-carotene
37	1.0, 0.74 (0.53–1.04), 0.57 (0.39–0.83),* 0.35 (0.23–0.53),* 0.43 (0.28–0.66)* [*p* (for trend) < 0.0001]*	Oral and pharyngeal cancers	Decreased*	Dietary intake of carotene

a: ORs and RRs are adjusted for other risk factors (see Table 1) *, statistical significance.

situation, inasmuch as there may be an optimal level beyond which further intake may not be beneficial.

Biological Plausibility

β-Carotene is an antioxidant. Free radicals of oxygen can damage DNA, which is an important step in development of cancer. Antioxidants act as scavengers of free radicals of oxygen, thus preventing or reducing DNA damage. Other mechanisms by which β-carotene could suppress cancer development have been proposed: 1) conversion to retinol, thus compensating for localized retinol deficiencies caused by carcinogens, 2) enhancement of the immune system, 3) stimulation of cell-cell communication, which could suppress replication of initiated cells, and 4) increase in activity of carcinogen detoxification enzymes (49).

Vitamin A

Temporal Relationship

Of the two prospective cohort studies described in Table 1, one found a decreased risk (not statistically significant) of incidence of upper digestive tract cancer (6) and the other found no clear trend (5) of increasing intake of retinol on second primary cancers. Of the intervention trials (where retinol plus other micronutrient supplementation had been done before development of the outcome), one (8) found an increased risk (not statistically significant) of esophageal dysplasia and cancer and one found a decreased risk (7) of esophageal cancer incidence and mortality (not statistically significant).

Consistency of Results

The OR/RR sets from 19 different studies are summarized in Table 3. The total number of OR/RR sets is 28, with 9 showing a decreased risk (3 were statistically significant), 12 showing an increased risk (6 were statistically significant), and 7 showing no clear trend with increasing intake of retinol. The number of OR/RR sets for esophageal cancer as outcome is 11, with 4 showing a decreased risk (none were statistically significant), 6 showing an increased risk (3 were statistically significant), and 1 showing no clear trend with increasing intake of retinol. The number of OR/RR sets for oral and pharyngeal cancer as outcome is nine, with one showing a decreased risk (statistically significant), five showing an increased risk (3 were statistically significant), and three showing no clear trend with increasing intake of retinol. The number of OR/RR sets for pharyngeal cancer as outcome is two, with one showing a decreased risk (statistically significant) and one showing no clear trend with increasing intake of retinol. The number of OR/RR sets for oral cancer as outcome is three, with two showing a decreased risk (1 was statistically significant) and one showing an increased risk (not statistically significant).

Studies on blood levels of vitamin A have shown low levels of vitamin A and other micronutrients in high-risk populations, including those who live in areas of high incidence of OPE cancers, such as Linxian, China (44), Samarkand Oblsat of Uzbek SSR (45), Transkei, South Africa (50), Andhra Pradesh, India (51), and Hyderabad, India (52), and those who have precancerous changes of the mucosa (47). OPE cancer patients with second primary cancers have also been shown to have lower levels of vitamin A than patients without second primary cancers (48).

A nested case-control study (61) found differences in blood levels of retinol between cases and controls that were not statistically significant. Mean levels were lower in the lip/oral/pharyngeal cancer group (n = 20) than in matched controls (n = 37), whereas mean levels were higher in the esophageal cancer group (n = 9) than in matched controls (n = 16).

Strength of Association

The OR/RRs from all listed studies range from 0.14 [from Ref. 13: OR for lowest intake = 7 (1.4–34.7)] to 4.5. Both values are statistically significant. For studies with esophageal cancer as outcome, the OR/RRs range from 0.66 to 2.27; statistically significant OR/RRs range from 2.0 to 2.27. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.4 to 4.5; both values are statistically significant. For studies with pharyngeal cancer as outcome, the two OR/RRs are 0.14 (significant) and 1.1 (not significant).

Dose Response

Of the 16 studies (5,6,9,11–13,15–18,20,28–30,35,37) where different intake levels were measured, 9 showed a dose response [with P (for trend) < 0.05], with 3 (13,16,18) showing a decreasing risk with increasing intake and the other 6 (11,12,15,20,30,37) showing an increasing risk with increasing intake.

Biological Plausibility

Retinol plays an important role in the control of cell differentiation, cell adhesion, and membrane permeability (49). A deregulation of these properties is seen in carcinogenesis; thus retinol may play a role in cancer prevention through regulation of these cell properties.

Vitamin C

Temporal Relationship

The two prospective cohort studies (5,6) showed decreased risk of cancer with higher intake of vitamin C. However, the effect of intake of vitamin C after development of the first cancer on risk of second primary cancers did not show a clear trend. Of the two intervention studies, one showed an increased risk (8) and the other a decreased risk (7). None of these results were statistically significant.

Table 3. Vitamin A[a]

Ref.	OR/RRs (95% CI)	Outcome	Risk With Higher Intake	Source
		Prospective studies		
5	1.0, 0.8, 0.8, 1.6 [p (for trend) = 0.09]	Development of 2nd primary cancer	No clear trend	Vitamin A from diet (from data collected on development of 1st oral/pharyngeal cancer)
	1.0, 0.8, 1.3, 0.6 [p (for trend) = 0.24]		No clear trend	Vitamin A-rich vegetable and fruit intake after original cancer diagnosis (follow-up data)
6	1.0, 1.1 (0.5,2.5), 0.9 (0.4–2.2) [p (for trend) = 0.82]	Incidence of OPE cancer	Decreased	retinol: diet and supplements
		Intervention trials		
7	RR = 0.94 (0.73–1.20)	Esophageal cancer incidence	Decreased	Multivitamin/mineral supplements (10,000 IU vitamin A)
	RR = 0.84 (0.54–1.29)	Esophageal cancer mortality	Decreased	
8	RR = 1.02, (0.36–2.91)	Esophageal cancer	Increased	retinol and zinc supplements (5,000 IU retinol)
	RR = 1.12, (0.57–2.20)	Esophageal dysplasia/cancer	Increased	
		Case-control studies		
9	From high to low intake: 1.0, 1.5, 1.5 [p (for trend) > 0.1]	Esophageal cancer	Decreased	Dietary intake of vitamin A
11	1.0, 1.91, 1.98, 3.09 [p (for trend) < 0.0001]*	Esophageal cancer	Increased*	Dietary intake of retinol (men)
12	1.0, 1.1,1.2,1.6* [p (for trend) = 0.007]*	Oral and pharyngeal cancer	Increased*	Total dietary intake of retinol (men)
	1.0, 1.2, 1.2, 1.4 [p (for trend) = 0.27]		Increased	Total dietary intake of retinol (women)
13	From high to low intake: 1.0, 0.8 (0.4–1.4), 0.9 (0.5–1.5), 1.1 (0.6–2.0) [p (for trend) = 0.701]	Pharyngeal cancer	No clear trend	Dietary intake of retinol
	1.0, 4.9 (0.5–46.9), 7.0 (1.4–34.7)* [p (for trend) = 0.004]*	Decreased*	Vitamin A supplements	
15	1.0, 1.8,3.6,*4.5* [p (for trend) = 0.001]*	Oral and pharyngeal cancer	Increased*	Dietary intake of retinol (men)
	1.0, 0.9, 1.4, 0.6 [p (for trend) = 0.79]		No clear trend	Dietary intake of retinol (women)
16	1.0, 0.8 (0.7–1.1), 0.9 (0.7–1.2), 0.4 (0.2–0.6)* [p (for trend) = 0.003]*	Oral/pharyngeal cancer	Decreased*	Vitamin A supplements (ORs are for increasing dos)
	1.0, 1.1 (0.8–1.4), 1.2 (0.8–1.6), 0.6 (0.4–1.1) [p (for trend) = 0.92]		No clear trend	Vitamin A supplements (ORs are for increasing dos adjusted for vitamin E)
17	1.0, 1.0, 1.0, 0.9 [p (for trend) = 0.82]	Esophageal cancer	No clear trend	Dietary intake of retinol (men)
	1.0, 1.0, 1.5, 1.3 [p (for trend) = 0.11]		Increased	Dietary intake of retinol (women)
18	0.69 (p < 0.05) [1 unit = 100,000 IU (monthly intake)]	Oral cancer	Decreased*	Dietary intake of retinol
20	1.0, 1.33 (0.64–2.75), 2.27 (1.13–4.52)* [p (for trend) = 0.02]*	Esophageal cancer	Increased*	Dietary intake of retinol
28	1.4 (0.9–2.1) (1 unit = single SD increase in intake)	Oral cancer	Increased	Dietary intake of retinol
29	1.0, 0.70 (0.37–1.33), 0.72 (0.43–1.21), 0.64 (0.35–1.16) [p (for trend) = 0.24]	Oral cancer	Decreased	Vitamin A from diet
30	1.0, 2.0 (1.1–3.7),* 1.2 (0.6–2.1), 1.3 (0.7–2.4) [p (for trend) = 0.99]	Esophageal cancer	Increased*	Dietary intake of retinol
34	1.2 (0.7–1.9)	Oral and pharyngeal cancer	Increased	Dietary intake of retinol
	0.9 (0.7–1.4)	Esophageal cancer	Decreased	
35	1.0, 0.6 (0.3–1.5), 1.3 (0.6–2.9)	Oral and pharyngeal cancer	No clear trend	Dietary intake of retinol
37	1.0, 1.29 (0.88–1.91), 1.61 (1.08–2.39),* 1.12 (0.77–1.64), 1.46 (0.99–2.16) [p (for trend) = 0.256]	Oral and pharyngeal cancer	Increased*	Dietary intake of retinol

