

Antioxidant Vitamins Reduce the Risk for Cancer: Part One

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Introduction

The published scientific evidence that increased consumption of antioxidant vitamins, vitamins C and E, reduces the risk of cancer has been growing over the last several decades. This review assesses the evidence that was reviewed previously by the Food and Drug Administration along with the evidence that has appeared since that review was completed. The conclusions that are drawn are based on the totality of publicly available scientific evidence, with emphasis on well-designed studies that were conducted in a manner which is consistent with generally recognized scientific procedures and principles and which provide credible scientific evidence. These conclusions are drawn with the recognition that an apparent finding of “no effect” is not equivalent to a finding of a “negative effect” and that studies that demonstrate neither beneficial nor harmful effects do not “oppose” studies that do observe a beneficial effect.

This scientific evidence reveals that vitamin C and vitamin E reduce the risk for cancer in general. Individually, they each reduce the risk of several site-specific cancers, including colon cancer, squamous cell carcinoma of the esophagus, gastric carcinoma, laryngeal cancer, lung cancer, cancer of the oral cavity, pancreatic cancer, pharyngeal cancer, renal cell cancer, cancer of the salivary glands, bladder cancer, brain cancer, cervical cancer, and rectal cancer.

Vitamin C Reduces the Risk for Cancer

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for cancer. In the 24-year

prospective Western Electric Company Study conducted in Chicago, IL, the risk of death from cancer was reduced significantly by greater intakes of vitamin C (RR, daily vitamin C intake 113 to 393 mg vs 21 to 82: 0.61; $p < 0.05$; adjusted for age, systolic blood pressure, BMI, serum total cholesterol concentration, smoking status, family history of cardiovascular disease, alcohol consumption and dietary intakes of energy, cholesterol, iron, saturated fatty acids and polyunsaturated fatty acids).¹ This protective effect of vitamin C was more pronounced among smokers. In another, 17-year prospective study of 2,974 men in Basel, Switzerland, mean serum vitamin C concentrations were significantly lower in men who died from cancer than they were in men who remained cancer-free.^{2,3}

Consistent with these reports, when men and women who had participated in the National Health and Nutritional Examination Survey II between 1976 and 1980 were contacted again, 12 to 16 years later, the adjusted risk of dying from any cancer was found to be increased significantly in men with serum ascorbate concentrations $< 28.4 \mu\text{M}$, compared to the risk in men with serum ascorbate concentrations $> 73.8 \mu\text{M}$, in 1976-1980 (RR: 1.62; 95% C.I.: 1.01, 2.59; adjusted for age, race, education, cigarette smoking, alcohol consumption, history of diabetes, serum total cholesterol concentration, systolic blood pressure and BMI).⁴ Women were not similarly affected. However, the results of observing a cohort of 11,580 initially cancer-free residents of a retirement community for 8 years indicated that the risk of developing cancer in women (but not in men) was inversely correlated with the daily consumption of vitamin

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C.⁵ In addition, in a case-control study, persons with cancer affecting different sites (breast, head and neck, genitourinary, lung, gastrointestinal and others) exhibited significantly lower mean serum vitamin C concentrations.⁶

On the other hand, the results of a 13.8-year prospective observational study of 2,112 Welsh men indicated that differences in vitamin C intakes did not affect mortality from cancers of the respiratory tract or from cancers of the digestive tract (adjusted for age, smoking status, social class, BMI, daily intakes of total energy and fat and alcohol consumption).⁷ In the 8-year prospective Nurses' Health Study of 89,494 women in the US, the risk of developing cancer was not affected by differences in vitamin C intakes.⁸ Consistent with these reports, in a prospective observational study of 605 men and women with coronary heart disease, there were no differences in the average vitamin C intakes between those subjects who developed cancer during the study and those who did not.⁹ Similarly, in a 28-year prospective observational study in Washington County, MD, differences in vitamin C intake had no effect on hazard ratios for all-cause mortality or death from cancer but 50% of subjects consumed less than the RDA for vitamin C.¹⁰ These data suggest that among vitamin C deficient adults, the degree of deficiency has no effect on all-cause mortality or death from cancer and increased risk for premature death is a feature of chronic vitamin C deficiency.

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for cancer. The evidence documented by a prospective observational study⁵ and a retrospective observational study⁶ supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for cancer. In addition, the scientific evidence indicates that increased consumption

of vitamin C reduces the risk for death from cancer. The evidence documented by 4 prospective observational studies¹⁻⁴ supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for death from cancer.

