Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships:

8B. Vitamin C and Cancer

December 1991

By
Howerde E. Sauberlich, Ph.D.

Prepared for
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20204

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Life Sciences Research Office
Federation of American Societies
For Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20814
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon literature reviews and the scientific analyses by knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with the provisions of Task Order #9 of Contract No. 223-88-2124. Potential authors and reviewing consultants were identified by the LSRO based on their qualifications, experience, and freedom from conflict of interest, with due consideration for balance and breadth in appropriate disciplines. The author and reviewing consultants were selected with the concurrence of the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB).

On March 14, 1991, the FDA requested submission of scientific data and information on the ten specific topics for which health claims might be made (Federal Register 56:12932–12933). The scientific data and information provided in response to this request were considered by LSRO in preparing this report. Copies of the submitted materials are available for public inspection at the Dockets Management Branch, FDA (Docket No. 91N–0101). Copies of documents cited in this report are available for public inspection at LSRO, FASEB.

Howerde E. Sauberlich, Ph.D., Professor and Director, Division of Experimental Nutrition, Department of Nutritional Science, University of Alabama, Birmingham, AL, should be cited as the author of this report. The LSRO acknowledges the efforts of Howerde E. Sauberlich, Ph.D. and also the critical assistance of Joachim G. Liehr, Ph.D., Professor, Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX, and Steven R. Tannenbaum, Ph.D., Professor of Chemistry and Toxicology, Division of Toxicology and Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, who reviewed several drafts of the manuscript. The appendix tables were prepared by the LSRO staff and author and were critically reviewed by the author and reviewers. Subsequently the draft report and tables were revised by the author, edited by the LSRO scientific staff, and received final concurrence from the author and reviewing consultants.

The evaluation of scientific literature, data, and information submitted to the LSRO was made by the author, reviewers, and the LSRO independently of FDA or any other group, governmental or non-governmental. The author and LSRO accept responsibility for the accuracy of the report conclusions and its appendix table(s). This final report was reviewed and approved by members of the LSRO Advisory Committee under authority delegated by the Federation Board. The LSRO Advisory Committee members who reviewed this report were free of conflicts of interest in regard to the subject matter under policies established by the Federation. Upon completion of these review procedures, the report was approved by the Executive Director, FASEB, and transmitted to FDA.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

[Signature]
December 31, 1991
Date
Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
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I. INTRODUCTION

This evaluation of the relationship of vitamin C with cancer will review reports of human studies published since 1987. Occasional reference will be made to those reviews that have considered the vitamin C and cancer literature prior to 1988 (Block and Menkes, 1989; Stähelin et al., 1987, 1989; Ziegler, 1986). The rationale for the 1988 cutoff was that information prior to 1988 on vitamin C and cancer was considered in the following benchmark references: The Surgeon General's Report on Nutrition and Health (U.S. Department of Health and Human Services, 1988); Diet and Health: Implications for Reducing Chronic Disease Risk (National Research Council, 1989a); Recommended Dietary Allowances, 10th ed., (National Research Council, 1989b), Nutrition and Your Health: Dietary Guidelines for Americans (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 1990), Healthy People 2000: National Health Promotion and Disease Prevention Objectives (U.S. Department of Health and Human Services, 1991).

A. BENCHMARK CONCLUSIONS

In 1988, a report of the Surgeon General (U.S. Department of Health and Human Services, 1988) concluded that human studies did show a protective association between foods containing vitamin C and cancers of the esophagus, stomach, and cervix. However, while many studies supported a role of vitamin C in reducing risk of various cancers, no wholly consistent view of the role of vitamin C in human cancers had been defined at that time. The National Research Council's Diet and Health report (1989a) concluded that epidemiological studies did suggest vitamin C-containing foods such as citrus fruits and vegetables may offer protection against stomach cancer, the evidence linking vitamin C or foods containing vitamin C with other cancers was more limited and less consistent. However, the report did note that animal investigations had shown protective effects of vitamin C against nitrosamine-induced stomach cancer. The Diet and Health report (National Research Council, 1989a) also pointed out that the association of vitamin C and various cancers was indirect, in that evidence was primarily from epidemiological studies concerning foods known to contain high or low levels of vitamin C rather than measured levels of vitamin C intake.

The Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans (U.S. Department of Health and Human Services, 1990) has provided two guidelines to ensure receiving the Recommended Dietary Allowances (RDA) for vitamin C: (a) eat a variety of foods and (b) choose a diet with plenty of vegetables, fruits, and grain products. Although comments were provided regarding diet and hypertension, heart disease, diabetes, and obesity, only a passing mention was given to cancer and diet in the context of fat intake.

Attainment of the RDA for vitamin C of 60 mg/d for adults can be readily accomplished with a diet containing fresh fruits, vegetables, and citrus juice (e.g., cooked fresh broccoli, peppers, Brussels sprouts, carrots, orange juice, strawberries, tomato, cantaloupe, etc.) (Block and Sorenson, 1987). Intakes of 100–200 mg of vitamin C are commonly observed in dietary intake surveys. However, inadequate intakes often due to poor food choices or specific food aversions are also frequently encountered. The Joint Nutrition Monitoring and Evaluation Committee expressed concern about the adequacy of vitamin C, among other nutrients, in the diets of many Americans (Block, 1991b; Patterson et al., 1990). The NHANES II survey, using 24-hour dietary recall data, estimated that 45 percent of the population had no servings of fruit or juice, and 22 percent had no servings of a vegetable on the recall day (Patterson et al., 1990).
B. VITAMIN C: METABOLISM

Vitamin C present in foods appears to be readily available and absorbed (Sauberlich, 1985). Intakes up to 100 mg/d of ascorbic acid are 80 to 90 percent absorbed by an active transport system. However, with intakes above 500 mg, efficiency of absorption of the vitamin rapidly declines. Vitamin C is metabolized to oxalate, 2,3-diketogulonic acid, and several other known metabolites which are excreted in the urine. Excess intakes of the vitamin are excreted unchanged.

Intakes of ascorbic acid of up to 1 g/d are well tolerated (Rivers, 1989). Occasionally, intakes above this may be associated with nausea and diarrhea. However, intakes of 4 g/d of ascorbic acid were used in a long-term intervention trial on rectal polyps without adverse effects. Ingestion of high doses of vitamin C should probably be avoided by patients on anticoagulant therapy, with renal impairment, recurrent renal stone formation, or disposed to chronic hemochromatosis.

The average adult has a body pool of vitamin C of 1.2–2.0 g that may be maintained with 75 mg/d of ascorbic acid. Approximately 140 mg/d of ascorbic acid will saturate the total body pool of vitamin C (Sauberlich, 1990). The vitamin is widely distributed throughout the body with concentrations ranging considerably among tissues. The highest concentrations are in the pituitary gland, leukocytes, liver, and brain. The major portion of the body vitamin C pool is located in the skeletal muscle, liver, and brain (Sauberlich, 1990).

C. VITAMIN C: FUNCTIONS

Although the essentiality of vitamin C for humans to prevent scurvy has long been recognized, the biochemical functions of the vitamin have been not been fully elucidated. It is now recognized that the vitamin has diverse roles in the body besides its role in collagen synthesis. Various dioxygenases and monooxygenases are stimulated by ascorbic acid. Thus, for example, collagen synthesis is dependent upon the action of prolyl-4-hydroxylase, prolyl-3-hydroxylase, and lysyl hydroxylase.

A prime function of vitamin C is that of an antioxidant (Padh, 1991). As an antioxidant, vitamin C can also serve as an effective free-radical scavenger to protect cells from damage by oxidants. It is in this capacity that vitamin C may provide protection against the influence of potential carcinogens. Vitamin C can inhibit nitrosation, particularly in the stomach, and thereby can serve as a blocking agent for the formation of potentially carcinogenic N-nitroso compounds (Schorah et al., 1991; Sobala et al., 1991; Tannenbaum, 1991). Hence, vitamin C could have a protective role against stomach cancer. The vitamin appears to be excreted into the gastric lumen which may enhance its protective capability. Overall, it has been suggested that vitamin C plays a role in maintaining the integrity of the intracellular matrix and enhancement of the immune system.
II. ISSUES IN STUDY SELECTION AND INTERPRETATION

A. INCLUSION CRITERIA

The cancer studies included in this report were restricted primarily to case-control and prospective studies published since 1987. As seen in Appendix Table 8, the studies reviewed were presented by cancer site which included breast, head and neck, lung, stomach, pancreas, colon and rectum, prostate, cervix, and bladder. Studies not designed specifically to investigate the association between vitamin C and cancer but which contained sufficient information relevant to this issue were included in the review. Human cancer studies that did not contain vitamin C-related data were omitted from this report.

The studies selected contained a component on diet or on dietary intake of specific nutrients (occasionally including non-nutrients) and an association with a form of cancer. The studies considered had a substantial number of subjects that could provide meaningful information for application to a larger population. Single case-type reports were not considered. Foreign studies and reports on ethnic or racial populations were included to indicate the possible effects of different cultural practices, environments, and dietary habits on the occurrence of cancer.

The cancer cases had to be properly diagnosed and matched with appropriate controls. Unfortunately, only a few studies reported on biochemical parameters associated with vitamin C that could be utilized to establish nutritional status and nutrient intakes of the vitamin. Studies with detailed dietary intake data derived from extensive food-frequency questionnaires containing specific food-intake habits, food frequency, and accurate portion size estimations were emphasized; however, it was necessary to consider studies that provided only general data on dietary habits based on the frequency of consumption of selected food groups (e.g., citrus fruits, fruit juices, vegetables, etc.). In some instances, only frequency of consumption of selected food groups was reported. Studies in which the data collected could not supply an accurate estimate of the intake of individual nutrients, such as vitamin C or carotene, were of limited use and provided only putative unsubstantiated evidence of an association.

B. TYPES OF STUDIES REVIEWED

Investigations of the possible relationship between diet and the etiology of cancer have used (a) correlational studies, (b) case-control studies, (c) prospective cohort studies, and (d) intervention trials (Vogel and McPherson, 1989). Each of these approaches has weaknesses or limitations.

Descriptive and correlational studies are useful for generation of hypotheses that may be examined with intervention trials; however, they provide little direct evidence as to the existence of an etiologic relationship between a particular dietary component, such as vitamin C, and the occurrence of cancer. Case-control studies are limited in their ability to obtain accurate dietary intake data by the reliance on retrospective food-frequency questionnaires and interviews. In many cases, the reference period for the dietary data collection extends over a long period of time. Yet, despite investigators' attempts to define reference periods that are relevant to the events associated with the initiation of the cancer, those events may be associated with the diet consumed over 10 years before the onset of the disease.

The validity of prospective cohort studies and intervention trials depends on a subject pool with a wide range of nutrient intakes (e.g., vitamin C). An association between an individual nutrient and cancer
risk may not be discernible when there is relative homogeneity of the diets of the population studied. Thus, if the vitamin C intake and status were excellent, any protective effect of this vitamin on cancer would not be seen. Similarly, if the vitamin C status was universally poor, no protective effect would be identified. This latter population could be appropriate for an intervention trial. Intervention trials are further hampered by problems of noncompliance and with changes in dietary habits and practices that might occur during the study. Additional concerns about prospective studies and intervention trials are expense and time required.

C. METHODOLOGICAL CONSIDERATIONS

Each study included in this report was evaluated as to adequacy of experimental design. Particular consideration was given to the length of study, adequacy of sample size, use of suitable controls, and appropriateness of methodology. Since the majority of the studies considered were case-control investigations, of particular concern were the adequacy and reliability of the dietary intake information (Hartman, 1990; Mertz, 1991; National Research Council, 1981). Unfortunately, a number of the studies reviewed had inadequate dietary intake information so that only qualified evaluations were possible.

Many of the studies reviewed were not designed to investigate vitamin C per se, but were an attempt to obtain information on general food intakes or frequency of intakes of selected representative food items or food groups. For some studies, vitamin C intakes were estimated from recorded portions of individual foods and adjusted for portion sizes. The adequacy of dietary intake data is dependent on the extensiveness and appropriateness of the items on the food-frequency questionnaire. Unfortunately, even when data are obtained with the use of extended diet records, food intakes may be over- or underestimated (Hartman et al., 1990; Mertz et al., 1991; National Research Council, 1981).

Additional concerns in the assessment of nutrient intakes, especially in studies that rely on retrospective data, are changing food consumption patterns and modifications in the availability of specific food items. For example, for the U.S. adult population, the consumption of 15 food items accounted for over 80 percent of the vitamin C consumed in the diet (Block and Sorensen, 1987). In fact, 6 food items contributed 60 percent of the vitamin C in the diet. Orange juice alone provided approximately 25 percent of the vitamin C in the diet. However, among the lower income populations, vitamin C intake patterns were considerably lower. Consequently, demographics, cultural practices, and seasonal variations in food availability were considered as important variables to be considered in the evaluation of these studies.

Dietary intake data provide no direct measurement of nutritional status or status for a given nutrient. However, poor food intakes may provide presumptive evidence of poor nutritional status. The reverse may be true if the nutrient intakes meet certain dietary criteria. However, factors seldom considered in the collection of dietary intake data include such confounding factors as nutrient interactions, bioavailability of nutrients, individual differences in nutrient requirements or changing food usage and patterns with time. Hence, considerable caution needs to be used in the interpretation of dietary intake data.

Frequently, other nutrients, such as carotenoids and folate, are obtained from the same foods that provide vitamin C. With only dietary data, one cannot be entirely certain that an observed protective effect was due to vitamin C alone or to a combination of factors. Vitamin C and vitamin E have been postulated to counteract, simultaneously, tumor initiation and promotion through their synergistic properties against lipid peroxidation (Sies, 1989; Stähelin, 1987). In this context, vitamin E protects
the lipid-soluble phase, and vitamin C interacts at the interface and in the water-soluble compartments.

An important consideration in drawing conclusions about the vitamin C and cancer relationship was the weight of evidence supplied by the number of studies conducted which focused on a specific type of cancer. Factors considered included consistency of findings among numerous studies of the same organ, the direction and strength of the effect, the generalizability of the effects across ethnic and racial groups, cultures, locations, and how the effects were reported (e.g., relative risks, odds ratios or correlations) and their significance.