a: ORs and RRs are adjusted for other risk factors (see Table 1). *, statistical significance.

Consistency of Results

The OR/RR sets from 17 different studies are summarized in Table 4. The total number of OR/RR sets is 33, with 27 showing a decreased risk (17 were statistically significant), 3 showing an increased risk (none were statistically significant), and 3 showing no clear trend with increasing intake of vitamin C. The number of OR/RR sets for esophageal cancer as outcome is 10, with 8 showing a decreased risk (5 were statistically significant) and 2 showing an increased risk (none were statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is 12, with 10 showing a decreased risk (7 were statistically significant), 1 showing an increased risk (not statistically significant), and 1 showing no clear trend with increasing intake of vitamin C. The number of OR/RR sets for pharyngeal cancer as out-

Table 4. Vitamin C[a]

Ref.	OR/RR (95% CI)	Outcome	Risk With Higher Intake	Source
		Prospective studies		
5	1.0, 1.0, 0.5, 0.7 [p (for trend) = 0.12]	Development of 2nd primary cancer	Decreased	Vitamin C from diet (from data collected on development of 1st oral/pharyngeal cancer)
	1.0, 0.4, 1.2, 0.6 [p (for trend) = 0.33]		No clear trend	Vitamin C-rich vegetable and fruit intake after original cancer diagnosis (follow-up data)
6	1.0, 0.9 (0.4, 2.0), 0.7 (0.3–1.7) [p (for trend) = 0.45]	Incidence of OPE cancer	Decreased	Vitamin C: diet and supplements
		Intervention trials		
7	RR = 0.94 (0.73–1.20)	Esophageal cancer incidence	Decreased	Multivitamin/mineral supplements (vitamin C: 180 mg)
	RR = 0.84 (0.54–1.29)	Esophageal cancer mortality	Decreased	
8	RR = 1.32, (0.46–3.83)	Esophageal cancer	Increased	Vitamin C and molybdenum supplements (vitamin C: 120 mg)
	RR = 1.31, (0.67–2.57)	Esophageal cancer/dysplasia	Increased	
		Case-control studies		
9	From high to low intake: 1.0, 1.2, 1.8 [p (for trend) < 0.05]	Esophageal cancer	Decreased*	Dietary intake of vitamin C
11	1.0, 0.80, 0.65, 0.53 [p (for trend) = 0.011]*	Esophageal cancer	Decreased*	Dietary intake of vitamin C (men)
12	1.0, 1.0, 0.5,* 0.6* [p (for trend) < 0.001]*	Oral and pharyngeal cancer	Decreased*	Total dietary intake of vitamin C (men)
	1.0, 0.9, 0.9, 0.5,* [p (for trend) = 0.04]*		Decreased*	Total dietary intake of vitamin C (women)
	1.0, 1.3, 1.2, 0.9 [p (for trend) = 0.53]		Increased	Dietary intake of vitamin C from vegetables (men)
	1.0, 0.7, 0.8, 0.7, [p (for trend) = 0.19]		Decreased	Dietary intake of vitamin C from vegetables (women)
	1.0, 0.7,* 0.6,* 0.5* [p (for trend) < 0.001]*		Decreased*	Dietary intake of vitamin C from fruits (men)
	1.0, 0.8, 0.8, 0.4* [p (for trend) = 0.01]*		Decreased*	Dietary intake of vitamin C from fruits (women)
13	1.0, 2.5 (1.3–4.8),* 2.1 (1.1–4.0),* 2.5 (1.3–4.8)* [p (for trend) = 0.017]*	Pharyngeal cancer	Decreased*	Dietary intake of vitamin C
	1.0, 1.9 (0.9–3.9), 2.2 (1.2–3.9)* [p (for trend) = 0.009]*		Decreased*	Vitamin C supplements
15	1.0, 0.6, 0.5, 0.3* [p (for trend) = 0.004]*	Oral and pharyngeal cancer	Decreased*	Dietary intake of vitamin C (men)
	1.0, 0.6, 0.9, 0.6 [p (for trend) = 0.65]		Decreased	Dietary intake of vitamin C (women)
16	1.0, 0.9 (0.7–1.2), 0.9 (0.6–1.3), 0.6 (0.4–0.9),* 0.6 (0.4–0.8),* 1.1 (0.7–1.7) [p (for trend) = 0.003]*	Oral/pharyngeal cancer	Decreased*	Vitamin C supplements (ORs are for increasing dos)
	1.0, 1.1 (0.8–1.4), 1.0 (0.7–1.5), 0.8 (0.6–1.3), 0.8 (0.6–1.2), 1.6 (1.0–2.5) [p (for trend) = 0.82		No clear trend	Vitamin C supplements (ORs are for increasing dos, adjusted for vitamin E)
17	1.0, 0.8, 0.6,* 0.5* [p (for trend) < 0.001]*	Esophageal cancer	Decreased*	Dietary intake of vitamin C (men)
	1.0, 0.9, 1.1, 0.6* [p (for trend) = 0.09]		Decreased*	Dietary intake of vitamin C (women)
18	0.75 (p < 0.05) {1 unit = 1,000 mg [monthly (?) intake]}	Oral cancer	Decreased*	Dietary intake of vitamin C
27	1.0, 1.2 (0.7–2.0), 0.9 (0.5–1.7), 1.6 (0.8–2.9)	Oral cancer	No clear trend	Vitamin C supplements (ORs are for increasing duration-adjusted for multivitamin, vitamin B, vitamin E intake)
	1.0, 0.4 (0.1–1.0), 0.4 (0.1–1.1), 0.4 (0.1–1.5)	Esophageal cancer	Decreased	
28	0.9 (0.7–1.2) (1 unit = single SD increase in intake)	Oral cancer	Decreased	Dietary intake of vitamin C
29	1.0, 0.68 (0.41–1.14), 0.60 (0.35–1.02), 0.46 (0.25–0.86)* [p (for trend) = 0.16]	Oral cancer	Decreased*	Total vitamin C from diet
	1.0, 0.46 (0.27–0.77),* 0.57 (0.34–0.97),* 0.52 (0.28–0.97)* [p (for trend) = 0.08]		Decreased*	Vitamin C from vegetables
	1.0, 0.59 (0.37–0.94),* 0.60 (0.35–1.02), 0.55 (0.30–0.99)* [p (for trend) = 0.11]		Decreased*	Vitamin C from fruits
34	0.7 (0.4–1.1)	Oral and pharyngeal cancer	Decreased	Dietary intake of vitamin C
	0.7 (0.5–0.9)*	Esophageal cancer	Decreased*	
37	1.0, 0.68 (0.49–0.93),* 0.44 (0.31–0.62),* 0.37 (0.25–0.55),* 0.34 (0.23–0.51)* [p (for trend) < 0.0001]*	Oral and pharyngeal cancer	Decreased*	Dietary intake of vitamin C

a: ORs and RRs are adjusted for other risk factors (see Table 1). *, statistical significance.

come is two, with both showing a decreased risk (2 were statistically significant). The number of OR/RR sets for oral cancer as outcome is six, with five showing a decreased risk (4 were statistically significant) and one showing no clear trend with increasing intake of vitamin C.

Studies on blood levels of vitamin C have shown low levels of vitamin C and other micronutrients in high-risk populations from areas of high incidence of OPE cancers, such as Linxian, China (44) and Transkei, South Africa (46), and those who have precancerous changes of the mucosa (47).

Strength of Association

The OR/RRs from all listed studies range from 0.3 to 1.6. Statistically significant values range from 0.3 to 0.75. Protective values range from 0.3 to 0.9. For studies with esophageal cancer as outcome, the OR/RRs range from 0.4 to 1.32; statistically significant OR/RRs range from 0.5 to 0.7. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.3 to 1.3; statistically significant OR/RRs range from 0.3 to 0.7. For studies with pharyngeal cancer as outcome, the OR/RRs range from 0.4 to 0.52; statistically significant OR/RRs range from 0.4 to 0.47. For studies with oral cancer as outcome, the OR/RRs range from 0.46 to 1.6; statistically significant OR/RRs range from 0.46 to 0.59.

Dose Response

Of the 15 studies where different intake levels were compared (5,6,9,11–13,15–18,27–29,34,37), a dose response [with P (for trend) < 0.05] was seen in 9 (9,11–13,15–17,18,37), all of which showed a decreasing risk with increasing intake of vitamin C.

Biological Plausibility

Vitamin C is an antioxidant that acts as a reducing compound within the cell. It is believed that it may act synergistically with vitamin E, which scavenges free radicals in cell membranes (53). It can also block the formation of carcinogens such as nitrosamines (54) and has been shown to reduce the binding of the carcinogen 7,12-dimethylbenz[*a*]anthracene to cellular DNA (55). Therefore, vitamin C could play a role in preventing cancer development through a number of different mechanisms.

Vitamin E

Temporal Relationship

The prospective cohort study (6) did not show a clear trend for the association between vitamin E and OPE cancers. The two intervention studies where supplementation with multiple micronutrients including vitamin E was done showed a decreased risk (7,8).

Consistency of Results

The OR/RR sets from 10 different studies are summarized in Table 5. The total number of OR/RR sets is 17, with 14 showing a decreased risk (7 were statistically significant), 1 showing an increased risk (not statistically significant), and 2 showing no clear trend with increasing intake of vitamin E. The number of OR/RR sets for esophageal cancer as outcome is 10, with all showing a decreased risk (3 were statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is six, with four showing a decreased risk (3 were statistically significant), one showing an increased risk (not statistically significant), and one showing no clear trend with increasing intake of vitamin E. The number of OR/RR sets for oral cancer as outcome is 1, which showed a decreased risk (statistically significant).

In addition to the animal studies mentioned above (see **Carotene**) that demonstrated a protective effect of vitamin E, a study done in mice showed that vitamin E supplementation in the diet of mice exposed to a carcinogen and ethanol resulted in a decrease in the size and frequency of the induced tumors (56). Studies on blood levels of vitamin E have shown low serum levels of vitamin E and other micronutrients in high-risk populations from areas of high incidence of OPE cancers, such as Linxian, China (44) and Transkei and Ciskei, South Africa (50). OPE cancer patients with second primary cancers have also been shown to have lower levels of vitamin E than patients without second primary cancers (48). In this situation, the effect of the cancer on blood levels of micronutrients must be considered.

A nested case-control study (61) found differences in blood levels of α-tocopherol between cases and controls that were not statistically significant. Mean levels were higher in the lip/oral/pharyngeal cancer group (n = 20) than in matched controls (n = 37), whereas mean levels were lower in the esophageal cancer group (n = 9) than in matched controls (n = 16).

Strength of Association

The OR/RRs from all listed studies range from 0.32 to 1.2. Statistically significant values range from 0.4 to 0.7. Protective values range from 0.32 to 0.94. For studies with esophageal cancer as outcome, the OR/RRs range from 0.32 to 0.94; statistically significant OR/RRs range from 0.5 to 0.7. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.44 to 1.2; statistically significant OR/RRs range from 0.44 to 0.68.

Dose Response

Of the seven studies where different intake levels were compared (6,11,12,16,17,27,37), a dose response [with P (for trend) < 0.05] was seen in four (11,16,7,37), all of which showed a decreasing risk with increasing dose of vitamin E.

Biological Plausibility

Vitamin E is an antioxidant that acts at the level of the lipid membranes. As mentioned above (see **Vitamin C**), it is

Table 5. Vitamin E[a]

Ref.	OR/RR (95% CI)	Outcome	Risk With Higher Intake	Source
		Prospective study		
6	1.0, 1.1 (0.5, 2.9), 0.8 (0.3–2.0) [p (for trend) = 0.67]	Incidence of OPE cancer	No clear trend	Vitamin E: diet and supplements
		Intervention trials		
7	RR = 0.94 (0.73–1.20)	Esophageal cancer incidence	Decreased	Multivitamin/mineral supplements (60 mg 2-ambo-α-tocopherol)
	RR = 0.84 (0.54–1.29)	Esophageal cancer mortality	Decreased	
8	RR = 0.58, (0.19–1.76)	Esophageal cancer	Decreased	β-carotene, selenium, α-tocopherol supplements (30 mg α-tocopherol), β-carotene, selenium, α-tocopherol supplements (30 mg α-tocopherol)
	RR = 0.80, (0.40–1.57)	Esophageal dysplasia/cancer	Decreased	
	RR = 0.58, (0.19–1.76)	Esophageal cancer	Decreased	
		Case-control studies		
11	1.0, 0.60, 0.51, 0.32 [p (for trend) < 0.0001]*	Esophageal cancer	Decreased*	Dietary intake of vitamin E (men)
12	1.0, 0.8, 0.8, 0.8 [p (for trend) = 0.34]	Oral and pharyngeal cancer	Decreased	Total dietary intake of vitamin E (men)
	1.0, 1.1, 0.9, 1.2, [p (for trend) = 0.83]		No clear trend	Total dietary intake of vitamin E (women)
16	1.0, 1.1 (0.8–1.5), 1.1 (0.8–1.4), 0.5 (0.3–0.7),* 0.5 (0.4–0.7)* [p (for trend) < 0.001]*	Oral/pharyngeal cancer	Decreased*	Vitamin E supplements (ORs are for increasing dos)
	1.0, 0.9 (0.6–1.2), 1.1 (0.8–1.4), 0.6 (0.4–0.8),* 0.5 (0.3–0.7)* [p (for trend) < 0.001]*		Decreased*	Vitamin E supplements (ORs are for increasing dose years)
17	1.0, 0.9, 0.6,* 0.7* [p (for trend) < 0.05]*	Esophageal cancer	Decreased*	Dietary intake of vitamin E (men)
	1.0, 1.0, 0.7, 0.8 [p (for trend) = 0.09]		Decreased	Dietary intake of vitamin E (women)
27	1.0, 0.5 (0.2–0.9),* 0.4 (0.1–0.8),* 0.7 (0.3–1.5)	Oral cancer	Decreased*	Vitamin E supplements (ORs are for increasing duration, adjusted for multivitamin, vitamin B, vitamin C intake)
	1.0, 0.7 (0.3–2.0), 0.7 (0.2–2.5), 0.7 (0.2–3.2)	Esophageal cancer	Decreased	
34	1.1 (0.6–1.8)	Oral and pharyngeal cancer	Increased	Dietary intake of vitamin E
	0.5 (0.3–0.7)*	Esophageal cancer	Decreased*	
37	1.0, 0.66 (0.46–0.94),* 0.68 (0.46–0.99),* 0.73 (0.49–1.09), 0.44 (0.28–0.71)* [p (for trend) < 0.01]	Oral and pharyngeal cancer	Decreased*	Dietary intake of vitamin E