Some reports were weakened by the limited amount of dietary information provided or by the methodology employed. Greater emphasis and reliance were placed on those epidemiology studies that made a concerted effort to obtain adequate and reliable dietary intake information, particularly with respect to vitamin C and associated nutrients (e.g., β-carotene, retinol, vitamin E). Whether or not statistical adjustments were made for such potentially confounding variables as occupation, smoking, alcohol use, age, sex, and demographic histories also influenced the interpretation and validity of the studies reviewed.

The general nutritional status of the population pool from which cases and controls were drawn was considered in weighting the evidence from a given study. In those populations that are well-supplied with vitamin C, any protective effect against cancer would already have occurred and thus any impact of the vitamin on a cancer would be masked (Block and Sorenson, 1987); however, the reverse could be true in a population with a marginal vitamin C status. Thus, if a high-risk population was studied where the subject pool may have a very low intake of vitamin C, negative results may be observed that cannot be interpreted with respect to a protective effect of ascorbic acid. Conversely, if all of the cases and controls were highly nourished with respect to vitamin C, the effect of "low" levels of vitamin C may not reveal an increased risk. The low levels under these conditions may have already provided optimum protection. Unfortunately, biochemical information, such as plasma ascorbate concentrations, was seldom available to provide a more direct confirmation of the vitamin C nutritional status. A greater emphasis was placed on those reports where biochemical data were available.

Intervention trials with vitamin C could have provided definitive information as to the protective effects of the vitamin on cancer risk. Unfortunately, only two small intervention trials, with design deficiencies, were reported during the review time period.
III. VITAMIN C AND HUMAN CANCER

A. BREAST CANCER

While both epidemiological and animal studies have suggested an association of high fat intake with increased risk of breast cancer (Willett, 1989), there was no evidence noted from these studies of a link between vitamin C and breast cancer. Toniolo et al. (1989), for instance, compared 250 cases of women with breast cancer with 499 community-based control women in Vercelli, Italy. Nutrient intakes were calculated from information obtained from a dietary questionnaire modified to include foods indigenous to that section of Italy. The study revealed no evidence of an association of vitamin C intake with breast cancer. However, a reduced risk of breast cancer was associated with a reduced consumption of fat, particularly of animal fat and saturated fat.

In a case–control study from Athens, Greece, Katsuyanni et al. (1988) compared 118 patients with histologically confirmed breast cancer to 115 hospital–based control patients with orthopedic disorders selected from a different hospital. Over a period of 12 months, all subjects completed a 120–item food–frequency questionnaire referenced to the period prior to the onset of their diseases. The calculated mean intakes of vitamin C were similar for both cases and controls (133 mg and 138 mg/d, respectively). No evidence was found of an association between vitamin C intake and the incidence of breast cancer. When adjusted for calorie intake, an increased intake of vitamin A was associated with a decreased risk of breast cancer. The study had weaknesses in the nutrient intake procedures and in the appropriateness of the controls used.

Recently, Howe and collaborators (1990) performed a meta–analysis of 12 case–control studies of diet and breast cancer. Original individual data records for all studies were used. Nine of the studies provided data on vitamin C. Overall, these studies were conducted in populations with very different breast cancer risks and dietary habits. The only U.S. population included in the analysis was a comparison of Japanese Hawaiians (183 cases, 183 population controls, 183 hospital controls) with a group of white Hawaiians (161 cases, 161 population controls, 161 hospital controls).

The meta–analysis, which included a total of 4437 cases of breast cancer, 4341 population controls, and 1754 hospital controls, demonstrated a consistent protective effect for a number of markers of fruit and vegetable intake. Of importance was the observation that vitamin C intake had the most consistent and statistically significant inverse association with breast cancer risk (RR = 0.69, for highest versus lowest quintile of vitamin C intake; p < 0.0001). The highest quintile represented an intake of 300 mg/d of vitamin C. Although the effects were less than that observed for vitamin C, dietary fiber and β-carotene also showed an inverse relationship with risk. In contrast, an increase in intake of saturated fat was associated with a significant increase in the risk for breast cancer (RR = 1.00 to 1.46; p = 0.0002 for trend). The findings of Howe et al. (1990) emphasize the need for further investigation of the role of diet in the control of breast cancer.

B. ESOPHAGEAL AND ORAL CANCERS

Rates of esophageal cancer vary more than 500–fold among countries, with particularly high rates in males in parts of Africa, Asia, Iran, and the Soviet Union (Ghadirian et al., 1988). Esophageal cancer has been found to be strongly associated with the consumption of alcohol and the use of tobacco and is more likely to occur in males than females. Several reviews have examined earlier (pre–1987) studies on the relationship of diet with oral cancer (Block, 1991a; Block and Menkes, 1989).
Brown et al. (1988) investigated the problem in South Carolina where the incidence of esophageal cancer among the black male population is markedly above the national rates. In this case–control study 207 cases of esophageal cancer (159 black, 48 white) and 422 control subjects (324 black, 98 white) were interviewed. All subjects were from eight coastal counties of South Carolina. The study consisted of two components. One part was a hospital–based incidence study that enrolled patients during the period of 1982–1984. The second part was a next-of-kin mortality study that covered deaths from esophageal cancer during 1977–1981. For the incidence study, two control patients per case were identified through admission records at the same hospital in the same time period. The controls were similar to the patients with respect to age and race. For the mortality study, two control subjects for each case were selected that were matched for race, age, county of residence, and year of death. Healthy population–based controls were not used in either phase. The 65–item dietary questionnaire used placed an emphasis on citrus fruits and juices (oranges, grapefruit, orange juice, grapefruit juice, and lemonade).

Tobacco and alcohol were found to be major determinants of esophageal cancer risk. However, the dietary questionnaire information indicated that increased risk also existed with a low intake of fresh fruits. After adjustment for smoking and drinking, the odds ratio (OR) for vitamin C for subjects with the highest intake was approximately one–half the OR for subjects with the lowest intake (p< 0.01 for trend). A similar effect was observed in subjects with the highest intakes of fiber. Approximately a twofold increase in risk was seen for subjects with the highest intakes of retinol compared with the lowest intake of the vitamin (primarily related to intakes of liver). The frequency of intake of vegetables and of β–carotene–rich fruits was not significantly associated with esophageal cancer risk.

Esophageal cancer is considered the second leading cause of death from cancer in China. Li et al. (1989) conducted a case–control study in Linxian, a rural county in north central China with an exceedingly high mortality rate from esophageal cancer. The study involved interviews with 758 male and 486 female cases of esophageal cancer and 1314 population–based controls (789 males, 525 females). Dietary information was obtained with the use of questionnaires administered by trained interviewers. Seventy–two food items common to the Linxian diet were included in the questionnaire.

The results indicated little or no association with fresh fruit consumption. However, the overall consumption of fresh fruits was low. Seventy–seven percent of the esophageal cancer patients and controls either never consumed fresh fruits or consumed them fewer than 35 times per year. Even the highest quartile of intake of fresh fruits appeared unsatisfactory to meet accepted criteria of an adequate diet. Of note, a high percentage of the Linxian population had deficiencies of many vitamins, including vitamin C. Despite the large patient population studied, the cause of the high incidence of esophageal cancer in Linxian remains undetermined. It may relate to unknown environmental factors or a genetic component.

Subsequently, Guo et al. (1990) reported on a broader study of diet and esophageal cancer mortality that was based on a 65–county nutrition survey conducted in the fall of 1983 in China. The counties were selected on the basis of their observed cancer mortality rates. Within this population, annual cumulative mortality rates from esophageal cancer ranged from 0.4 to 153 per 1000 population among the males and 0 to 99.8 per 1000 among the females. From each county, 100 persons were selected with a balance in age and sex. Each person was administered a food–frequency questionnaire that provided information on intakes of fruits, green vegetables, moldy pickled vegetables, other foods, alcohol, and smoking. Blood specimens were obtained for the measurement of plasma vitamin C, retinol, β–carotene, α–tocopherol, and other nutrients.

Data analysis revealed that the esophageal cancer mortality rates between counties had a strong inverse association with plasma vitamin C and fruit consumption in both sexes. The standardized regression coefficients between county esophageal cancer mortality rates and vitamin C were ~0.36
for males and -0.31 for females. Correlations between esophageal cancer mortality and fruit intake were -0.37 for males and -0.37 for females. Esophageal cancer mortality rates were 3.3 times (males) and 2.6 times (females) higher in counties with the lowest plasma vitamin C levels when compared with the highest quartile levels. Mean plasma concentrations of ascorbic acid by quartile were 0.53, 0.84, 1.17, and 1.63 mg/dL among males and 0.68, 1.07, 1.38, and 1.95 mg/dL among females. These plasma levels of ascorbic acid appear unusually high in view of the low frequency of fruit intake. Cross-classification of the cancer rates by vitamin C level and fruit intake revealed separate effects.

Although the study suggests that low levels of intake of vitamin C and fruit may be involved in an increased risk of esophageal cancer, other factors may be involved as well. Included are the intakes of moldy pickled vegetables, wheat consumption, low intakes of selenium, riboflavin, and fluids. Information was not available on the dietary practices or other environmental factors possibly affecting individual esophageal cancer patients. No case-control comparisons were reported.

Tuyns et al. (1987a) reported on a case-control study conducted in the Calvados region of France where a high mortality rate for esophageal cancer occurs among the male population. The study considered 704 male and 39 female cases of esophageal cancer compared with a control group of 922 males and 1053 females from the same region. The results presented related primarily to the males studied. From a 40-item diet questionnaire, the frequency of consumption per week of each item and an estimate of the portion size were obtained. The daily intakes of nutrients were computed from these data with the use of food composition tables. For each nutrient, relative risks were derived for heavy and moderate consumers versus light consumers. Adjustments were made for alcohol and tobacco use, age, and residential area.

High intakes of several vitamins, as calculated, were associated with a reduction of risk of esophageal cancer. The relative risks were significantly lower with high intakes of vitamins C, E, and niacin. However, high intakes of retinol were associated with an increased risk, while carotene decreased the risk. In view of the possible errors in the estimation of retinol intakes, the investigators suggested that the risk associated with retinol should be disregarded. Use of vegetable oils decreased the risk while butter increased the risk.

High intakes of citrus fruits and vegetables were associated with a reduced risk. While citrus fruits serve as a rich source of vitamin C, they provide little carotene or vitamin E. The protective effect of vegetable oils may have been associated with their significant vitamin E content. Although certain foods appeared to provide protective effects against esophageal cancer, high alcohol consumption is largely responsible for the high frequency of this cancer in the Calvados area of France.

Incidence rates for oral cancer are high in certain areas of the world, such as in parts of India and France and metropolitan areas of Brazil. Franco et al. (1989) conducted a case-control study of potential risk factors for oral cancer in Brazil. Dietary information, as well as health and demographic characteristics were obtained from interviews with 232 cases of oral cancer and 464 hospital-based controls. The dietary habits were based on past consumption frequency for only 20 food items.

Of the factors studied, tobacco use and alcohol consumption were the strongest risk factors. However, a decrease in risk was observed with the more frequent use of citrus fruits (adjusted RR = 0.5; p = 0.03). Although it was not possible to calculate vitamin C intakes in this study, the protective effect may have been a reflection of intake of this vitamin. Reductions in risk were also associated with more frequent consumption of carotene-rich foods, such as carrots, papaya, and pumpkins. The association was of less strength than that observed for citrus fruits (smoking and alcohol adjusted associations: p = 0.06 for carotene versus p = 0.03 for citrus fruits).
In the study by McLaughlin et al. (1988), 871 pathologically confirmed cases of oral and pharyngeal cancer were ascertained from the population-based cancer registries of New Jersey; Atlanta, Georgia; and the Santa Clara, San Mateo, and Los Angeles counties of California. The 979 population-based controls were selected in an age- and sex-stratified manner. All subjects were white. A 61-item food-frequency questionnaire was used to determine dietary habits with specific reference to foods that were sources of vitamins C and A and carotene. Fruit and vegetable intakes were adjusted for seasonal variations. Information was obtained on vitamin supplement use, but their use did not affect the results.

These investigators observed a strong protective effect for citrus fruits and vitamin C from fruits on the incidence of oral cancer (OR = 0.5; p = 0.001 for trend). The decreased risk occurred in both men and women. A comparable protective effect was also obtained from the carotene and fiber derived from the fruits consumed. Vitamin C, carotene, and fiber derived from the vegetables consumed provided little protective effect on oral cancer. This suggested to the investigators that additional components present in fruits may contribute to the reduced risk of oral cancer. Phenols, aromatic isothiocyanates, flavones, and other non-nutritive compounds were suggested as possible contributing factors present in fruits. However, since McLaughlin et al. (1988) did not report on the mean or median intakes for any of the vitamins, no comparison can be made between the level of intake of vitamin C and carotene provided by the fruits and the amounts provided by the vegetables. In general, vegetables are not the major contributors of vitamin C to the diet. Furthermore, the absence of biochemical confirmation of vitamin status renders any conclusions about vitamin C presumptive.

C. LUNG CANCER

Earlier epidemiologic studies of the relationship between vitamins and lung cancer reviewed by Ziegler (1986) and Fontham (1990) found no association between vitamin C or fruit intake and the risk of lung cancer.

Byers et al. (1987) compared 450 Caucasian lung cancer cases (296 males and 154 females) diagnosed between August 1980 and July 1984, with 902 race, sex, and residentially-matched controls (587 males and 315 females) from three western New York counties. All subjects were given a standardized interview of approximately two and one-half hours duration designed to obtain information on occupation; tobacco, drug, and alcohol use; oral health; and medical and dietary history. The interviews for both the cases and controls were conducted between August 1980 and August 1984.

The dietary history used a 129-item food-frequency questionnaire to determine average frequency of consumption and portion size. Nutrient supplements were included. The reference period for the cases was the year before the onset of symptoms of the lung cancer, while the controls reported on their dietary habits up to the time of the interview. The dietary focus was on total vitamin A, vitamin A from fruit and vegetable sources, vitamin C, vitamin E, calories, fat, cholesterol, protein, and dietary fiber. Vitamin A and carotene intakes were calculated from food composition tables. Case-control comparisons were made on quartiles for the nutrient intakes with relative risks computed for each quartile. No biochemical assessments were performed.