a: ORs and RRs are adjusted for other risk factors (see Table 1). *, statistical significance.

believed to act synergistically with vitamin C, which acts in aqueous media to prevent carcinogenesis. It can block the formation of carcinogenic nitrosamines (53) and has been shown to protect cells exposed to carcinogens from chromosomal damage in vitro (57).

Total Vegetable Intake

Temporal Relationship

Of the two prospective cohort studies described in Table 1, one (6) did not show a clear trend for the association between total vegetable intake and OPE cancers and the other (5) showed a decreased risk for second primary cancers with a higher intake of vegetables before (not statistically significant) and after (statistically significant) development of the first cancer.

Consistency of Results

The OR/RR sets from 17 different studies are summarized in Table 6A. The total number of OR/RR sets is 28, with 20 showing a decreased risk (12 were statistically significant), 3 showing an increased risk (none were statistically significant), and 2 showing no clear trend with increasing intake of vegetables. The number of OR/RR sets for esophageal cancer as outcome is nine, with six showing a decreased risk (5 were statistically significant), one showing an increased risk (not statistically significant), and two showing no clear trend with increasing intake of vegetables. The number of OR/RR sets for oral and pharyngeal cancer as outcome is 11, with 9 showing a decreased risk (5 were statistically significant) and 2 showing no clear trend with increasing intake of vegetables. The number of OR/RR sets for pharyngeal cancer as outcome is two, with one showing a decreased risk (statistically significant) and the other showing an increased risk (not statistically significant). The number of OR/RR sets for oral cancer as outcome is three, with two showing a decreased risk (2 were statistically significant) and one showing an increased risk (not statistically significant).

Strength of Association

The OR/RRs from all the listed studies range from 0.14 to 1.4. Statistically significant values range from 0.14 to 0.7. Protective values range from 0.14 to 0.9. For studies with

Table 6. Vegetable Intake[a]

Ref.	OR/RR (95% CI)	Outcome	Risk With Higher Intake	Source
A: Total Vegetable Intake				
		Prospective studies		
5[b]	1.0, 0.3,* 0.6, 0.4 [*p* (for trend) = 0.10]	Development of 2nd primary cancer	Decreased	Total vegetable intake
	1.0, 0.6, 0.5, 0.3* [*p* (for trend) = 0.02]*		Decreased*	Total vegetable intake after original cancer diagnosis (follow-up data)
6	Not reported	Incidence of OPE cancer	No consistent association	Total vegetable green leafy, cruciferous vegetable intake
		Case-control studies		
9	From high to low intake: 1.0, 1.5, 1.6 [*p* (for trend) < 0.1]	Esophageal cancer	Decreased	Vegetable intake
11	1.0, 1.42, 1.11, 0.58 [*p* (for trend) = 0.029*	Esophageal cancer	No clear trend	Total fresh vegetable intake (men)
12	1.0, 1.1, 1.0, 1.0 [*p* (for trend) = 0.69	Oral and pharyngeal cancer	No clear trend	Total vegetable intake (men)
	1.0, 1.1, 0.7, 0.8 [*p* (for trend) = 0.20]		No clear trend	Total vegetable intake (women)
14	1.0, 0.49 (0.3–0.7),* 0.48 (0.3–0.8),* 0.56 (0.3–1.0)	Esophageal cancer	Decreased*	Vegetable intake
17	1.0, 0.9, 0.8, 0.8 [*p* (for trend) < 0.05]*	Esophageal cancer	Decreased*	Total vegetable intake (men)
	1.0, 1.2, 0.7, 0.9 [*p* (for trend) = 0.25]		No clear trend	Total vegetable intake (women)
19	1.0, 0.7 (0.5–1.1), 0.7 (0.4–1.3) [*p* (for trend) = 0.08]	Oral/pharyngeal cancer	Decreased	Vegetable intake excluding green vegetables
21	Hospital controls, low vs high: 0.95 (0.6–1.4)	Oral cancer	Increased	Vegetable intake
	Population controls, low vs high: 2.39 (1.4–4.0)		Decreased*	
	Hospital controls, low vs high: 0.97 (0.6–1.5)	Pharyngeal cancer	Increased	
	Population controls, low vs high: 2.65 (1.6–4.5)		Decreased*	
	Hospital controls, low vs high: 0.93 (0.6–1.4)	Esophageal cancer	Increased	
	Population controls, low vs high: 2.62 (1.5–4.4)		Decreased*	
23	1.0, 0.7, 0.8 [*p* (for trend) = 0.34]	Oral and pharyngeal cancer	Decreased	Total vegetable intake
26	From high to low intake: 1.0, 2.5 (0.9–6.7), 3.2 (1.1–9.0),* 5.3 (1.5–19.4)* [*p* (for trend) = 0.002]*	Oral (tongue) cancer	Decreased*	Vegetable intake
30	1.0, 0.9 (0.5–1.5), 1.3 (0.8–2.3), 0.6 (0.3–1.06) [*p* (for trend) = 0.05]*	Esophageal cancer	Decreased*	Total fresh vegetable intake
31	1.0, 0.6 (0.4–0.8),* 0.5 (0.4–0.7)*	Oral and pharyngeal cancer	Decreased*	Raw vegetable intake
32	1.0, 0.63 (0.37–1.08), 0.30 (0.16–0.58),* [*p* (for trend) < 0.01]	Oral and pharyngeal cancer	Decreased*	Raw vegetable intake
	1.0, 0.42 (0.25–0.72),* 0.14 (0.07–0.19),* [*p* (for trend) < 0.01]		Decreased*	Cooked vegetable intake
33	0.8 (0.4–1.4)	Oral and pharyngeal cancer	Decreased	Vegetable intake
	0.7 (0.5–0.9)*	Esophageal cancer	Decreased*	
36	1.0, 0.4 (0.3–0.6),* 0.5 (0.3–0.7),* 0.5 (0.3–0.7),*0.4 (0.3–0.6),* [*p* (for trend) < 0.01]*	Oral/pharyngeal cancer	Decreased*	Raw vegetable intake
	1.0, 0.8 (0.5–1.1), 1.0 (0.7–1.4), 0.7 (0.5–1.0), 0.5 (0.3–0.7),* [*p* (for trend) < 0.01]*		Decreased*	Cooked vegetable intake
38	1.0, 0.67 (0.36–1.23), 0.78 (0.40–1.51), [*p* (for trend) = 0.49]	Oral and pharyngeal cancer	Decreased	Vegetable intake
B: Green Vegetable Intake				
		Prospective studies		
5[b]	1.0, 0.7, 0.7, 0.6, [*p* (for trend) = 0.13]	Development of 2nd primary cancer	Decreased	Green leafy vegetable intake
6	Not reported	Incidence of OPE cancer	No consistent association	Total vegetable, green leafy, cruciferous vegetable intake
		Case-control studies		
9	From high to low intake: 1.0, 1.0, 1.3 [*p* (for trend) > 0.1]	Esophageal cancer	Decreased	Green vegetable intake
12	1.0, 0.6,*0.8,0.8 [*p* (for trend) = 0.39]	Oral and pharyngeal cancer	Decreased*	Green leafy vegetable intake (men)
	1.0, 0.9, 1.3, 0.8 [*p* (for trend) = 0.19]		No clear trend	Green leafy vegetable intake (women)

(continued)

Table 6. *(Continued)*

Ref.	OR/RR (95% CI)	Outcome	Risk With Higher Intake	Source
15	1.0, 0.6, 0.6,0.2* [*p* (for trend) = 0.0002]*	Oral and pharyngeal cancer	Decreased*	Green leafy vegetable intake (men)
	1.0, 0.4, 0.5, 0.4 [*p* (for trend) = 0.29]		Decreased	Green leafy vegetable intake (women)
17	1.0, 0.9, 0.9, 0.8 [*p* (for trend) = 0.22]	Esophageal cancer	Decreased	Green leafy vegetable intake (men)
	1.0, 1.5, 1.2, 1.1 [*p* (for trend) = 0.89]		Increased	Green leafy vegetable intake (women)
19	1.0, 0.7 (0.5–1.1), 0.7 (0.5–1.1) [*p* (for trend) = 0.06]	Oral/pharyngeal cancer	Decreased	Green leafy vegetable intake
20	1.0, 1.07 (0.52–2.20), 0.62 (0.26–1.48) [*p* (for trend) = NS	Esophageal cancer	Decreased	Green vegetable intake
22	1.0, 0.8 (0.5–1.4), 0.7 (0.4–1.4)	Oral cancer	Decreased	Green vegetable intake
24	1.0, 1.1 (0.6–1.8), 1.0 (0.5–2.0) [*p* (for trend) = NS	Oral and pharyngeal cancer	Increased	Green vegetable intake
25	1.0, 0.6 (0.4–0.9),* 0.3 (0.1–0.5)*. [*p* (for trend) < 0.01]*	Oral/pharyngeal cancer	Decreased*	Green vegetable intake
	1.0, 0.5 (0.4–0.6),* 0.2 (0.1–0.3)*. [*p* (for trend) < 0.01]*	Esophageal cancer	Decreased*	
31	1.0, 1.0 (0.7–1.3), 1.0 (0.7–1.3)	Oral and pharyngeal cancer	No change	Green yellow vegetable intake
35	1.0, 1.3 (0.5–3.4), 1.2 (0.5–3.4)	Oral and pharyngeal cancer	Increased	Green vegetable intake
39	1.0, 0.30 (0.15–0.60),* 0.37 (0.16–0.88)* [*p* (for trend) < 0.01]*	Oral and pharyngeal cancer	Decreased*	Green vegetable intake
C: Yellow–Orange Vegetable Intake				
		Prospective studies		
5[b]	1.0, 0.8, 0.8, 0.5 [*p* (for trend) = 0.10]	Development of 2nd primary cancer	Decreased	Dark yellow vegetable intake
6	1.0, 0.6, 0.5 [*p* (for trend) = 0.10]	Incidence of OPE cancer	Decreased	Yellow–orange vegetable intake
		Case-control studies		
9	From high to low intake: 1.0, 1.0, 1.7 [*p* (for trend) > 0.1]	Esophageal cancer	Decreased	Yellow vegetable intake
12	1.0, 0.9, 0.7,* 0.7 [*p* (for trend) = 0.05]*	Oral and pharyngeal cancer	Decreased*	Yellow/orange vegetable intake (men)
	1.0, 0.9, 1.2, 0.7 [*p* (for trend) = 0.40]		No clear trend	Yellow/orange vegetable intake (women)
15	1.0, 0.9, 0.9, 0.5 [*p* (for trend) = 0.10]	Oral and pharyngeal cancer	Decreased	Yellow/orange vegetable intake (men)
	1.0, 0.9,1.7, 1.6 [*p* (for trend) = 0.38]		Increased	Yellow/orange vegetable intake (women)
17	1.0, 1.0, 0.8, 0.7* [*p* (for trend) < 0.05]*	Esophageal cancer	Decreased*	Yellow/orange vegetable intake (men)
	1.0, 0.8, 0.8, 0.6* [*p* (for trend) < 0.05]*		Decreased*	Yellow/orange vegetable intake (women)
D: CruciferousVegetable Intake				
		Prospective studies		
5[b]	1.0, 0.7, 0.3,* 0.6 [*p* (for trend) = 0.10]	Development of 2nd primary cancer	Decreased*	Cruciferous vegetable intake
6	Not reported	Incidence of OPE cancer	No consistent association	Total Vegetable green leafy, cruciferous vegetable intake
		Case-control studies		
12	1.0, 1.0, 0.7, 0.6* [*p* (for trend) = 0.006]*	Oral and pharyngeal cancer	Decreased*	Cruciferous vegetable intake (men)
	1.0, 1.0, 1.8,* 0.8 [*p* (for trend) = 0.83]		Increased*	Cruciferous vegetable intake (women)
15	1.0, 0.6, 0.6, 0.5 [*p* (for trend) = 0.10]	Oral and pharyngeal cancer	Decreased	Cruciferous vegetable intake (men)
	1.0, 0.2, 0.3,* 0.2* [*p* (for trend) = 0.03]*		Decreased*	Cruciferous vegetable intake (women)
17	1.0, 0.6,* 0.8, 0.8 [*p* (for trend) = 0.51]	Esophageal cancer	Decreased*	Cruciferous vegetable intake (men)
	1.0, 1.0, 1.6, 1.1 [*p* (for trend) = 0.28]		Increased	Cruciferous vegetable intake (women)
38	1.0, 1.70 (0.99–2.93), 1.1 (0.62–2.01), [*p* (for trend) = 0.54]	Oral and pharyngeal cancer	Increased	Cruciferous vegetable intake

a: ORs and RRs are adjusted for other risk factors (see Table 1). *, statistical significance.
b: From baseline data collected on development of 1st oral/pharyngeal cancer.

esophageal cancer as outcome, the OR/RRs range from 0.38 to 1.2; statistically significant OR/RRs range from 0.38 to 0.7. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.14 to 1.1; statistically significant OR/RRs range from 0.14 to 0.6. For studies with pharyngeal cancer as outcome, the OR/RRs were 0.37 (significant) and 1.03 (not significant). For studies with oral cancer as outcome, the OR/RRs range from 0.18 to 1.05; statistically significant OR/RRs range from 0.18 to 0.31.

Dose Response

Of the 14 studies where different intake levels were compared (5,9,11,12,14,17,19,23,26,30–32,36,38), a dose response [with P (for trend) < 0.05] was seen in six (5,26,30–32,36), all of which showed a decreasing risk with increasing intake of vegetables).

Biological Plausibility

Vegetables contain a variety of micronutrients, including retinol and the antioxidants reviewed above. Other phytochemicals and fiber in vegetables are also believed to have protective properties against cancer. Many of these chemicals are believed to act synergistically with each other. Vegetables may contain these numerous protective compounds in the right combinations for anticancer activity.

Green Vegetables

Temporal Relationship

Of the two prospective cohort studies, one (6) did not show a clear trend for the association between green leafy vegetable intake and OPE cancers and the other (5) showed a decreased risk for second primary cancers with a higher intake of vegetables before (not statistically significant) development of the first cancer.