No protective effect was observed between dietary vitamin C (estimated intakes) and lung cancer. Similarly, no association was observed between lung cancer and retinol intakes (vitamin A from animal sources). However, an inverse association was found between lung cancer and carotene intakes (calculated from fruit and vegetable intakes). The strongest protective association of carotene was with the squamous cell carcinoma cases, with a weaker association with adenocarcinoma cases. The greatest effect of carotene on lung cancers was for those over 60 years of age. For this group, the relative risk with the lowest quartile of carotene intake was 3.1 for men and 2.0 for women. The
greatest reduction in risk was apparent in those individuals who never smoked or were ex-smokers (quit for > 3 yrs). No data were presented as to a quantitative estimate of the intakes of vitamin C, carotene, or other nutrients. Thus, the level of intake of nutrients that may provide a protective effect cannot be computed. It was noted that risk estimates were not substantially affected by the addition of supplements to the nutrient indices.

In 1988, Fontham et al. conducted a hospital-based incidence case-control study of lung cancer over a period of 28 months in a high-risk region of southern Louisiana. The controls were subjects admitted to the same hospitals and matched by race, sex, and age within 5 years. Dietary intakes of vitamin C, carotene, and retinol were estimated from food-frequency questionnaires administered to 1253 cases and 1274 controls. The questionnaire provided information on the frequency of consumption of each of the 59 food items on a monthly basis before the onset of illness or symptoms. Additional information was obtained on the use of tobacco, occupation, residence, and medical history. Indices for vitamin C, carotene, and retinol intake were created by summing the frequency of consumption of each of the food items multiplied by the median nutrient content of a typical serving. The nutrient indices were stratified into tertiles. The upper tertile consumed 150 mg of vitamin C per day, while the lower tertile consumed less than 90 mg per day.

Although an inverse association was found between the level of carotene intake and lung cancer (squamous and small cell carcinomas), a stronger protective effect for these tumors was associated with dietary vitamin C intake. An odds ratio of 0.65 (confidence interval 0.50–0.87, for highest vitamin C intake) was reported. Fruit consumption adjusted for vegetable intake remained a protective factor for all lung cancers combined. No protective effects of carotene or vitamin C were observed for adenocarcinoma. However, an inverse relationship between dietary retinol and adenocarcinoma was observed, particularly for the black males. The investigators suggest that the protective effect associated with vitamin C may be expressed only in populations with a relatively low intake of the vitamin as apparently occurs in the Louisiana population studied. Fontham (1990) recently reviewed epidemiological studies on the effects of dietary components on lung cancer risk. The majority of these studies focused the protective effects of retinol and ß-carotene.

It should be noted that only 51 of the cases never smoked compared to 388 of the controls. The majority of the cases were current smokers. Although not considered, the intakes of vitamin C by the hospital controls may not reflect the intakes of the general population. Blood levels of vitamin C would have given more information about adequacy of the intakes of the vitamin and the impact of smoking on vitamin C levels and the relationship between these levels and cancer risk.

Koo (1988) conducted a retrospective study in which 88 lung cancer patients and 137 matched controls were interviewed concerning the effect of diet on lung cancer risk among Chinese women from Hong Kong who never smoked. The diet information was obtained by food-frequency inquiry. The cases provided information on their usual food habits one year before the diagnosis of cancer, while the controls provided information on their current eating habits. The assessment focused on the consumption patterns of broad groups or types of foods in order to accommodate Chinese cooking habits.

A higher consumption of leafy green vegetables, carrots, fresh fruits, tofu, and fresh fish was inversely associated with development of adenocarcinoma and large cell tumors. Of the dietary components investigated, only the consumption of fresh fruit showed a negative relationship against squamous or small cell tumors. The protective effect was reflected in a relative risk of 0.42 (trend p = 0.014). Sources of vitamin C also conferred some protection against adenocarcinomas. No quantitative information was provided regarding the intakes of vitamin C. Any protective effects on vitamin C must be considered presumptive.
Le Marchand et al. (1989) investigated the effect of vegetable consumption on lung cancer risk in a Hawaiian population. Interviews were conducted on 230 men and 102 women with lung cancer and 597 men and 268 women as controls. The cases were identified by the Hawaii Tumor Registry and had been diagnosed during the period of March 1983 and September 30, 1985. Difficulties occurred in obtaining suitable controls that resulted in an imbalance in the ethnic composition of the study groups. Age, sex, smoking, alcohol consumption, and occupation were factors considered in the conduct of the study. A quantitative dietary history using a 130–item food–frequency questionnaire was completed to assess the usual intake of foods rich in vitamins C and A and carotenoids. The interviews were conducted at home with the subject or a surrogate.

Total vitamin C (from food sources and supplements) was inversely associated with lung cancer risk among males only. A reverse effect was observed for Caucasian women. The investigators considered the results an aberration and did not explore them further. No biochemical data were available on plasma levels of vitamin C that could have been used to explore the relationship of the vitamin and smoking to lung cancer risk. A significant negative association between dietary β–carotene and lung cancer was observed in males only. However, all vegetables, dark green vegetables, cruciferous vegetables, and tomatoes were found to have a stronger inverse association with risk than β–carotene.

LeGardeur et al. (1990) measured serum vitamins C, A (retinol), E, and carotenoids in 59 cases of newly diagnosed lung cancer, 59 matched hospital controls, and 31 community–based controls. Information on smoking habits and dietary intakes was obtained from the lung cancer cases and the hospitalized controls but not the non–institutionalized subjects.

Serum levels of vitamin C were significantly lower in the lung cancer patients when compared to the hospital controls (0.41 +0.04 mg/dL vs 0.59 + 0.06 mg/dL; p = 0.014). Correcting for smoking may have eliminated these differences. However, the investigators did not comment on these findings. Their emphasis was placed on the observed lower serum levels of vitamin E and carotenoids found in the lung cancer patients. This study had serious problems in design and analysis that are noted in Appendix Table 8.

D. GASTRIC CANCER

Because ascorbic acid can function as a free radical scavenger and can block the formation of nitrosamines in the stomach, various studies have investigated the possible role of vitamin C or dietary sources of the vitamin in stomach cancer (Leaf et al., 1987; Stähelin et al., 1987). Many of these studies have been reviewed by Block (1991a) and Block and Menkes (1989). Recently, additional studies have examined the relationship between ascorbic acid's interference in the formation of N–nitroso compounds and their by–products and the occurrence of stomach cancer (Schorah et al., 1991; Sobala, 1991). This is the only case of a plausible explanation of the protective effect of vitamin C for a specific cancer type.

You et al. (1988) interviewed 564 diagnosed stomach cancer patients and 1131 population–based controls in Linqu, a rural county in Shandong Province in northeast China. This area has an exceptionally high rate of stomach cancer. A structured questionnaire was used that provided information on dietary habits and on the frequency of consumption and portion size of 85 food items that had been eaten several years before the start of the investigation.

The findings indicate that dietary factors contribute, but only partially, to the high rates of stomach cancer in this population. Increased intakes of fresh fruits and total fresh vegetables reduced the risk of stomach cancer (OR = 0.5 – 0.6). Increased intakes of vitamin C (estimated) also conferred a protective effect (OR = 0.5; 95 percent confidence interval = 0.3 – 0.6). Increased intakes of carotene
were also associated with a protective effect on stomach cancer. The effect of vitamin C was independent of the carotene effect. However, the study suggests a complex of dietary variables which may relate to the high rates of stomach cancer in this area of China.

Japan continues to have a high incidence of stomach cancer. Kono et al. (1988) conducted a case-control study of stomach cancer and diet in northern Kyushu, Japan, during the period of 1979 to 1982. The study involved 139 cases of newly diagnosed stomach cancer at a single institute, 2574 hospital controls, and 278 controls from the area. A questionnaire was employed that provided information on dietary habits and on the frequency of consumption of food items. Analysis of the data revealed a protective effect against stomach cancer with increased frequency of consumption of fruits, mandarin oranges, and green tea (an important source of vitamin C in the Japanese diet). The relative risk of stomach cancer with the upper tertile frequency of consumption of these food items ranged from 0.4 to 0.6 (p < 0.05). Because of the design of the study, vitamin C intakes were not estimated. Although a role for vitamin C suggests itself, it must be considered presumptive as the study focused on food groups and could not estimate intakes of individual nutrients.

Buiatti et al. (1989) conducted a case-control study in areas of Italy with either a high or low risk for stomach cancer. The study involved 1016 histologically confirmed stomach cancer cases and 1159 population controls. Dietary patterns were obtained with the use of a structured 146-item food-frequency questionnaire. Consistent throughout the several areas of Italy studied was the decreased risk of stomach cancer with increasing consumption of citrus fruits, other fresh fruits, and raw vegetables. Relative risks for the highest tertile of consumption for these food groups ranged from 0.4 to 0.6 (p = 0.001 for trend). The protective effect of fresh fruits appeared to be at least partially independent of the effect of raw vegetables. High consumption of both food groups resulted in a relative risk of 0.3. Hence, a participation of vitamin C in the protective effect was suggested.

Data from this study were also used to examine a possible relationship between diet and stomach cancer (Buiatti et al., 1990). Estimates of intake of individual nutrients were calculated from the food-frequency data. The results suggested that the lowered risk associated with increasing intake of fresh fruits, fresh vegetables, and olive oil may result from the vitamin C and vitamin E present in these items. Notably, the most significant effect was the geographical gradient in vitamin C intake; the highest consumption was found in the areas with lowest risk. Estimates of the intake of nitrates and nitrites were calculated for the several geographic areas studied. The results indicated an increasing relative risk of stomach cancer with an increasing consumption of nitrates and protein. The risk decreased with increased intakes of ascorbic acid and α-tocopherol both for male and female subjects.

In a similar study, Boeing and Frentzel-Beyme (1991) investigated risk factors for stomach cancer in high- and low-risk areas of Germany. In this case-control study conducted during 1985–1987, 143 cases and 579 hospital- and community-based controls from 3 high-risk regions and 1 low-risk region were interviewed about sociodemographic characteristics, occupation, medical and smoking histories, water supply, food conservation methods, and intake of food for the 5 years prior to the onset of their disease.

Risk of stomach cancer was associated with several factors including: vitamin C intake, type of water supply, type of wood used for smoking meats, and years of refrigerator use. When compared with a central water supply, the use of well water was associated with an increased risk of stomach cancer (relative risk = 2.17). Although not assessed, this risk may have been the consequence of nitrate in the well water. Use of spruce wood rather than other types for smoking meats was also associated with increased risk (relative risk = 3.32). Long-term availability of a home refrigerator was associated with a lower relative risk (1.0 vs 1.33). Low intakes of vitamin C were associated with an increased risk of stomach cancer with the lowest quintile of intake associated with significant elevation in risk (relative risk = 2.32). However, no information was provided as to how the vitamin C intakes of the
cases and controls were estimated. Similarly, there were no biochemical measures of vitamin C status. There was little detail supplied about methods of diet assessment or subject selection.

Chyou et al. (1990) initiated a case-cohort study during the period of 1965 to 1968 on 8006 Hawaiian men of Japanese ancestry. Each subject was interviewed during this period with the use of a 24-hour dietary-recall questionnaire. Over the next 18 years, 111 stomach cancer incident cases were identified. Dietary data from these cases and from 361 cancer-free men revealed that the consumption of all types of vegetables was protective against stomach cancer. Subjects with the highest vegetable consumption had a relative risk for stomach cancer of 0.6 (95 percent confidence interval = 0.3 - 0.9) in comparison with non-consumers. A protective effect against stomach cancer was also observed with increased intake of fruits (p = 0.05), although this trend was weakened when cigarette smoking was taken into account. From the limited data presented, an association of stomach cancer with foods containing vitamin C, vitamin A, and β-carotene was suggestive, although the intake of individual nutrients such as vitamin C and vitamin A was not assessed.

Coggon et al. (1989) examined the influence of food storage habits, i.e., fresh versus frozen or preserved, on the development of stomach cancer by comparing 95 patients with cancer identified during 1985-1987 and 190 controls from two areas of the United Kingdom. As part of the investigation, a questionnaire was completed by each subject that provided information regarding the frequency of consumption of selected food items, including fresh and frozen fruit and salad vegetables. Evaluation of the data indicated a protective effect against stomach cancer by an increased frequency of consumption of fresh or frozen fruit (RR = 0.4; 95 percent confidence interval = 0.2 - 0.8) and by salad vegetables (RR = 0.2; 95 percent confidence interval = 0.1 - 0.5). Because of the design of the study, the effect of individual nutrients was not assessed. A more detailed cohort study is in progress by these investigators.

Burr et al. (1987) conducted a cross-sectional study in two British towns (Bath and Caerphilly) with regard to vitamin C status and stomach cancer and atrophic gastritis. Bath (southwest England) has a low mortality rate for stomach cancer, while Caerphilly (south Wales) has a high mortality incidence. For the study, 4078 men in Bath and 2789 men in Caerphilly, aged 65-74 years, were identified. From these groups, 267 persons from Bath and 246 persons from Caerphilly were selected for study. A questionnaire was completed that provided information on height and smoking, as well as limited dietary information. Blood samples were obtained at least two hours after the last meal for ascorbate and pepsinogen measurements. Serum pepsinogen levels served to diagnose atrophic gastritis. The participants were classified into social classes as well as manual workers and non-manual workers.

The Bath subjects, who were of somewhat higher social class, had significantly higher plasma ascorbate concentrations than those from Caerphilly (0.37 mg/dL versus 0.24 mg/dL). The consumption of fruit was considerably higher for the Bath men and the plasma ascorbate concentrations were directly associated with the frequency of fruit consumption (r = 0.274, P <0.01). This relationship has been reported also by other investigators, particularly with respect to intakes of citrus fruits and juices.

The incidence of smoking was about 25 percent higher among the Caerphilly participants. Smoking commonly lowers plasma ascorbate concentrations. The influence of smoking on the plasma ascorbate levels in the populations studied was not considered. Since no estimates of vitamin C intakes were made, no consideration can be made as to the level of intake of the vitamin necessary to provide an apparent protection.

Severe atrophic gastritis, as assessed by pepsinogen concentrations, was nearly twice as common among the subjects from Caerphilly as from Bath. This difference did not appear to be related to plasma ascorbate levels. Mortality incidence (standard mortality ratio of 138) of stomach cancer was high in Caerphilly, while Bath had a low mortality rate for stomach cancer (standard mortality ratio
of 77). The inverse relationship of ascorbate status to the occurrence of stomach cancer supports the concept of a role for vitamin C in the prevention of this cancer. Since the intake and status for other nutrients such as vitamin E and carotenoids were not investigated, their participation in the prevention of stomach cancer remains uncertain.

E. PANCREATIC CANCER

The etiology of pancreatic cancer is unknown. Pancreatic cancer is common in developed countries, such as Japan, where a sharp increase in the disease has occurred in recent years (Boyle et al., 1989; Hirayama, 1989). In a large-scale cohort study conducted in Japan by Hirayama (1989), the occurrence of pancreatic cancer was observed to have a close association with cigarette smoking and the daily consumption of meat. Information was not reported whereby any association with vitamin C could be evaluated.

La Vecchia et al. (1990) conducted a hospital–based case–control study in northern Italy on 247 patients with pancreatic cancer and on 1089 age– and sex–matched hospital–based controls with acute, non–digestive, non–neoplastic diseases. Information was obtained by interview about sociodemographic characteristics, medical history, smoking habits, alcohol and coffee intakes, and on 14 selected indicator foods that included the major sources of vitamin A, fats, and fibers. A more frequent consumption of fish, oil (presumably vegetable, although not described), and fresh fruit was inversely associated with risk. Relative risk estimate decreased to 0.65 - 0.68 with an increased intake of fresh fruit (trend 4.53, p < 0.05). The data collection did not have a particular focus on vitamin C intake. Consequently, without additional information, any association of a vitamin C effect would be presumptive.

Mills et al. (1988) examined dietary habits and risk of pancreatic cancer in a prospective study of fatal pancreatic cancer among 34,000 non–Hispanic Seventh Day Adventists during the period of 1974–1982. Forty deaths from pancreatic cancer occurred during this period. An increased consumption of vegetable protein products, beans, lentils or peas, and dried fruits was inversely associated with risk of fatal pancreatic cancer. The consumption of fresh fruits (fresh citrus and fresh winter fruit) was associated with a non–significant protective effect suggestive of a prophylactic role for vitamin C in pancreatic cancer; however, because of the limited data, confounding variables, and inadequate dietary information, such a role for vitamin C is conjecture.

Farrow and Davis (1990) investigated the relationship between diet and risk of pancreatic cancer in a population–based case–control study in western Washington. One hundred forty–eight married men diagnosed with pancreatic cancer and 188 controls were studied. Wives of the cases and controls were mailed a self–administered 135–item food–frequency questionnaire to provide information on the dietary intakes of their husbands for the previous 3 years. Dietary information was provided for 68 percent of the cases. No association was found between pancreatic cancer risk and the intake of total fat, saturated fat, cholesterol, vegetables, all fruits, citrus fruits, and vitamin C (calculated). The investigators recognized several limitations in their data. Information collected from surrogate respondents may be susceptible to recall bias related to the long retrospective period, and a larger portion of the cases were deceased than in the control group.

Falk et al. (1988) described a hospital–based, incident case–control study of pancreatic cancer, conducted between 1979 and 1983 in a high risk area of southern Louisiana. The study involved 363 cases and 1234 race–, sex–, and age–matched controls admitted to the same hospital. Because of the rapid fatal course of the disease, data from 50 percent of the cases were provided by the spouse or relatives. A 59–item food–frequency questionnaire was used to obtain dietary patterns prior to illness or onset of symptoms.
Of the dietary food items included, fruit consumption (oranges, bananas, orange juice, etc.) exhibited a protective effect against pancreatic cancer in both men and women. An odds ratio of 0.63 (95 percent confidence interval = 0.49 – 0.82) was reported. The highest risk was associated with an estimated intake of 65 mg/d of vitamin C and the lowest risk with an estimated intake above 150 mg/d. Smoking in both sexes was related to a significant trend for increased risk.

F. COLORECTAL CANCER

Epidemiological studies of colon cancer have implicated diet as a causative factor. Evidence is strong that the occurrence of colon cancer may be reduced in diets containing less animal fat and more fruit and vegetables (Willett, 1989). Several reviewers have considered the causative factors associated with colorectal cancers (Bingham, 1988; Block, 1991a; Block and Menkes, 1989; Hargreaves et al., 1989; Vogel and McPherson, 1989; Walker and Segal, 1989; Willett, 1989). As was the case with gastric cancer, the possible protective effect of vitamin C in colorectal carcinogenesis could be associated with its prevention of the formation of fecal N-nitrosoamines or by action against other fecal mutagens (Block, 1991a; Block and Menkes, 1989; Schiffman, 1987).

Freudenheim et al. (1990) conducted a case-control study on primary rectal cancer in 277 case-control pairs of males and 145 case-control pairs of females in western New York. Extensive testing of the dietary intake assessment tools and interviewers was performed to ensure the reliability of the data. The focus of the interview was on the usual intake of 129 foods. The reference period was the usual intake in the year prior to interview for the controls and for the cases, a year prior to the onset of symptoms. During the two and one-half hour interview, information was also obtained on tobacco and alcohol use, occupation, health history, seasonal effects on diet, food preparation, and storage.

Although the study was well conceived, the duration of the interviews and the reliance on retrospective food frequency information may have limits. The dietary information provided evidence of a reduction in risk of rectal cancer with an increasing intake of vitamin C for both sexes. However, the protective effect was statistically significant for females only (OR = 0.45; 95 percent confidence interval = 0.24–0.85). Increased dietary intakes of carotenoids and fiber from vegetables were also associated with a decreased risk of rectal cancer. In an earlier separate report by Graham et al. (1988) using an approach similar to that used by Freudenheim et al. (1990), vitamin C and carotenoids were not found to be associated with a lowered risk of colon cancer.

The relationship between dietary factors and the risk of colorectal cancer in northern Italy was investigated in a case-control study conducted on 339 cases of colon cancer, 236 cases of rectal cancer, and 778 controls selected from hospital patients admitted for acute non-neoplastic or digestive disorders (La Vecchia et al., 1988). No population based-controls were used. Information was obtained on the current frequency of consumption per week of only 29 selected food items. Additional information was obtained about tobacco and alcohol use, consumption of coffee and methylxanthine-containing drinks, and health histories.

These investigators found that frequent consumption of green vegetables conveyed significant protective effect against both colon cancer (RR = 0.50) and rectal cancer (RR = 0.51). However, no significant protective effect was observed for either type of cancer with increased levels of intake of total fresh fruit, citrus fruit, or dietary vitamin C. With age and sex adjustments, an inverse relationship existed between risk and indices of carotenoid and vitamin C.

The limitations in the study included: 1) a limited number of food items in the food-frequency questionnaire; 2) no quantitative estimate of portion size; 3) a focus on current dietary practices rather
than a reference period that may have been more relevant to initiation of colorectal cancers; and 4) reliance on hospital-based controls with no community-based control group.

Adenomatous polyps have been presumed to be precursor lesions for colorectal cancer. Several researchers have investigated the effect of vitamin C and other vitamin supplements in patients with colorectal polyps (DeCosse et al., 1989; McKeown-Eyssen et al., 1988; McLaughlin et al., 1988; Meyskens, 1990; Mills et al., 1988; Neugut et al., 1988). During the period of 1983-1985, Neugut et al. (1988) interviewed 244 women from New York who had undergone a colonoscopy. The cases consisted of 105 patients with adenomatous polyps, 56 patients with colon cancer, and 83 women without colorectal neoplasia on colonoscopy. Information was obtained from the women about their use of supplemental vitamins A, C, and E. Approximately 20 percent of the subjects in each group used vitamin C supplements. Information was not obtained as to the quantitative contribution of the supplements to the intake of vitamin C or of other vitamins. The study failed to demonstrate significant benefits from any of the vitamin supplements in preventing colon polyps or cancer.

Tuyns et al. (1987b) conducted a case-control study on colorectal cancer in the Belgian provinces of Oost-Vlaanderen and Liege. For the study, 453 colon cancer patients and 365 rectal cancer patients were selected along with 2851 controls from the adult populations of the two provinces. Approximately equal numbers of males and females were studied. Food consumption data were obtained from all subjects with the use of a previously tested dietary history procedure referenced to the week prior to onset of the disease symptoms for the cases and current intakes for the controls. Portion weights were estimated with the use of photographs of standard portions. Seasonal foods, such as fruits and vegetables, were considered in frequency of consumption data. Average daily intakes of individual nutrients were calculated with the use of Dutch food composition tables.

The average intakes for vitamin C and β-carotene were slightly lower in the cancer patients. This difference was not significant in view of the considerable age and sex differences associated with the food intake data. The average intake of vitamin C for the populations studied ranged from 91 to 109 mg per day. The relative risks (odds ratios) for vitamin C intake did not indicate a protective effect of the vitamin against rectal or colon cancer. While fiber in the diet had a protective effect, the investigators did not observe an association of fats with rectal or colon cancers. The effect of food groups, sources of vitamin C, vitamin supplements, smoking, and alcohol consumption were not considered as to their possible association with rectal or colon cancers.

West et al. (1989) conducted a case-control study in Utah between July 1979 and June 1983 in which 231 cases of colon cancer and 391 matched controls were interviewed. A comprehensive food frequency questionnaire was used to obtain information on foods eaten in the two to three years prior to the interview. Results indicated a protective effect against colon cancer was provided by fiber, β-carotene, and cruciferous vegetables. However, intake of vitamin C did not provide any protection against colon cancer after adjustment for body mass index, age, crude fiber, and energy intake.

McKeown-Eyssen et al. (1988) conducted a double-blind randomized trial in Toronto, Canada, to examine the effect of vitamin C and vitamin E on the rate of recurrence of colorectal polyps. The study included 185 cases presumed to be free of polyps after the removal of at least 1 colorectal polyp. The subjects received either a supplement of 400 mg each of ascorbic acid and α-tocopherol (n = 96) or a placebo (n = 89) for up to 2 years. Random urine samples were collected to test for compliance. The findings of the investigation suggest that the vitamin C and vitamin E supplements produced very little, if any, effect in the reduced rate of polyp recurrence. Of the 137 (75 percent) subjects that completed the study, polyps were observed in the second colonoscopy in 41.4 percent of 70 subjects on vitamin supplements and in 50.7 percent of 67 subjects on placebo. Whether this small reduction in the rate of polyp recurrence is of significance would require a larger study.
DeCosse et al. (1989) studied the effects of ascorbic acid plus α-tocopherol with and without grain-fiber supplements on rectal polyps. Over a period of 4 years, 58 patients from the New York City area with familial adenomatous polyposis were followed in a random, double-blind, placebo-controlled trial. There were 3 treatment groups: 22 patients received 8 capsules daily of a lactose placebo along with 2.2 grams of a low-fiber supplement; 16 patients received 8 capsules that provided 4 g of ascorbic acid, 400 mg of α-tocopherol and 2.2 g of the low-fiber supplement per day; and 20 patients received both vitamins at the same dosage as for the second group, plus 22.5 g of a high-fiber supplement. In addition, all groups received 30 mg of ascorbic acid, 2000 IU of vitamin A, and equivalent amounts of several other vitamins and minerals approximating 30 percent of the Recommended Dietary Allowances. Over the 4 years of the trial, each patient underwent proctosigmoidoscopy every 3 months and provided extensive food consumption information that included a 3-day diet diary recorded during the week preceding each examination and a food frequency questionnaire completed at the time of the examination.

The results did not indicate any protective effect of the vitamin C and vitamin E supplements on the occurrence of rectal polyps. A beneficial effect was obtained from the high fiber supplements, particularly during the middle two years of the trial. Compliance for all groups decreased over the course of the trial. No biochemical measurements were performed, either at baseline or during the trial, that could indicate the level of compliance or the response to the supplements. Since all subjects received some vitamin supplements, their independent effects cannot be ascertained.

G. PROSTATE CANCER

Prostate cancer is the leading cancer in incidence in black men and the second leading cancer in white men. The 1985 estimated cancer incidence by site for men was lung cancer, 22 percent; prostate cancer, 19 percent; and colon cancer and rectal cancer combined, 15 percent (Horn et al., 1984). The possible role of diet in the etiology of prostate cancer has been investigated in several studies.

Kolonel et al. (1988) conducted a well-designed case-controlled study on diet and prostate cancer in Hawaii that covered the period of 1977–1983. Four hundred fifty-two cases of prostate cancer, identified through the population-based Hawaii Tumor Registry, were compared to 899 age-matched controls. A detailed quantitative dietary history method was used that included information on vitamins C and A. The results showed no effect on risk from either total (food plus supplements) or food sources of vitamin C in younger or older men irrespective of ethnic group. The mean total vitamin C intake ranged from 357 to 428 mg/d, representing a high intake.

Vitamin C intake of 100 prostate cancer patients and 2 different control groups (100 benign prostatic hyperplasia patients and 100 general hospital patients) was compared in a case-control study in Kyoto, Japan, from January 1981 to December 1984 (Ohno et al., 1988). No community-based control subjects were used. Quantitative food frequency information obtained from each subject showed that the mean daily intake of vitamin C was comparable for the 3 groups (92–103 mg/d). Contributions of vitamin supplements were not provided. No significant association of vitamin C intake and prostate cancer risk was observed. Following a more detailed analysis of information on dietary habits of participants in this study (Oishi et al., 1988), the conclusion concerning vitamin C remained unchanged.

H. CERVICAL/OVARIAN CANCER

Cervical cancer rates in the U.S. are generally elevated in regions of low socioeconomic status. An association of diet with the risk of cervical cancer and cervical dysplasia, a premalignant lesion of the
uterine cervix, has been proposed. Studies on the role of vitamin C and other vitamins in the development of cervical cancer have been reviewed recently (Block, 1991a; Block and Menkes, 1989; Schneider and Shah, 1989; Ziegler, 1986). These reviews suggested a consistent correlation between an increased prevalence of cervical neoplasia and low tissue concentrations, low serum levels, and low intakes of vitamin C, β-carotene, or folate.

During the years 1980–1983, Brock et al. (1988) conducted a study on 117 confirmed in situ cervical cancer patients and on 196 matched community controls in Sydney, Australia. Blood samples were obtained on 100 of the cases and 143 of the controls. Dietary patterns over the previous year were established with the use of a 160-item quantitative food–frequency questionnaire specifically designed to cover the significant dietary sources of retinol, carotene, vitamin C, and folate in the Australian diet. Reliability was evaluated by a repeated interview. Information was also obtained on smoking, sexual habits, and contraceptive use, and on the use of vitamin supplements. Fasting plasma levels were measured for retinol, total carotenes, and β-carotene, but not for vitamin C.