Consistency of Results

The OR/RR sets from 14 different studies are summarized in Table 6B. The total number of OR/RR sets is 18, with 12 showing a decreased risk (2 were statistically significant), 3 showing an increased risk (none were statistically significant), 1 reporting no change in risk with OR = 1, and 2 showing no clear trends with increasing intake of green vegetables. The number of OR/RR sets for esophageal cancer as outcome is five, with four showing a decreased risk (1 was statistically significant) and one showing an increased risk (not statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is 10, with 6 showing a decreased risk (4 were statistically significant), 2 showing an increased risk (none were statistically significant), 1 reporting no change in risk with OR = 1, and 2 showing no clear trends with increasing intake of green vegetables. The number of OR/RR sets for oral cancer as outcome is 1, which showed a decreased risk (not statistically significant).

Strength of Association

The OR/RRs from all listed studies range from 0.2 to 1.5. Statistically significant values range from 0.2 to 0.6. Protective values range from 0.2 to 0.9. For studies with esophageal cancer as outcome, the OR/RRs range from 0.2 to 1.3; statistically significant OR/RRs range from 0.2 to 0.5. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.2 to 1.3; statistically significant OR/RRs range from 0.2 to 0.6.

Dose Response

Of the 13 studies where different intake levels were compared (5,9,12,15,17,19,20,22,24,25,31,35,39), a dose response [with P (for trend) < 0.05] was seen in 3 (15,25,39), which showed a decreasing risk with increasing intake of green vegetables.

Biological Plausibility

Green vegetables contain a large number of micronutrients, including α-carotene, β-carotene, lutein, lycopene, xanthins, vitamin A, vitamin C, and vitamin E (65). A number of these are suspected to have anticarcinogenic potential.

Yellow-Orange Vegetables

Temporal Relationship

Both prospective cohort studies (5,6) showed a decreased risk for cancers with a higher intake of yellow-orange vegetables.

Consistency of Results

The OR/RR sets from six studies are summarized in Table 6C. Total number of OR/RR sets is nine, with seven showing a decreased risk (3 were statistically significant), one showing an increased risk (not statistically significant), and one showing no clear trends with increasing intake of yellow-orange vegetables. The number of OR/RR sets for esophageal cancer as outcome is three, all of which showed a decreased risk (2 were statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is four, with two showing a decreased risk (1 was statistically significant), one showing an increased risk (not statistically significant), and one showing no clear trend with increasing intake of yellow-orange vegetables.

Strength of Association

The OR/RRs range from 0.5 to 1.7. Statistically significant values range from 0.6 to 0.7. Protective values range from 0.5 to 0.9. For studies with esophageal cancer as outcome, the OR/RRs range from 0.6 to 1.7; statistically significant OR/RRs range from 0.6 to 0.7. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.5 to 1.7; statistically significant OR = 0.7.

Dose Response

Of the six studies where different intake levels were compared (5,6,9,12,15,17), a dose response [with *P* (for trend) < 0.05] was seen in two (12,17), which showed a decreasing risk with increasing intake of yellow-orange vegetables.

Biological Plausibility

Yellow-orange vegetables are good sources of such micronutrients as vitamin A, α-carotene, β-carotene, lycopene, β-cryptoxanthin, lutein, and astaxanthin (65). In addition, they contain a number of other components that may play a role in preventing cancers.

Cruciferous Vegetables

Temporal Relationship

Of the two prospective cohort studies, one (6) did not show a clear trend for the association between cruciferous vegetable intake and OPE cancers and the other (5) showed a decreased risk for second primary cancers with a higher intake of cruciferous vegetables before (not statistically significant) development of the first cancer.

Consistency of Results

The OR/RR sets from six studies are summarized in Table 6D. The total number of OR/RR sets is nine, with five showing a decreased risk (2 were statistically significant), two showing an increased risk (none were statistically significant), and two showing no clear trends with increasing intake of cruciferous vegetables. The number of OR/RR sets for esophageal cancer as outcome is two, with one showing a decreased risk (statistically significant) and one showing an increased risk (not statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is five, with three showing a decreased risk (2 were statistically significant) and two showing an increased risk (1 was statistically significant).

Strength of Association

The OR/RRs from all listed studies range from 0.2 to 1.8. Statistically significant values range from 0.2 to 1.8. Protective values range from 0.2 to 0.8. For studies with esophageal cancer as outcome, the OR/RRs range from 0.6 to 1.6; statistically significant OR = 0.6. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.2 to 1.8; both values are statistically significant.

Dose Response

Of the five studies where different intake levels were compared (5,12,15,17,38), a dose response [with *P* (for trend) < 0.05] was seen in two (12,15), both of which showed a decreasing risk with increasing intake of cruciferous vegetables.

Biological Plausibility

Cruciferous vegetables contain a number of components such as indoles, isothiocyanates, dithiolethiones, flavonoids, polyphenols, vitamins, fibers, and pigments with potentially protective activity against carcinogenesis (66,67).

Total Fruit Intake

Temporal Relationship

Of the two prospective cohort studies, one (6) did not show a clear trend for the association between total fruit intake and OPE cancers and the other (5) showed a decreased risk for second primary cancers with a higher intake of total fruit after (not statistically significant) development of the first cancer.

Consistency of Results

The OR/RR sets from 22 different studies are summarized in Table 7A. The total number of OR/RR sets is 33, with 24 showing a decreased risk (16 were statistically significant), 6 showing an increased risk (none were statistically significant), and 3 showing no clear trends with increasing intake of fruits. The number of OR/RR sets for esophageal cancer as outcome is 12, with 10 showing a decreased risk (9 were statistically significant) and 2 showing an increased risk (none were statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is 13, with 12 showing a decreased risk (9 were statistically significant) and 1 showing no clear trends with increasing intake of fruits. The number of OR/RR sets for pharyngeal cancer as outcome is two, both of which showed an increased risk (none were statistically significant). The number of OR/RR sets for oral cancer as outcome is three, with one showing a decreased risk (statistically significant) and two showing an increased risk (none were statistically significant).

Strength of Association

The OR/RRs from all listed studies range from 0.2 to 1.6. Statistically significant values range from 0.2 to 0.7. Protective values range from 0.2 to 0.9. For studies with esophageal cancer as outcome, the OR/RRs range from 0.29 to 1.6; statistically significant OR/RRs range from 0.29 to 0.65. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.2 to 1.1; statistically significant OR/RRs range from 0.2 to 0.6.

Dose Response

Of the 18 studies where different intake levels were compared (5,9,12,14,17,19,20,23–26,30–32,35,36,38,39), a dose response [with *P* (for trend) < 0.05] was seen in 12 (12,14,17,19,20,24–26,31,32,38,39).