Dietary intakes of vitamin C, derived by calculation, suggested that an increased intake of the vitamin provided a protective effect. Plasma β-carotene levels and dietary intakes of vitamin C and fruit juices showed protective effects. The higher plasma β-carotene levels were associated with a reduced risk of 80 percent, while a higher intake of vitamin C reduced risk by 60 percent and fruit juices by 50 percent. With a calculated intake of vitamin C of 170 mg and above per day, the relative risk was 0.5 when adjusted for smoking, contraceptive use, and sexual habits. However, the trend was not significant. It is unfortunate that plasma ascorbate levels were not measured; these may have more accurately reflected the vitamin C status and dietary intakes.

Similar results were obtained by Verreault et al. (1989) who conducted a case–controlled study that involved 189 women diagnosed with cervical carcinoma between 1979 and 1983 in Seattle, Washington, and 227 randomly selected age–matched controls. A food frequency questionnaire was used to obtain intake information on 66 food items. Data were obtained on demographic characteristics, reproductive history, contraceptive use, smoking history, sexual habits, and anthropometries. All subjects were asked to refer to the time prior to a reference date (date of diagnosis for cases and December 1981 for controls). The average delay between the reference date and the interview was 2.8 years for the cases and 2.7 years for the controls.

This study found a significant inverse relationship between calculated vitamin C intake and the risk of cervical cancer. The adjusted relative risk (RR) was 0.5 (95 percent confidence interval = 0.2–1.0, p = 0.04 for trend) for the highest quartile of intake of vitamin C. The estimated intake of vitamin C for this quartile was 77 mg and above per day. The effect of fruit juices was even stronger with an RR of 0.3 (p < 0.01). After adjustment for known risk factors, frequent consumption of dark green or yellow vegetables and of fruit juices was related to a reduced risk of cervical cancer. High intakes of vitamin E and of carotene were also associated with a lower risk of cervical cancer. However, plasma levels of vitamin C, vitamin E, or carotene were not determined.

These studies offer considerable evidence of a protective effect for vitamin C in cervical cancer. Nevertheless, carefully conducted longitudinal and prospective cohort studies are needed to establish the significance of vitamin C as a protective factor against cervical cancer. Such studies should include multiple measurements of ascorbic acid levels in plasma and blood components as indicators of vitamin C status and its relationship to protective effects.

Contrasting results were obtained by Ziegler et al. (1990) in a case–control study of invasive cervical cancer among white women in five U.S. metropolitan areas (Birmingham, Chicago, Denver, Miami, and Philadelphia) during the period 1982–1983. The study involved an examination of dietary habits and information on the frequency of consumption of 75 food items and vitamin supplements by 271 cases
and 502 matched controls. Information was also obtained on demographic characteristics, sexual behavior, use of contraceptives and female hormones, reproductive and menstrual history, personal and familial medical history, and smoking.

In this study, the risk of invasive cervical cancer was not affected by increased consumption of fruits, vegetables, dark green vegetables, dark yellow–orange vegetables, or legumes. No increased risk of cervical cancer could be associated with a decreased intake of vitamin A, vitamin C, carotenoids, or folate. However, among heavy smokers, vitamin C intake appeared to be protective. The contrast of these findings to those obtained in previous epidemiologic studies is not readily explained.

Cigarette smoking has been hypothesized to be a causative factor in the development of cervical cancer. Of interest is the study of Basu et al. (1990) on the influence of cigarette smoking on ascorbic acid levels in plasma, leukocyte, and cervicovaginal cells from 16 women who smoked and 30 women who did not. The levels of ascorbic acid in the cervicovaginal cells and in the plasma were significantly lower in the smokers when compared to the nonsmokers (p < 0.001, p < 0.01, respectively).

Ovarian cancer is considered responsible for more cancer deaths in women than any other cancer in the female genital tract. A few studies have reported an association between ovarian cancer and specific nutrients (Shu et al., 1989; Slattery et al., 1989). Recently, Slattery et al. (1989) conducted a population–based, case–control study in Utah to examine the association between nutrient intake and ovarian cancer. During 1984 and 1987, information on contraceptive use, smoking history, demographics, anthropometrics, medical history, and pregnancy history, plus detailed dietary information was obtained on 85 first primary ovarian cancer cases and 492 population–based, age–matched controls. The questionnaire contained 183 food items. Vitamin C intake appeared to decrease slightly the risk of ovarian cancer, but the magnitude of the effect was small, with an adjusted odds ratio of 0.7. Similar slight non–significant increases in risk were observed with a decreased intake of vitamin A or of fiber. A protective effect was observed between dietary β–carotene and ovarian cancer.

In Shanghai, Shu et al. (1989) investigated dietary factors and epithelial ovarian cancer in a population–based, case–control study of 172 cases and 172 controls matched for age and residence. Dietary information was obtained on the frequency of consumption of 63 food items. A slight protective effect was observed with high intakes of total vegetables. However, no protective effect was associated with an increased intake of vitamin C. High fat intake was significantly related to an increased risk of ovarian cancer (trends in risk for total fat: p = 0.03; for animal fat: p = 0.07). Again, the lack of biochemical analyses, accurate portions size estimation, and the limited number of food items assessed attenuates the interpretation of these results.

I. OTHER CANCERS

La Vecchia et al. (1989) studied the relationship between bladder cancer risk and vitamin A and other dietary factors in a case–control study of histologically confirmed invasive bladder cancer in 136 male and 27 female cases below the age of 75 years, recruited from hospitals in Milan, Italy. The age–matched controls (129 males, 52 females) admitted for traumatic conditions (fractures and sprains), surgical conditions, non–traumatic orthopedic disorders, or other illnesses were recruited from the same hospitals.

A structured questionnaire was used to obtain information on sociodemographic factors, smoking, consumption of alcohol, coffee, and methylxanthine–containing beverages, family medical history, and drug use. Dietary information was limited to the frequency, but not quantity, of consumption of only 10 selected foods items (milk and dairy products, meat, fish, liver, ham, eggs, carrots, green vegetables,
and fruits) prior to the onset of the disease or condition which led to their admission. The results presented focused on vitamin A and provitamin A with no mention of vitamin C. Mean monthly intakes of carotenoids and retinoids were lower for the cases, but the differences were statistically significant only for the carotenoids. Intakes of green vegetables and carrots were significantly lower for the cases, but the consumption of fresh fruits was essentially the same for the cases and controls. The risk of bladder cancer decreased with increasing intakes of carotenoids and retinoids. Consumption of fresh fruits did not appear to be associated with a reduction of risk for bladder cancer in this study.

Stähelin et al. (1987, 1989) reported on 2975 male participants evaluated between 1971–1973 who had taken part in a large prospective cohort study of cardiovascular disease, the Basel Study, begun in 1960. Blood concentrations and dietary intakes of vitamin C, vitamin E, vitamin A, and β-carotene were evaluated in this prospective study of cancer deaths. By 1980, a total of 102 cancer cases occurred which consisted of 37 lung cancers, 17 stomach cancers, 9 colorectal cancers, and 39 cancers of other sites.

Compared to survivors, the plasma concentrations of vitamin C were significantly lower (p < 0.05) in all death cases (n = 286, 9 percent of the cohort), all cancer cases, and stomach cancer. After adjustment for smoking, the impact of all studied vitamins on mortality was markedly diminished and for vitamin C, a significantly lower plasma concentration was observed only for stomach cancer. For stomach cancer, vitamin C and β-carotene, as well as vitamin C and vitamin E, appeared to act independently yet synergistically (Stähelin et al., 1987, 1989). Subjects with low plasma vitamin C and vitamin E values had a high risk ratio (2.39), while subjects with high levels of these two vitamins had a lower risk ratio (0.68). In this study, neither food consumption data nor estimates of the intake of these vitamins were provided. Thus, it is not possible to relate the amount of vitamin C, β-carotene, or vitamin E that might provide a protective effect against stomach cancer.
IV. CONCLUSIONS AND RECOMMENDATIONS

A. GENERAL CONCLUSIONS AND RECOMMENDATIONS

The majority of the investigations on the association of vitamin C with various types of cancer are epidemiologic studies that have depended on retrospective questionnaires, usually food–frequency techniques, in order to examine this relationship. The retrospective nature of these studies is necessitated by the long period that may elapse between induction and the appearance of a specific cancer. Although studies reported protective effects against specific types of cancer with an increased frequency of use of vegetables, fresh green leafy vegetables, fresh fruit, and citrus fruit/juices, collection of data on the actual intakes of specific nutrients was not possible. Plasma levels of ascorbic acid were rarely measured. Calculated estimates occasionally provided an indication of the association of vitamins C, A, and E, and β–carotene. For some studies, it was not possible to discern whether the suggested protective activity was due to the presence of vitamin C or β–carotene, or a combined effect of both or of additional factors, such as fiber. In some of the investigations, however, a specific effect from vitamin C alone was evident.

It is well recognized that the multistage process of carcinogenesis permits various opportunities for the intervention of nutrients such as vitamin C to prevent or impede the transformation of a normal cell into a cancer cell. But how specific nutrients may participate in this process remains to be clarified. To date, an over–reliance has probably been placed on the outcomes of epidemiology studies. Such data are necessary in order to conceive intervention and preventive strategies against cancer. Knowledge gained from the studies reviewed should provide guidance in the design and conduct of needed cancer intervention trials with vitamin C.

However, the design and implementation of controlled intervention trials are difficult and exceedingly expensive. The ability to attain replicate data about the influence of any single nutrient factor on cancer development is difficult for several reasons: 1) more than one nutrient factor may be involved; 2) there may be differences in the racial/ethnic makeup of the population sample; and 3) results may be further confounded by geographic and demographic patterns of dietary intake. Similarly, while few studies have paid attention to the relationship of diet to the occurrence of cancer in various racial and ethnic groups in the U.S. (Hargreaves et al., 1989), the overall incidence of cancer is much lower in American Indians than in whites, blacks, and other racial and ethnic groups in the U.S. Yet, the potential role of diet in the higher prevalence of certain cancers in groups such as Native American Indians remains unresolved. The results of the several human intervention trials in progress may provide definitive and quantitative assessments as to the role of vitamin C in cancer prevention (Boone et al., 1990; Costa et al., 1990). In the meantime, in view of the consistency of dietary findings, it seems appropriate and prudent to direct efforts towards increasing the consumption of fruits and vegetables.

In addition, evidence suggests that vitamin C may interact with other dietary components in the prevention of cancer. Thus, for example, both vitamin C and β–carotene have been reported to reduce the risk of cervical dysplasia (Basu et al., 1990; Brock et al., 1988). Other studies indicate a protective role for folate. Interactions of vitamin C with nutrients, such as vitamin E, vitamin A, carotenoids, and fiber require a better understanding in order to appreciate the role of vitamin C in cancer prevention. Furthermore, mechanisms other than the nitrosamine inhibition, whereby vitamin C may produce an anti–cancer effect, require investigation. A better understanding of the functions of vitamin C would clarify the magnitude of influence of the vitamin on tumorigenesis.
Finally, among the plethora of studies reviewed, few have attempted to quantify the actual intakes of vitamin C and associate the level of intakes with cancer prevention. An optimum intake of vitamin C for cancer prevention is therefore uncertain. Intakes of vitamin C that maintain blood vitamin C concentrations (plasma, leukocytes, etc.) at the concentrations associated with reduced cancer risk may serve as an initial guide as to desired intakes. For example, in the Basel Study, men with stomach cancer had a mean plasma vitamin C concentration of 35.8 μmol/L (Stähelin et al., 1987, 1989). Subjects free of cancer had a vitamin C concentration of 47.0 μmol/L. A plasma vitamin C concentration of approximately 40 μmol/L may be attained in men with a daily intake of 75 mg of ascorbic acid. This level of intake has been reported to maintain the high levels of ascorbic acid present in leukocytes and to provide for optimum immunocompetence. Individuals who smoke require an increased intake of vitamin C to attain these blood concentrations.

B. SPECIFIC CONCLUSIONS

1. Effects of vitamin C in reducing the occurrence of breast cancer remain uncertain at present. Two studies (Katsouyani et al., 1988; Toniolo et al., 1989) indicated no protective effect. While a meta-analysis of 12 case-controlled studies by Howe et al. (1990) found that 9 studies indicated a consistent protective effect of diets with calculated high vitamin C intakes, Howe et al. (1990) concluded that the inverse association between breast cancer and markers of fruit and vegetable consumption lent support to the hypothesis that increased consumption of these foods may reduce breast cancer risk.

2. Citrus fruits provided a significant negative association with risk of oral cancer (Franco et al., 1989; McLaughlin et al., 1988). The design of the studies, i.e., the lack of direct measures of vitamin C intake and or status, provides only presumptive evidence that vitamin C was the active agent.

Risk of esophageal cancer was reduced with higher intakes of vitamin C–rich fruits and juices (Brown et al., 1988; Li et al., 1989; Tuyns et al., 1987a). In one study (Li et al., 1989), the high incidence of esophageal cancer found in China appeared to be unrelated to vitamin C; however, in another (Guo et al., 1990) there was a significant association between both intake and serum levels of vitamin C and esophageal cancer. The vitamin C status of the first population studied (Li et al., 1989) appeared poor, so that a protective effect of the vitamin may not have been discernible. Further, that study was not designed to address specifically the relationship of vitamin C and cancer.

3. Although not consistent, some studies have demonstrated an inverse association between lung cancer risk and vitamin C (Fontham et al., 1988; Koo et al., 1988; LeGardeur et al., 1990; Le Marchand et al., 1989); however, the studies reviewed had design problems, e.g., lack of community–based control groups, focus on food groups rather than accurate estimates of intakes of individual nutrients, and lack of biochemical confirmation of vitamin C status, that precluded a definitive link with vitamin C.

4. One of the most consistent epidemiological findings has been an association with high intakes of vitamin C or vitamin C–rich foods and a reduced risk of stomach cancer. This relationship may have been mediated through the action of vitamin C in blocking the formation of nitrosamines and other carcinogens in the stomach. Considerable biochemical and physiological evidence exists to support this action of vitamin C.
5. For pancreatic cancer, the effect of vitamin C was equivocal, although a presumptive protective effect was observed in two studies (Falk et al., 1988; La Vecchia et al., 1990). Difficulties of design similar to those previously discussed were found in the investigations of dietary associations with this form of cancer.

6. Vitamin C appeared to provide no protection against colon cancer (Graham et al., 1988; Tuyns et al., 1987b; West et al., 1989). Weak protection was observed in one study against rectal cancer (Freudenheim et al., 1990). No benefit was observed from the use of vitamin C and other vitamin supplements on colorectal cancer or on the incidence of recurrence of polyps (McKeown-Eyssens et al., 1988; DeCosse et al., 1989).

7. Low intakes of vitamin C were associated with an increased risk of cervical cancer in two of three studies reported (Brock et al., 1988; Verreault et al., 1989). This relationship deserves further study, because results of these studies suggest that several nutrients either individually or in synergy may impart a protective effect.

8. Vitamin C was not associated with reproducible significant changes in risk for ovarian, prostate, bladder, or other cancers.
V. BIBLIOGRAPHY*


*This bibliography contains all reference citations that are either in the text or the appendix table or both.


APPENDIX

CRITERIA FOR INCLUSION OF ARTICLES IN APPENDIX TABLES

Articles in peer-reviewed journals related to the topic of this review were selected primarily on the basis of date and content. In general, papers appearing in 1987 or thereafter were included, provided that they presented original data from studies in humans. Certain items tabulated for the sake of completeness may not have been cited in the body of the text if their weight or relevance did not add significantly to development of the author’s argument. Reviews have not been listed except as they included new data or useful meta-analyses.
## APPENDIX TABLE. VITAMIN C AND BREAST CANCER