Table 7. Fruit Intake[a]

Ref.	OR/RR (95% CI)	Outcome	Risk With Higher Intake	Source
A: Total Fruit Intake				
		Prospective studies		
5[b]	1.0, 1.1,1.0, 0.9 [p (for trend) = 0.32]	Development of 2nd primary cancer	No clear trend	Total fruit intake
	1.0, 0.5,1.2, 0.5 [p (for trend) = 0.24]		Decreased	Total fruit intake after original cancer diagnosis (follow-up data)
6	Not reported	Incidence of OPE cancer	No consistent association	Total fruit and citrus fruit
		Case-control studies		
9	From high to low intake: 1.0, 2.4, 2.0 [p (for trend) < 0.05]*	Esophageal cancer	Decreased*	Total fruit intake
10	Directly interviewed pairs only: 0.55 (p = 0.033)	Esophageal cancer	Decreased*	Fresh fruit or raw vegetable intake
	All pairs: 0.65 (p = 0.024)		Decreased*	
12	1.0, 0.6,* 0.4,* 0.4* [p (for trend) = 0.001*	Oral and pharyngeal cancer	Decreased*	Total fruit intake (men)
	1.0, 0.9, 0.8, 0.5* [p (for trend) = 0.01]*		Decreased*	Total fruit intake (women)
14	1.0, 0.6 (0.4–0.9),* 0.48 (0.3–0.8),* 0.33 (0.2–0.5)*	Esophageal cancer	Decreased*	Fruit intake
17	1.0, 0.6,* 0.6,* 0.6* [p (for trend) < 0.001]*	Esophageal cancer	Decreased*	Total fruit intake (men)
	1.0, 0.8, 1.0, 0.6* [p (for trend) = 0.11]		Decreased*	Total fruit intake (women)
19	1.0, 0.7 (0.5–1.2), 0.6 (0.4–0.8)*. [p (for trend) = 0.001]	Oral/pharyngeal cancer	Decreased*	Fresh fruit intake
20	1.0, 0.65 (0.30–1.38), 0.29 (0.13–0.62)* [p (for trend) < 0.001]*	Esophageal cancer	Decreased*	Total fresh fruit intake
21	Hospital controls low vs high: 0.87 (0.6–1.3)	Oral cancer	Increased	Fruit intake
	Population controls, low vs high: 0.89 (0.5–1.4)		Increased	
	Hospital controls, low vs high: 0.86 (0.6–1.3)	Pharyngeal cancer	Increased	
	Population controls, low vs high: 0.99 (0.6–1.6)		Increased	
	Hospital controls, low vs high: 0.99 (0.6–1.5)	Esophageal cancer	Increased	
	Population controls, low vs high: 1.23 (0.8–2.0)		Decreased	
23	1.0, 0.9, 1.1 [p (for trend) = 0.75]	Oral and pharyngeal cancer	No clear trend	Total fruit intake
24	1.0, 0.7 (0.4–1.3), 0.3 (0.1–0.5)* [p (for trend) < 0.001]*	Oral and pharyngeal cancer	Decreased*	Fresh fruit intake
25	1.0, 0.6 (0.4–0.8),* 0.2 (0.1–0.3)*. [p (for trend) < 0.01]*	Oral/pharyngeal cancer	Decreased*	Fruit intake
	1.0, 0.5 (0.4–0.7),* 0.3 (0.2–0.4)*. [p (for trend) < 0.01]*	Esophageal cancer	Decreased*	
26	From high to low intake: 1.0, 1.4 (0.5–3.9), 1.7 (0.7–4.0), 2.4 (0.8–7.2) [p (for trend) = 0.03]*	Oral (tongue) cancer	Decreased*	Fruit intake
30	1.0, 1.6 (0.9–2.8), 1.2 (0.7–2.1), 1.5 (0.8–2.9) [p (for trend) = 0.29]	Esophageal cancer	Increased	Fruit intake
31	1.0, 0.7 (0.5–0.99),* 0.5 (0.4–0.7)*	Oral and pharyngeal cancer	Decreased*	Fruit intake
32	1.0, 0.42 (0.25–0.73),* 0.22 (0.11–0.44),* [p (for trend) < 0.01]*	Oral and pharyngeal cancer	Decreased*	Fruit intake excluding citrus fruits
33	0.7 (0.4–1.3)	Oral and pharyngeal cancer	Decreased	Total fruit intake
	0.4 (0.3–0.6)*	Esophageal cancer	Decreased*	
35	1.0, 0.7 (0.3–1.9), 0.7 (0.3–1.6)	Oral and pharyngeal cancer	Decreased	Total fresh fruit intake
36	1.0, 0.7 (0.5–1.0), 0.7 (0.5–1.0), 0.8 (0.6–1.2), 0.7 (0.5–1.1) [p (for trend) > 0.05]	Oral/pharyngeal cancer	Decreased	Fruit intake excluding citrus fruits
38	1.0, 0.71 (0.39–1.29), 0.43 (0.21–0.89),* [p (for trend) < 0.05]*	Oral and pharyngeal cancer	Decreased*	Total fruit intake
39	1.0, 0.51 (0.22–1.21), 0.34 (0.13–0.87)* [p (for trend) < 0.05]*	Oral and pharyngeal cancer	Decreased*	Total fruit intake
B: Citrus Fruit Intake				
		Prospective studies		
5	1.0, 0.9, 0.7, 0.8 [p (for trend) = 0.31]	Development of 2nd primary cancer	Decreased	Citrus fruit intake
6	Not reported	Incidence of OPE cancer	No consistent association	Total fruit and citrus fruit

(continued)

Table 7. *(Continued)*

Ref.	OR/RR (95% CI)	Outcome	Risk With Higher Intake	Source
		Case-control studies		
11	1.0, 1.14, 0.76, 0.33 [*p* (for trend) = 0.004]*	Esophageal cancer	Decreased*	Citrus fruit intake (men)
12	1.0, 0.7,0.5,*0.5* [*p* (for trend) < 0.001]*	Oral and pharyngeal cancer	Decreased*	Citrus fruit intake (men)
	1.0, 0.9, 0.8, 0.4* [*p* (for trend) = 0.008]*		Decreased*	Citrus fruit intake (women)
15	1.0, 0.7,0.7, 0.6 [*p* (for trend) = 0.19]	Oral and pharyngeal cancer	Decreased	Citrus fruit intake (men)
	1.0, 1.9,2.3, 0.7 [*p* (for trend) = 0.92]		Increased	Citrus fruit intake (women)
17	1.0, 0.6,* 0.5,* 0.5* [*p* (for trend) < 0.001]*	Esophageal cancer	Decreased*	Citrus (oranges/tangerines) fruit intake (men)
	1.0, 0.7, 0.6, 0.6* [*p* (for trend) < 0.05]*		Decreased*	Citrus (oranges/tangerines) fruit intake (women)
22	1.0, 0.5 (0.3–0.8),* 0.5 (0.3–0.9)* [*p* (for trend) = 0.03]*	Oral cancer	Decreased*	Citrus fruit intake
23	1.0, 0.7, 1.0	Oral and pharyngeal cancer	Decreased	Citrus fruit intake
32	1.0, 0.34 (0.20–0.60),* 0.38 (0.20–0.73),* [*p* (for trend) < 0.01]*	Oral and pharyngeal cancer	Decreased*	Citrus fruit intake
36	1.0, 0.8 (0.5–1.1), 0.7 (0.5–1.0), 0.6 (0.4–0.8),* 0.5 (0.3–0.7)* [*p* (for trend) < 0.01]*	Oral/pharyngeal cancer	Decreased*	Citrus fruit intake
38	1.0, 0.85 (0.47–1.55), 0.78 (0.42–1.45), [*p* (for trend) = 0.44	Oral and pharyngeal cancer	Decreased	Citrus fruit intake
39	1.0, 0.83 (0.43–1.63), 0.72 (0.30–1.71) [*p* (for trend) = NS]	Oral and pharyngeal cancer	Decreased	Citrus fruit intake
C: Dark Yellow Fruit Intake				
		Prospective study		
5[b]	1.0, 1.0, 0.9,1.3 [*p* (for trend) = 0.29]	Development of 2nd primary cancer	No clear trend	Dark-yellow fruit intake
		Case-control studies		
12	1.0, 0.8, 0.6,* 0.5* [*p* (for trend) < 0.001]*	Oral and pharyngeal cancer	Decreased*	Dark-yellow fruit intake (men)
	1.0, 0.8, 0.5,* 0.6 [*p* (for trend) = 0.014]*		Decreased*	Dark yellow fruit intake (women)
15	1.0, 1.0, 0.9, 0.7 [*p* (for trend) = 0.39]	Oral and pharyngeal cancer	Decreased	Dark-yellow fruit intake (men)
	1.0, 0.6, 0.5, 0.6 [*p* (for trend) = 0.43]		Decreased	Dark-yellow fruit intake (women)

a: ORs and RRs are adjusted for other risk factors (see Table 1). *, statistical significance.
b: From baseline data collected on development of 1st oral/pharyngeal cancer.