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<thead>
<tr>
<th>Study</th>
<th>Type/location</th>
<th>Subject # &amp; Description</th>
<th>Methods</th>
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<tr>
<td>Howe et al., 1990</td>
<td>Case-control Meta-analysis of 12 studies</td>
<td>4437 cases of breast cancer (BC) 4341 population controls 1754 hospital controls</td>
<td>Analysis included all studies of diet and BC completed by 1986. Authors made diet data available from each of 12 studies. Where data had not been available, estimates of intake were made using food frequency answers. Data on vitamin C were available from 9 of 12 studies. Pre- and post-menopausal women were analyzed separately.</td>
<td>Vitamin C had the most consistent statistically significant inverse association with BC risk. There was a significant positive association between saturated fat intake and risk in postmenopausal cases. Other markers of fruits and vegetable consumption, e.g., β-carotene, fiber, and carotenoids also showed an inverse relationship with risk.</td>
<td>Questions about the validity of meta-analysis in terms of lack of control of independent variables that could influence outcomes, i.e., socioeconomic status (SES), supplement use, clinical stage, medications, and smoking habits. Reliability of dietary data.</td>
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<td>Katsoulanni et al., 1988</td>
<td>Case-control Athens, Greece</td>
<td>120 BC cases 120 hospital controls (patients in orthopedic ward in a different hospital than BC cases)</td>
<td>All subjects interviewed before discharge on first hospital admission. Data collected included demographics, socioeconomic, and reproductive and medical histories. Dietary histories were collected with a 120-item food-frequency questionnaire. To assess the impact of individual nutrients on BC, nutrient intakes were adjusted for calories.</td>
<td>There were no differences in actual or calorie adjusted intakes of vitamin C between cases and controls. Similarly there was no association between vitamin C and risk of BC. Total vitamin A intake was inversely associated with BC risk.</td>
<td>Inappropriate controls (about 25% had osteoarthritis which is known to affect vitamin C metabolism). No biochemistry. Diet data was related to the period preceding the onset of the disease which was not controlled nor was it documented. Supplement use not documented. Data collected over a 12-mo period with no control for seasonal variations in intakes.</td>
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<td>Toniolo et al., 1989</td>
<td>Case-control Italy</td>
<td>250 cases of breast cancer (free of metastases, except in regional lymph nodes. Controls were 499 ‰ from general population stratified by age (± 10 yr) and geographical area.</td>
<td>All subjects interviewed (unblinded) given modified food frequency questionnaire structured by meals. Indigenous foods and recipes were added to the data base. General demographic data were obtained from electoral rolls. Interview data included SES data, and health and reproductive histories.</td>
<td>No difference in vitamin E intake between groups. Reduced risk was associated with decreased intakes of fat, especially saturated fat and animal protein.</td>
<td>Not blinded, no biochemistry, long period of time between diagnosis or treatment and study (on average 7.8 mo after diagnosis). Retrospective diet data not necessarily indicative of diets prior to diagnosis. Smoking histories not reported.</td>
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<td>Brown et al., 1988</td>
<td>Case-control</td>
<td>207 cases of esophageal cancer (EC) all ≥ 74 hospitalized cases and 133 deaths from EC during the period of 1977–81. 422 controls: 157 hospitalized without cancer and 265 non-cancer related deaths. All subjects were from the same 8 coastal counties in SC. The control group for the mortality study was matched for race, age, residence, and year of death.</td>
<td>There were two studies: a hospital based case-control in which all patients were interviewed about alcohol, tobacco, and diet (65-item food-frequency questionnaire) medical and dental history, occupation, family health history (with specific reference to cancer), and other demographics. In the second phase, next-of-kin (usually a spouse or close relative) of the cancer and control subjects were interviewed at home.</td>
<td>After adjustments for smoking and alcohol consumption (the leading risk factors in both studies), significantly increased risks of EC were associated with low intake of fruits, particularly citrus fruits and juices and high intakes of liver. Low vitamin C and fiber intakes were associated with increased risk. High intakes of retinol were associated with higher risk.</td>
<td>No population-based control group or biochemistry. Reliance on retrospective diet data and the use of proxy data in the mortality study. Possibly inappropriate controls in both phases may have lead to conservative estimates of effects. Duration and type of disease in controls may have affected dietary outcomes. Dietary effects may have been secondary to alcohol and tobacco use and/or related diseases.</td>
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<tr>
<td>Franco et al., 1989</td>
<td>Case-control</td>
<td>232 cases of oral cancer (tongue, gum, floor of the mouth, and other parts of the oral cavity). 464 hospital non-cancer controls, 2/case matched for sex, age (≤ 5 yr), and trimester of hospital admission. Patients with neoplastic disease and mental disorders were excluded.</td>
<td>All subjects given a 40 to 60 min structured interview by interviewers blinded to case-control status. Information included SES and demographics, general health, environmental and occupational exposure history, tobacco and alcohol use, 20-item food-frequency questionnaire and oral hygiene habits.</td>
<td>Significantly reduced risk associated with intake of citrus fruits adjusted for smoking and alcohol (the strongest risk factors irrespective of site). Without adjustment, significantly reduced risk associated with increased consumption of carotene-rich foods (e.g., carrots, pumpkins, and papayas) and citrus fruits. No protection noted for green vegetables in general.</td>
<td>No population-based controls, no biochemistry. Retrospective diet data based on limited (20-item) questionnaire. No data regarding vitamin C specifically.</td>
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<td>Li et al., 1989</td>
<td>Case-control Linxian, China</td>
<td>1244 cases of cancer of the esophagus or gastric cardia, ages 35–65 yr 1314 controls age- and sex-matched from same geographical area</td>
<td>All subjects given structured interview. Data collected included demographics, occupation, smoking, diet history (72-item food frequency questionnaire), food preparation and storage methods, beverage consumption, anthropometrics, and family and personal health history. Questions were referenced to 2 time periods, the late 1950s and the late 1970s.</td>
<td>All subjects consumed a diet low in fruits and vegetables. No association with risk. Low water and high wheat intakes were associated with increased risk.</td>
<td>Not designed to address specific vitamin C relationship with cancer. Not enough variability in intake to assess risk relationship. Strong genetic and or geographical component to risk in this population.</td>
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<td>McLaughlin et al., 1988</td>
<td>Case-control 4 regions: New Jersey, Atlanta, GA; Los Angeles, Santa Clara, and San Mateo in CA.</td>
<td>871 cases of oral (and pharyngeal) cancer. 979 population-based controls matched for race (all white) age and sex.</td>
<td>All subjects (or next-of-kin in those cases who were too ill) were given a structured interview to get data on tobacco and alcohol use, diet (61-item food-frequency questionnaire), medical history, occupation, and demographics. Reference period for food was normal intake during adulthood. Intakes were adjusted for seasonal variations in availability. Vitamin supplement usage was collected but did not affect outcomes.</td>
<td>Vitamin C was associated with decreased OR (odds ratios) and risk of oral cancer in men and women. Protective effects were seen for fruit consumption. Highest quartile had 1/2 the risk of lowest. No association with calories, methods of food preservation, or cooking. When derived from fruit, there was a significant protective effect of vitamin C, vitamin A and fiber. This effect was not apparent for vegetable sources of these nutrients. No effect for other vitamins or nutrients.</td>
<td>No biochemistry, reliance of retrospective diet data, no data on time period between diagnosis and participation (cases obtained from a cancer registry). The study not designed to address vitamin C specifically. Mean or median intakes for nutrients not reported.</td>
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<tr>
<td>Tuyns et al., 1987a</td>
<td>Case-control France</td>
<td>743 cases (704 males and 39 females) of esophageal cancer. 1975 controls from the same geographical region.</td>
<td>All subjects interviewed about usual food intake with a 40-item food-frequency questionnaire. Risk analysis was done for heavy vs light consumers adjusted for age and 2 levels of alcohol and tobacco consumption, and residence (rural vs urban).</td>
<td>Higher intakes of vitamin C associated with decreased risk. Significant association between vitamin E intake and relative risk. Higher intakes of several other vitamins (retinol, β-carotene, niacin) also associated with significantly decreased risk. Cases consumed fewer proteins of animal origin and more proteins of vegetable origin and had a higher intake of sugars and starches of vegetable origin. Cases had a lower P:S ratio, oils associated with decreased risk, butter associated with increased risk.</td>
<td>No biochemistry. No control for time between diagnosis and study. No documentation of medications or other treatment. No data on medical or family health history. Hard to determine environmental from genetic effects.</td>
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<td>Guo et al., 1990</td>
<td>Cross-sectional survey China</td>
<td>Survey of 65 counties in China selected for their high incidence of certain types of cancer. 100 subjects were randomly selected from each county, with equal distributions of sex and 5 groups into three age brackets: 35-44, 45-54, 55-64.</td>
<td>A fasting 10 ml blood sample was drawn from each subject. Aliquots were formed by pooling plasma samples from individuals in the same age-sex group within each county and stored at ~30°C. Red blood cells were similarly aliquoted. Diet data regarding frequency of intake of selected foods was collected at time of blood sample. Nutrients assessed included: plasma vitamin C, β-carotene, α-tocopherol, zinc, selenium, and erythrocyte glutathione reductase (an indicator of riboflavin status).</td>
<td>Correlations between county esophageal cancer mortality rates and nutritional data indicated that the strongest association was with plasma vitamin C and dietary fruit consumption. These associations were significant across sexes. Riboflavin status was also inversely related to risk of esophageal cancer but only in sex. Consumption of moldy pickled vegetables was significantly associated with risk.</td>
<td>No information about the composition of the subject pool. There was no data regarding health status of subjects. Small diet data base.</td>
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<td>Byers et al., 1987</td>
<td>Case-control western New York</td>
<td>450 cases of lung cancer (LC) 296 67, 154 5 diagnosed between 1980 and 1984 902 controls matched for sex, age (≥ 5 yr), and neighborhood of residence. Subjects were white and from the same 3-county area of western N.Y.</td>
<td>A structured interview (c. 2.5 hr) containing information about demographics, occupation, health history, oral health, drug, alcohol, and tobacco use, and occupational exposures was given to all subjects. Interviews occurred typically within 3 mo of diagnosis for cases. Diet history was collected with a modified 129-item food-frequency questionnaire. Subjects were asked to give average frequency of consumption and typical serving size. Reference time for cases was a year before the appearance of symptoms; for controls the period just prior to the interview.</td>
<td>The age and smoking history (pack-years) adjusted risk analysis showed no difference in vitamin C intake between groups. There was a significantly reduced risk associated with vitamin A (carotene) intake and lower quartiles of fat consumption. The vitamin A association was statistically significant for 6, for those with squamous cell carcinoma, for light or ex-smokers, and for those &gt;60 yr.</td>
<td>Retrospective food frequency was only source of diet data, no data on supplement use. Much longer period between interview for cases than controls. Mean nutrient data not given. No descriptive statistics (t-tests) given. Health history of controls not reported. No biochemistry.</td>
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<td>Fontham et al., 1988</td>
<td>Case-control Los Angeles</td>
<td>1253 cases of lung cancer 1274 controls matched for race, sex, and age (≥ 5 yr) were all admitted to the same hospitals as cases. There were significantly more non-smokers in the control group (31.6% vs 4.3%).</td>
<td>All subjects were given a questionnaire containing diet and tobacco history, occupational, residential, medical and family health histories. A 59-item food-frequency questionnaire was given with the reference period being before appearance of symptoms. Surrogates were interviewed in both cases (26.7%) and controls (11.5%) were subjects when unable to respond.</td>
<td>An inverse association was found between vitamin C intake and specific types of LC (squamous and small cell). A similar, though not as strong, effect was found for vitamin A (carotene). There was a significant inverse relationship between retinol intake and adenocarcinoma in blacks.</td>
<td>Time from diagnosis for either group not given. No community-based control group. Since comparisons were based on tertiles of intakes for control group, there may have been an underestimation of intake and associated risk due to low intakes of hospital controls. No data on supplement use. No descriptive data reported for nutrient intake. No comparisons to intake standards, e.g., RDA. No biochemistry.</td>
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<td>Koo et al., 1988</td>
<td>Case-control</td>
<td>88 cases of lung cancer 137 district-matched controls All subjects were ≥ 9 with no known history of smoking.</td>
<td>All subjects were interviewed for demographic data, including household number, and a food frequency questionnaire. Cases asked about intake 1 yr prior to diagnosis. Controls asked about current intake and were interviewed within 6 wk of matched cases.</td>
<td>Protective effect of high consumption of leafy green vegetables, carrots, tofu, fresh fruit, and fresh fish in cases of adenocarcinoma and large cell cancer. Fresh fruits found to offer protection against squamous cell tumors.</td>
<td>Data analyzed by foods, no analysis for specific nutrients, no biochemistry. Retrospective data, large difference in reference intervals: cases, 1 yr prior to diagnosis, controls, current diet. Conclusions regarding potential protective effects of vitamin C, retinol and calcium are presumptive.</td>
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<td>LeGardeur et al., 1990</td>
<td>Case-control</td>
<td>59 cases of lung cancer 59 hospital controls (HC) selected in a next-patient-encountered procedure. 31 community controls (CC) subjects were matched for age (≥ 5 yr), race, county.</td>
<td>LC and HC subjects given a structured interview to obtain data about smoking history and dietary intake (method not described). 20 ml non-fasting venipuncture samples were collected from all subjects. Measures included serum ascorbate, retinol and carotenoids, vitamin E and cholesterol. Assays were done within a month of collection. CC group was not interviewed, only blood was collected.</td>
<td>Mean serum levels of carotenoids, vitamin E, and total cholesterol for LC cases were significantly lower than HC. Although reported as not different, HC subjects had significantly lower levels of vitamin C and vitamin E than CC. Cholesterol adjusted serum levels of vitamin E were still significantly lower in LC cases than HC.</td>
<td>No diet data reported. No questionnaire data for CC group. The CC group was compared to HC group to test for appropriateness of HC as controls for LC group. Text reported no difference. Data in table indicated significant differences in the major dependent variables, vitamins C and E. LC and HC group were not matched for smoking history. In addition the nature of the illnesses (e.g., 20% CHD, 14% metabolic, endocrine, or nutritional disorders) of the HC group also made it an inappropriate control. No comparisons between CC group and LC cases, although the LC cases did have lower levels of vitamins E and C and retinol and carotenoids. Retinol binding protein was significantly associated with all variables except vitamin C; this could reflect a general malnutrition or a metabolic defect. Insufficient data to make appropriate interpretation. Given the inappropriateness of the controls and poor matching, the use of a paired t-test must be questioned. Poorly designed study.</td>
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<td>Le Marchand et al., 1989</td>
<td>Case-control</td>
<td>432 cases of lung cancer (230 ᵃ, 102 ᵃ) 885 community controls matched for age and sex. Cases diagnosed over 2-yr period 1983–85.</td>
<td>All subjects given a structured interview to garner data on smoking and alcohol consumption history. Interviews were done at home with the subject or surrogate (29% for cases, 7% for controls). 130-item food-frequency questionnaire was given to all subjects. The reference period was a usual wk, mo, or yr before onset of symptoms for the patients and a corresponding time period for the controls.</td>
<td>An inverse association between total vitamin C (from food and supplements) in males only. Total vitamin A (food and supplements) was also inversely associated with risk, but not significantly, in ᵃ. There was an apparent interaction between sex and race for vitamin C. A dose-dependent negative association was found between dietary β-carotene and LC. All vegetables, dark green vegetables, cruciferous vegetables, and tomatoes showed stronger association than β-carotene.</td>
<td>Did not control for ethnic differences in intake. No biochemistry. The authors concluded that the effects associated with vitamin C (resulting from interaction between sex and race) were aberrations that could not be explained by any known biological mechanism and therefore did not explore the vitamin C question further.</td>
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<tr>
<td>Boeing and Frentzel-Beyme, 1991</td>
<td>Case-control Germany</td>
<td>142 cases of stomach cancer  579 controls, either patients or visitors to local hospital. No other details supplied.</td>
<td>Subjects selected from either 3 counties with high incidence or 1 with low incidence. All subjects given an interview about demographics, residential, occupational, medical and smoking histories, water supply, food conservation methods. Reference period for dietary questions was 5 yr prior to onset of a severe disease. No other details about dietary information given.</td>
<td>Vitamin C, the type of water supply (well vs public), years of refrigerator use, and type of wood used for smoking were associated with risk. Other factors such as smoking, food groups, and alcohol consumption were not considered because &quot;of their uncertain mode of action or the possibility of spurious associations.&quot; Use of spruce wood, well water, limited refrigerator use, and low intake of vitamin C were all associated with increased risk for stomach cancer.</td>
<td>Limited data on methods used for collection of dietary data and no description of how the vitamin C intake levels were derived. No biochemical assessment of vitamin C status. Limited description of subjects with no description of duration or stage of disease in cases. The control group contained both hospital patients and visitors (presumably healthy). There was no reference period given for the healthy controls.</td>
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<td>Bulatti et al., 1989, 1990</td>
<td>Case-control Italy</td>
<td>1016 cases of gastric cancer (GC) histologically confirmed between 6/85 and 12/87  1159 controls matched for age (5-yr strata) and sex. All subjects chosen from area surrounding the clinical centers involved.</td>
<td>All subjects given a structured interview to garner data about demographics, socioeconomic status, occupational histories, smoking and medical histories, and diet. 146-item food-frequency questionnaire used. Reference period for cases and controls was the 12-mo period 2 yr prior to the interview. 94% of cases were interviewed in hospital, 69% of controls interviewed at home, 30% of controls interviewed at local health department.</td>
<td>In the 1989 report on foods only, there was significantly reduced risk associated with increased intakes of raw vegetables, fresh fruit and citrus fruits. Increased risk with consumption of traditional soups, meat, salted dried fish and a combination of cold cuts and seasoned cheeses. The 1990 report focused on individual nutrients and found risk decreased in proportion to intake of vitamin C, β-carotene, α-tocopherol, and vegetable fat. Vitamin C had the largest geographical gradient with highest consumption in lowest risk areas.</td>
<td>Long time period between reference period and interview. Reliance on retrospective data. No biochemistry. Stage of disease of cases not reported. No descriptive statistics. There was an apparent difference (no statistics) in SES with cases being lower than controls. No means given to compare with known standards of intake, e.g., RDA. Control group diet is of unknown quality.</td>
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<td>Chyou et al., 1990</td>
<td>Case-cohort</td>
<td>111 cases of GC 361 controls. All subjects came from a larger cohort of 8068 American</td>
<td>All subjects from original cohort were interviewed and examined and gave</td>
<td>There were no significant differences in age-adjusted mean nutrient intakes between groups. Cases consumed significantly less vegetables than controls. There was a nonsignificant difference in fruits (cases &lt; controls, p &lt; 0.07). There was a statistically significant inverse relationship between risk of GC and intake of all vegetables. There was also an inverse relationship between fruit consumption and GC but that failed to reach significance after adjustment for cigarette smoking.</td>
<td>No matching for SES or any other demographic factors. Variable period between interview and diagnosis in cases. No biochemistry. Association with vitamin C is presumptive as study did not assess specific nutrients.</td>
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<td>Hawaii</td>
<td># of Japanese ancestry interviewed from 1965-1968. Cases were identified from 1966-1983.</td>
<td>a 24-hr dietary recall which is the source of the data for this report.</td>
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<td>Kono et al., 1988</td>
<td>Case-control</td>
<td>139 cases of newly diagnosed GC 2574 hospital based controls (HC) 278 randomly selected</td>
<td>GC and HC subjects interviewed in hospital, CC at home. Data collected</td>
<td>In comparison with both control groups, there was an inverse relationship between intake of fruits and GC. Also, there was decreased risk associated with increased intake of green tea (&gt;10 cups/day).</td>
<td>No controls for SES (except approximate geographic area). No biochemistry. No data on nature of health problems in HC group. Evidence of relationship between vitamin C and GC presumptive as study did not evaluate individual nutrients.</td>
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<td>Japan</td>
<td>community controls (CC) Subjects matched for age and sex.</td>
<td>included occupational smoking and dietary histories. Reference period for</td>
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<td>You et al., 1988</td>
<td>Case-control China</td>
<td>564 cases of GC 1131 population-based controls matched for age and sex. Cases identified over a 2.5-yr period.</td>
<td>All subjects given a structured interview to collect data about demographics, medical history, occupation, smoking history, and diet. 88-item food-frequency questionnaire. Reference period 'several years prior to the interview (about 1960) and just prior to the Cultural Revolution (1965). The majority of subjects were interviewed at home (96% cases, 75% controls). Data presented represented 1980 interviews.</td>
<td>There was a decline in risk of GC with increased consumption of carotene, vitamin C, and calcium which was associated with high intakes of fresh vegetables and fruits.</td>
<td>Very long time between reference period and interview for all subjects. No biochemistry. No descriptive statistics given to indicate mean intakes of nutrients. The control group's intake was of unknown quality.</td>
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<tr>
<td>Burr et al., 1987</td>
<td>Cross-sectional England and Wales, UK</td>
<td>75-74 yr from 2 towns with differing death rates from stomach cancer (1 high-risk, 1 low-risk compared to relative rates for England and Wales) were compared. Random selection from pools of 4078 in the low-risk town and 2789 eligible in the high-risk town resulted in samples of 267 and 246 subjects used for comparisons.</td>
<td>Data included items from a standardized questionnaire and anthropometric measures. Blood samples were taken for assessment of ascorbate and pepticogin. Samples were collected 'at least 2 hours after last meal'.</td>
<td>Plasma ascorbate levels and fruit intake were significantly higher in the low-risk sample. There was no direct relationship between ascorbate levels and the presence of severe atrophic gastritis.</td>
<td>No diet data given. Nature of the food frequency-questionnaire not described. Significant difference between towns in terms of SIS. No matching of subjects in terms of smoking, demographics, or health history. Significant difference in gastric surgery incidence and severe atrophic gastritis between towns. Case-control comparison within and between towns might have garnered more useful data.</td>
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<td>Study</td>
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<td>Falk et al., 1988</td>
<td>Case-control Louisiana</td>
<td>363 cases of pancreatic cancer (PC) 1234 hospital based controls (HC) matched on hospital of admittance, race, sex, and age (± 5 yr).</td>
<td>All subjects were given an interview to obtain data on smoking, occupational and residential history, alcohol use, family health history, medical history, leisure time activities, and diet. A 59-item food-frequency questionnaire was used. The reference period was the time (unspecified) prior to diagnosis or onset of symptoms. &gt;50% of cases were unable to be interviewed personally, necessitating the use of surrogates (next-of-kin, usually a spouse), 13% of controls were unavailable.</td>
<td>Fruit consumption (fresh and juice) showed a significant inverse relationship with PC. There was a smaller inverse association with vegetable intake. Risks associated with consumption of fruits and with an index of vitamin C showed significant decreasing gradients across sexes. Cigarette smoking was a strong risk factor for PC.</td>
<td>Control diet of unknown quality used as reference. No descriptive data reported nor comparisons of diet to reference standard, i.e., RDA. No community-based control group. Unknown time period between time of interview and diagnosis and/or onset of symptoms. Controls’ diet response reflective of recent intake patterns. No data on supplement use. No biochemistry. No testing for the potential interaction between smoking and vitamin C index or fruit consumption.</td>
</tr>
<tr>
<td>Farrow and Davis, 1990</td>
<td>Case-control Washington</td>
<td>148 married &amp; cases of PC diagnosed between 1982–1986 188 married &amp; controls randomly selected and frequency matched by age (± 5 yr)</td>
<td>Data from all subjects was collected from surrogates (wives). Two-stage data collection: 1) a telephone interview was used to collect demographic data, medical and occupational history, and use of tobacco, alcohol, coffee, and vitamin supplements, and 2) a dietary questionnaire containing a 135-item food-frequency questionnaire was mailed. Reference period was 3 yr prior to diagnosis.</td>
<td>No association between PC risk and intake of vitamin C or total fat, saturated fat, cholesterol, omega-3 fatty acids, or vitamin A.</td>
<td>Reliability and validity of data acquisition is questionable. Reliance on retrospective data collected from surrogates. Reference period was 3 yr prior to interview.</td>
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<td>La Vecchia et al., 1990</td>
<td>Case-control Italy</td>
<td>247 cases of PC 1089 age- and sex-matched hospital-based controls with acute non-digestive, non-neoplastic disease.</td>
<td>All subjects were given a structured interview to obtain data on SES, smoking, alcohol and coffee intake, medical history, and dietary intake of 14 &quot;indicator foods.&quot; Reference period 1 yr prior to treatment.</td>
<td>Statistically significant decreased risk with increased intake of fresh fruits. Similar inverse relationship between risk and intake of fish and oil (uncharacterized).</td>
<td>No biochemistry, long period between reference period and interview, no adjustment in analysis or matching for SES or other confounding variables, i.e., smoking. No descriptive data. No community-based control or comparisons to reference standards of normal intake. Vitamin C effect would be presumptive. No assessment of individual nutrients.</td>
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<td>Mills et al., 1988</td>
<td>Cohort California</td>
<td>Study population was 84,188 non-Hispanic, Seventh Day Adventists &gt;25 yr of age. 40 cases of death from PC occurring during the follow-up period of 1974–1982</td>
<td>All subjects completed a lifestyle questionnaire, details of which were not supplied.</td>
<td>Current use of meat, poultry, or fish was associated with increasing risk. There was a significant increase in risk associated with increasing consumption of eggs. Intake of vegetarian protein products, legumes, and dried fruits were significantly inversely related to risk. No relationship between risk and intake of other fresh fruit, canned or frozen fruit, fresh citrus fruit, fresh winter fruit, green salads, or cooked green vegetables. These results were age- and sex-adjusted.</td>
<td>Problems include no comparison group, no data on quality of diet, no details on diet data, no data on individual nutrients, no data on supplement use, no biochemistry, and no demographics.</td>
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## APPENDIX TABLE. VITAMIN C AND COLORECTAL CANCER

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<td>DeCosse et al., 1989</td>
<td>Intervention-randomized double-blind, placebo-controlled. New York, NY</td>
<td>58 patients with familial adenomatous polyposis drawn from an initial pool of 72 who had total colectomy and ileorectal anastomosis 1 yr prior to the study</td>
<td>Control group got 8 caps placebo (lactose/d) + 2.2 g of low fiber. Vitamin group got 4 g vitamin C/d + 400 mg vitamin E/d + 2.2 g of low fiber. Fiber group got both vitamins + 22.5 g of high fiber/d. All subjects had a 3-mo placebo period, 4-yr trial. All groups received 30 mg vitamin C, 2,000 IU vitamin A and equivalent amounts of several other vitamins and minerals (about 30% RDA). Patients had 18 examinations over test period. Each completed a 3-d diet diary prior to each visit. Subjects also completed a food frequency questionnaire at each visit.</td>
<td>Subject groups were comparable in demographics, median time since colectomy, median intake of fiber at baseline, and prior supplementation with vitamins C and E. There were no discernible effects for the vitamins. The high-fiber group had the stronger benefit especially during the middle years of the trial. Compliance for all groups decreased over the course of the trial.</td>
<td>No blood levels of the vitamins were reported for baseline or during the trial. No data of dietary vitamin intakes at baseline or during trial were reported. Because of combined use of vitamins, an analysis of independent effects or interactions of individual vitamins was not possible.</td>
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<td>Freudenheim et al., 1990</td>
<td>Case-control New York</td>
<td>422 cases of rectal cancer (277 d, 145 f) 422 sex-, race-, age-, neighborhood-matched controls.</td>
<td>Subjects given a 2.5 hr interview consisting of food-frequency questionnaire covering the previous yr for controls and for cases a yr prior to the onset of symptoms. Additional information included smoking and alcohol use, occupational and health histories, seasonality of intake, preparation, and food storage.</td>
<td>Decreased risk with increasing intake of carotenoids, vitamin C and dietary fiber from vegetables. No association between intake of vitamin E and risk. Increased risk with increasing intakes of calories, fat, carbohydrate, and iron.</td>
<td>Reliance on retrospective food-frequency interviews. No data on use of supplements or stage of disease (except that &quot;only relatively alert, healthy subjects could tolerate the 2.5 hr. interview&quot;). Well-conceived study.</td>
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<td>Graham et al., 1988</td>
<td>Case-control</td>
<td>New York, 428 cases of colon cancer (CC) and 428 controls matched for age, sex, and neighborhood.</td>
<td>All subjects given a structured 2.5 hr interview similar to that used by Freudenstein et al. (1980) No reference period was noted for the diet data. No surrogates were used.</td>
<td>No significant risks associated with intake of protein, vitamin A from vegetables and fruits, carbohydrates, vitamin C, cruciferous vegetables, calcium, or phosphorous. There was significantly reduced risk associated with high intakes of tomatoes, peppers, carrots, onions, and celery. Risk of CC was positively associated with increasing intake of total fats (predominantly animal fat) and total calories.</td>
<td>No reference period for food-frequency questionnaire given. No data on supplement use.</td>
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<td>La Vecchia et al., 1988</td>
<td>Case-control</td>
<td>Italy, 339 cases of colon cancer (CC) and 236 cases of rectal cancer (RC) 778 hospital controls admitted for acute, non-neoplastic, or digestive disorders.</td>
<td>All subjects given a questionnaire to obtain data on SES, smoking, alcohol, coffee and other methylxanthine-containing drinks, personal and family health history, and use of selected drugs. 29-item food-frequency questionnaire. Reference period was an unspecified period before current hospital admission. Subjects also asked to report changes over previous 10 yr.</td>
<td>Risk of both CC and RC was inversely related to intake of green vegetables, tomatoes, melon, and coffee. There was also an inverse relationship between risk and indices of carotenoid and vitamin C intake. Consumption of pasta and rice associated with increased risk of both cancers.</td>
<td>No supplement data, variable reference times for cases and controls, no population based-control. Diet database was small (only 29 items). Individual nutrient estimation unreliable due to lack of portion size information. No biochemistry. No descriptive data or comparisons with normal standards of intake.</td>
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<td>McKeown-Eyssen et al., 1988</td>
<td>Intervention (randomized double-blind trial) Toronto, Canada</td>
<td>185 cases with at least 1 polyp in the colon or rectum. 96 received vitamins 89 received placebo All subjects were presumed to be poly-free at start of the trial.</td>
<td>Subjects completed questionnaire containing a limited (9-item) food-frequency questionnaire, demographic data, smoking status, bowel habits, previous polyp history, and vitamin supplement use. Subjects randomized to receive 400 mg vitamin E and C or lactose placebo over 2-yr period and re-examined (blinded). Random urine samples were collected to test for compliance. The two groups were matched for all parameters except that the vitamin group had more members who used vitamin C supplements prior to trial.</td>
<td>There were no differences in food frequency items. 137 subjects (75%) completed the trial. Polyps found in 41.4% of vitamin group and 60.7% of placebo.</td>
<td>No biochemical data either at baseline or after trial. Insufficient power due to small sample size. Because of the design, the study could not distinguish differences in effect of individual vitamins.</td>
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<td>Neugut et al., 1988</td>
<td>Cross-sectional New York</td>
<td>244 ° who had undergone colonoscopy 105 cases of polyps 56 cases of colon cancer 83 ° without colonic neoplasia</td>
<td>All subjects were given a structured telephone interview. Information garnered included demographics, SES factors, lifestyle, personal and family health history, and reproductive history. Subjects were asked about use of multivitamins and individual vitamin supplements (A, C, E).</td>
<td>Significant differences in SES factors, e.g., education, between CC group and either of the others. Use of any vitamins in the 3 groups were 45% of CC compared to 61 and 69% of the other 2. This was not statistically significant.</td>
<td>No data on amount of supplement, current or past diet, or duration of supplement use. Reference period was after surgical procedure. No appropriate control group.</td>
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<td>Tuyns et al., 1997b</td>
<td>Case-control Belgium</td>
<td>453 cases of colon cancer (CC) 365 cases of rectal cancer (RC) 2851 controls All subjects were from same 2 provinces and adjusted for age and sex.</td>
<td>All subjects interviewed about diet using food frequency questionnaire. Reference period for cases 1 wk period prior to onset of disease, controls current intake. Portion sizes were estimated using food models (pictures). Cases interviewed in hospital, controls at home.</td>
<td>No association between risk for either CC or RC and vitamin C intake. Positive associations were found for retinol, oligosaccharides. Negative associations for fiber, linoleic acid, thiamine, and iron.</td>
<td>Retrospective data collection. Differences in reference period between controls and cases. Group differences by province and sex. No biochemistry, supplementation data, descriptive data on intake, demographics, smoking, alcohol, medical histories, or comparisons to normal standards for intake.</td>
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<td>West et al., 1989</td>
<td>Case-control</td>
<td>231 cases of newly diagnosed colon cancer (CC) 391 controls matched by age (± 5 yr), sex, and county of residence.</td>
<td>All subjects were interviewed in their homes. Questionnaire consisted of demographic, health history, current height and weight (2 yr before interview), computed body mass index, physical activity, and dietary data. 49-item food-frequency questionnaire. Reference period was &quot;2–3 years prior to the interview.&quot; Portion sizes were estimated with food models.</td>
<td>No association between CC risk and intake of vitamin C. Protective effects of β-carotene and cruciferous vegetables. Fiber was protective in %.</td>
<td>Unknown relationship between reference period and time of diagnosis in cases. No biochemistry, comparisons to intake standards or descriptive statistics. No data for SES, or alcohol, smoking, or supplement history.</td>
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<td>Kolonel et al., 1988</td>
<td>Case-control</td>
<td>452 cases of histologically confirmed prostatic cancer (PC) 899 age-matched controls Subjects &gt;65 yr were randomly selected from a central insurance registry, those &lt;65 yr selected with random-digit dialing</td>
<td>All subjects were given an extensive home interview to collect data on dietary, occupational, medical, social, and demographic histories. Food-frequency questionnaire (100+ items) was used. Reference period was a usual mo prior to onset of the disease for cases and a corresponding period for controls. Surrogates were used for those subjects who could not be interviewed.</td>
<td>There were no associations between risk and either total or food sources of vitamin C. No differences found in potential confounding variables: SES, marital status, anthropometries, or family history. Older cases consumed significantly more saturated fat, total vitamin A, and zinc than age-matched controls. These differences were reflected in increased risk associated with saturated fat and zinc. No differences in younger subjects.</td>
<td>Total vitamin C (food + supplements) intakes ranged from 2500–3000 mg/wk across all groups. This is a well-designed and executed study.</td>
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<tr>
<td>Ohno et al., 1988</td>
<td>Case-control</td>
<td>180 cases newly diagnosed of prostatic cancer (PC) 100 controls with benign prostatic hyperplasia (BPH) 100 hospital controls without BPH, other malignancies, liver disease, or hormonal disorders All subjects were matched for hospital, age (≤3 yr) and date of admission (≤3 mo).</td>
<td>Data collected by interview upon admission to hospital included birthplace, occupational history, marital history, religion, body type, medical history, sex-life, and dietary practices. Food-frequency questionnaire assessed dietary habits during the period 8 yr prior to current admission.</td>
<td>Intake of vitamin C from foods was not significantly associated with PC risk. Low intakes of vitamin A (retinol and β-carotene) were associated with increased risk. The risk reduction associated with vitamin A and β-carotene was seen in older but not younger males.</td>
<td>No supplement data, confusing statistics, lack of community-based control. Long retrospective period, 8 yr. No smoking data.</td>
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## Appendix Table: Vitamin C and Cervical/Ovarian Cancer

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<tr>
<td>Brock et al., 1988</td>
<td>Case-control</td>
<td>117 cases of cervical cancer 100 controls matched for SES, age (≥ 5 yr) 100 of the</td>
<td>All subjects interviewed either at home or at work. Cases interviewed within 6 mo of diagnosis. Questioned on demographics, reproductive,</td>
<td>Cases were not matched on sexual habits, smoking, or use of oral contraceptives. Crude risk estimates showed a significant protective effect from carotene, vitamin C, and folate. After adjustment for known risk factors the protective trends for all except vitamin C (p &lt; 0.07) disappeared. When combined together, vitamin C, fruit</td>
<td>No data on amount or type of supplements used nor were any comparisons made with regard to dietary intake or blood levels. No vitamin C biochemistry. Blood sampling of cases may have reflected state vs trait phenomena.</td>
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<td>Australia</td>
<td>interviewed cases and 140 of the controls agreed to blood sampling</td>
<td>contraceptive, and gynecological factors. 160-item food-frequency questionnaire with an emphasis on vitamins A, C, and folate. Blood collected after an overnight fast and assessed for β-carotene, retinol, and other carotenoids with HPLC methods.</td>
<td>adjusted for known risk factors the protective trends for all except vitamin C (p &lt; 0.07) disappeared. When considered together, vitamin C, fruit juices, and plasma β-carotene showed a significant protective effect. Fruits did not show a protective effect.</td>
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<tr>
<td>Shu et al., 1989</td>
<td>Case-control</td>
<td>172 cases of epithelial ovarian cancer 172 controls matched for age (≥ 5 yr), residence</td>
<td>All subjects interviewed about demographics, reproductive history, personal and family health histories, occupational history, and diet. 63-item food-frequency questionnaire.</td>
<td>No effect of dietary vitamin C. Significantly increased risk associated with total and saturated fat.</td>
<td>No time frame between interview and diagnosis given; no reference period given for cases. No biochemistry, no supplement data, no descriptive statistics or comparisons to known standards of intake. Groups were not matched for SES, cases were more educated.</td>
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<td>Shanghai, China</td>
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<td>Slattery et al., 1989</td>
<td>Case-control</td>
<td>85 cases of primary ovarian cancer 482 population-based controls matched for age</td>
<td>All subjects interviewed in-person at home by 8. Data collected included demographics, smoking history, medical history, contraceptive use, pregnancy history, and anthropometrics. 183-item food-frequency questionnaire used to obtain usual adult dietary habits. No reference period given.</td>
<td>No effect of vitamin C. Small non-significant decrease in risk associated with vitamin A, C, and fiber. Adjusted risk reduced for high intakes of β-carotene.</td>
<td>Used nutrient analysis rather than food groups. No supplement data. Low response rate in cases.</td>
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<td>Verresut et al., 1989</td>
<td>Case-control Washington (state)</td>
<td>189 cases of cervical cancer 227 controls, age-matched and identified by random-digit-dialing methods</td>
<td>All subjects were given a telephone interview by a female interviewer to collect data on demographics, reproductive history, contraceptive methods, smoking history, anthropometries (self-reported), health history, and sexual habits. 66-item food-frequency questionnaire included vitamin supplement use. Reference period was the year prior to a reference date (date of diagnosis for cases and Dec. 31, 1981 for controls).</td>
<td>Decreased risk associated with high intakes of vitamin C. After adjustment for known risk factors, increased intakes of dark green or yellow vegetables and fruit juices were associated with significantly reduced risk.</td>
<td>No portion sizes given on food-frequency questionnaire; portion sizes estimated from food composition tables. No biochemistry. Use of a long retrospective period; the average delay between interview and reference period was 2.8 yr for cases and 2.7 yr for controls.</td>
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<td>Ziegler et al., 1990</td>
<td>Case-control Cross-sectional multicenter study: Chicago, IL, Birmingham, AL, Denver, CO, Miami, FL, Philadelphia, PA</td>
<td>271 cases of cervical cancer 602 controls matched by age, race, and telephone exchange All subjects were white, non-Hispanic</td>
<td>All subjects interviewed at home Data collected included demographics, sexual behavior, reproductive and menstrual history, use of contraceptives and female hormones, personal and family health history, smoking habits, and diet. 75-item food-frequency questionnaire about usual adult intake of foods and vitamin supplements. Subjects asked about number of servings per d, wk, mo, or yr.</td>
<td>No effect of either vitamin C or vitamin C-rich foods or any other foods or nutrients.</td>
<td>No reference period relative to onset of symptoms or diagnosis in cases. Cases were histologically confirmed during period 4/82-12/83.</td>
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<td>La Vecchia et al., 1989</td>
<td>Case-control northern Italy</td>
<td>163 cases of bladder cancer histologically confirmed within 1 yr before interview (total pool eligible not given) 181 hospital controls (HC)</td>
<td>All subjects given interview to obtain information about SES factors, smoking, alcohol, coffee and other methylxanthine consumption habits, personal and family health history, and specific medication history. Subjects were asked about frequency of consumption of 10 food items. Reference period for cases was the period before onset of symptoms; none was given for controls.</td>
<td>No effect from either fruit or vitamin C. The frequency of consumption of green vegetables and carrots was lower in cases; increased risk for BC associated with low intake. Protective effect was stronger in current smokers.</td>
<td>Reference period was at least 2 yr before interview for cases. Very limited number of items (10) on food-frequency questionnaire. No supplement use data.</td>
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<td>Stähelin et al., 1989</td>
<td>Prospective cohort study Basel, Switzerland</td>
<td>2975 ♂ comprised the original pool from which 102 total cancer deaths occurred (37 lung cancer, 17 stomach cancer, 8 colorectal cancer, and 39 cancers at &quot;other sites&quot;)</td>
<td>Samples were collected over a 2-yr period (1971–73). Analysis was done immediately.</td>
<td>After adjustment for smoking, blood vitamin C was significantly lower in stomach cancer deaths.</td>
<td>No diet data, no supplement data, and no control for seasonal variations in diet that might influence blood vitamin levels. Reliance on point-sample procedure.</td>
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