Biological Plausibility

Similar to vegetables, fruits are also nutrient-dense foods and may decrease cancer risk by providing numerous micronutrients that individually, or more likely in combination, act to prevent carcinogenesis. Also, fruits are generally eaten raw; therefore, there is less potential loss of micronutrients from fruits as occurs during cooking or processing of foods.

Citrus Fruits

Temporal Relationship

Of the two prospective cohort studies, one (6) did not show a clear trend for the association between citrus fruit intake and OPE cancers and the other (5) showed a decreased risk for second primary cancers with a higher intake of citrus fruit before (not statistically significant) development of the first cancer.

Consistency of Results

The OR/RR sets from 12 different studies are summarized in Table 7B. The total number of OR/RR sets is 15, with 13 showing a decreased risk (8 were statistically significant), 1 showing an increased risk (not statistically significant), and 2 showing no clear trends with increasing intake of citrus fruits. The number of OR/RR sets for esophageal cancer as outcome is 3, all of which showed a decreased risk (3 were statistically significant). The number of OR/RR sets for oral and pharyngeal cancer as outcome is nine, with eight showing a decreased risk (4 were statistically significant) and one showing an increased risk (not statistically significant). The number of OR/RR sets for oral cancer as outcome is one, which showed a decreased risk (statistically significant).

Strength of Association

The OR/RRs from all listed studies range from 0.33 to 2.3. Statistically significant values range from 0.34 to 0.6. Protective values range from 0.33 to 0.9. For studies with esophageal cancer as outcome, the OR/RRs range from 0.33 to 1.14; statistically significant OR/RRs range from 0.5 to 0.6. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.34 to 2.3; statistically significant OR/RRs range from 0.34 to 0.6.

Dose Response

Of 11 studies where different intake levels were compared (5,11,12,15,17,22,23,32,36,38,39), a dose response [with *P*

(for trend) < 0.05] was seen in 6 (11,12,17,22,32,36), all of which showed a decreasing risk with increasing intake of citrus fruits.

Biological Plausibility

Citrus fruits are rich sources of various micronutrients, including the antioxidants vitamin C and β-carotene. They also contain terpenes (e.g., limonene, perillyl alcohol, geraniol, and farnesol), which are believed to influence cell cycle progression and induce apoptosis (65).

Dark Yellow Fruits

Temporal Relationship

The prospective cohort study (5) did not show a clear trend for the association between dark yellow fruit intake and OPE cancers.

Consistency of Results

The OR/RR sets from three studies are summarized in Table 7C. The total number of OR/RR sets is five, with four showing a decreased risk (2 were statistically significant), none showing an increased risk, and one showing no clear trends with increasing intake of dark yellow fruit. The number of OR/RR sets for oral and pharyngeal cancer as outcome is four, all of which showed a decreased risk (2 were statistically significant).

Strength of Association

The OR/RRs range from 0.5 to 1.3. Statistically significant values range from 0.5 to 0.6. Protective values range from 0.5 to 0.9. For studies with oral/pharyngeal cancer as outcome, the OR/RRs range from 0.5 to 1.0; statistically significant OR/RRs range from 0.5 to 0.6.

Dose Response

Of the three studies where different intake levels were compared (5,12,15), a dose response was seen in one study (12), which showed a decreasing risk with increasing intake of yellow fruits.

Biological Plausibility

Information on biological plausibility is the same as for yellow-orange vegetables.

Discussion

Carotene, vitamin C, and vitamin E seem to satisfy the criteria of causal assumption; however, the role of confounding by other components in the diet cannot be ruled out. Most of the studies reviewed did not control for the effect of intake of other known micronutrients. The animal studies conducted using β-carotene and vitamin E (42,43) and the in vitro studies of vitamin C (55) provide evidence of their protective effect even when used alone, and it is likely that they do have a protective role in humans. However, none of the epidemiological studies reviewed, including the intervention trials, have examined the effect of any individual vitamin in isolation. Studies on the blood levels of micronutrients in high-risk populations mentioned above have found deficiencies of multiple micronutrients. Therefore, it is not possible to point to one single nutrient as being responsible for the protective effect; rather, it is more likely that all nutrients play a role. The mechanism of action of these vitamins suggests a synergistic role.

The role of vitamin A in OPE cancer development is not clear, inasmuch as the evidence is conflicting. Very high doses of vitamin A, as well as a deficiency of vitamin A, are known to have adverse effects on human epithelial cells. It may be that an excess and a deficiency of vitamin A are risk factors for oral cancer and that an intermediate optimum level is protective. The studies reviewed have been conducted in different populations, and the average intake of vitamin A in these populations may differ quite substantially. This may explain why different studies found conflicting results. However, because the amount of vitamin A ingested by the study subjects was not reported in the publications, it was not possible to confirm this hypothesis.

Ecological studies have found very high incidence of upper digestive tract cancers, in Iran (58) and Transkei and Ciskei (59), South Africa, where consumption of fruits and vegetables is very low.

In this review of prospective and case-control studies, vegetables and fruits satisfy the criteria for causal assumption in decreasing oral/pharyngeal/esophageal cancer risk. The possible confounders, such as age, gender, tobacco, alcohol, socioeconomic status, race, education, occupation, residence, birthplace, tea drinking, inadequate dentition, total calorie intake, and intake of other foods, such as meat, milk, cheese, and bread type, have been adjusted for in one or more of the studies reviewed (Table 1).

Total vegetable intake, green vegetable intake, cruciferous vegetable intake, yellow vegetable intake, total fruit intake, and citrus fruit intake have shown strong and consistent results. The associations for fruit intake have been somewhat stronger than that for vegetable intake. This may be due to the fact that fruits are not cooked; therefore, there is no loss of nutrients as occurs when vegetables are cooked. When intake of raw vegetables and cooked vegetables was analyzed separately (Table 6A) (36), raw vegetables were found to be more protective.

Because fruits are relatively expensive in most places, increased consumption may reflect higher socioeconomic status. However, studies that have controlled for this variable (20,24) and education as a proxy for socioeconomic status (17,24,25,33,35,36,38,39) have still found a protective effect of fruit consumption.

The results suggest that increased intake of dark yellow fruits is protective. The high nutrient content of dark yellow fruits, including carotene and vitamin C, would support this

suggestion. However, this association has been studied in only three of the studies (Table 7C): the prospective cohort study did not find any association, and the two case-control studies found a decreased risk; however, neither of the case-control studies had controlled for socioeconomic status.

This research points to recommending high intake of fruits and vegetables and promoting methods of cooking vegetables that minimize loss of nutrients. The intervention trials (7,8) suggest that multivitamin supplements containing carotene, vitamin C, and vitamin E, along with other micronutrients, may be beneficial, especially in populations with inadequate consumption of fruits and vegetables. However, where availability is not a problem, supplements should not be used as a substitute for fruit and vegetable intake, inasmuch as it is likely that other beneficial nutrients are contained in these foods, which may act in synergy with the above-mentioned vitamins in preventing cancers of the upper digestive tract.

Conclusion

On the basis of the findings from the listed studies, there is enough evidence to point to a preventive role of vegetable intake, including green vegetables, cruciferous vegetables, and yellow vegetables, total fruit intake, and citrus fruit intake in oral, pharyngeal, and esophageal cancer development. Yellow fruits are likely to be protective. Carotene, vitamin C, and vitamin E are protective, most likely in combination with each other and other micronutrients. The role of vitamin A is not clear because of conflicting findings in the studies reviewed.

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