Vitamin C Reduces the Risk for Bladder Cancer

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for bladder cancer. The results of several retrospective observational studies are consistent with this conclusion. In a case-control study conducted in Los Angeles, CA, compared to the consumption of less than 62 mg/day of vitamin C, the consumption of more than 168 mg/day of vitamin C reduced significantly the multivariate-adjusted odds of developing bladder cancer (OR: 0.52; 95% C.I.: 0.56, 0.95; adjusted for education, number of cigarettes smoked per day, number of years smoking, current smoking status, lifetime use of nonsteroidal anti-inflammatory drugs and number of years employed as a hairdresser or barber).¹¹ In a similar case-control study of middle-aged men and women conducted in Washington State, individuals consuming the most dietary vitamin C experienced significantly less risk for bladder cancer (OR, dietary vitamin C intake > 156 mg/day vs < 78 mg/day: 0.50; 95% C.I.: 0.28, 0.88; adjusted for age, sex, county, smoking and daily energy intake).¹² Similarly, individuals who consumed the most vitamin C from dietary supplements experienced significantly less risk for bladder cancer (OR, supplemental vitamin C intake > 502 mg/day vs none: 0.40; 95% C.I.: 0.21, 0.76; adjusted for age, sex, county, smoking and daily energy intake) and individuals who consumed the most total vitamin C from foods and dietary supplements experienced significantly less risk for bladder cancer

(OR, total vitamin C intake from foods and dietary supplements > 335 mg/day vs < 95 mg/day: 0.45; 95% C.I.: 0.26, 0.79; adjusted for age, sex, county, smoking and daily energy intake).¹² Consistent with the results of these studies conducted within the US, investigators reported that men and women in Turkey with grade 1, 2 or 3 transitional cell carcinoma of the bladder had significantly lower serum concentrations of vitamin C than cancer-free men and women.¹³

In contrast, an epidemiologic analysis of the data obtained during the prospective, double-blind, randomized, placebo-controlled Alpha-Tocopherol, Beta-Carotene Cancer Prevention study of 29,133 middle-aged male cigarette smokers in Finland who supplemented their diets with 50 mg of vitamin E, 20 mg of beta-carotene or placebo for 5 to 8 years, indicated that the risk of developing bladder cancer was not affected by differences in the dietary vitamin C intakes of smokers.¹⁴ However, the results of this epidemiologic analysis are relevant only to populations that match the parent experiment's subjects – middle-aged male life-long cigarette smokers, and despite the design of the parent experiment, carry no more “weight” than any other epidemiologic findings.

Several other prospective observational studies have failed to document a chemopreventive effect of vitamin C against bladder cancer. The results of the 12-year prospective observational Health Professionals Follow-Up Study of 51,529 initially cancer-free men aged 40 to 75 years indicated that the risk for bladder cancer was not affected by differences in vitamin C intakes (adjusted for cigarette smoking, region of the US, total daily fluid intake and total daily consumption of cruciferous vegetables).¹⁵ Similarly, in the 20-year prospective Nurses' Health Study of 88,796 women in the US, differences in daily vitamin C intakes from

foods or supplements did not affect the multivariate-adjusted risk of developing bladder cancer (adjusted for age, pack-years of cigarette smoking, current smoking status and total daily energy intake).¹⁶ In the largest of such studies, the 16-year prospective observational American Cancer Society Cancer Prevention Study II of 991,522 men and women in the US, the regular consumption of any amount of supplemental vitamin C for any length of time had no effect on the risk of dying from bladder cancer.¹⁷ A lack of effect of vitamin C consumption on the prevention of bladder cancer also has been observed outside of the US; for example, the results of a 6.3-year Dutch prospective observational study of 58,279 men and 62,573 women aged 55 to 69 years (the Netherlands Cohort Study) indicated that the age- and sex-adjusted risk of developing bladder cancer was not affected by differences in vitamin C intakes.¹⁸

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for bladder cancer. The evidence documented by three retrospective observational studies¹¹⁻¹³ supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for bladder cancer.

Vitamin C Reduces the Risk for Breast Cancer

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for breast cancer. In an 8-year prospective observational study of 59,036 women aged 40 to 76 years in Sweden (the Swedish Mammography Cohort), among women with BMI > 25, consuming more than the RDA for vitamin C reduced significantly the risk of developing breast cancer (HR: 0.61; 95% C.I.: 0.45, 0.82; adjusted for age, family history of breast cancer, BMI, education, parity, age at first birth, total daily energy intake, alcohol consumption and daily intakes of dietary

fiber, monounsaturated fatty acids and polyunsaturated fatty acids).¹⁹

The results of several retrospective observational studies also support the conclusion that increased consumption of vitamin C reduces the risk for breast cancer.²⁰⁻³² In a case-control study conducted in western New York state, the multivariate-adjusted odds of developing breast cancer were reduced significantly among premenopausal women by daily vitamin C intakes greater than 223 mg (OR, daily vitamin C intakes > 223 mg vs < 132 mg: 0.53; 95% C.I.: 0.33, 0.86; adjusted for age, education, age at first birth, age at menarche, history of first-degree relatives with breast cancer, personal history of benign breast disease, BMI and total daily energy intake).²⁰ This significant reduction in risk was independent of the intakes of other dietary antioxidants and did not require but was not attenuated by dietary supplementation with vitamin C, although the protection afforded by supplemental vitamin C became slightly less important with increasing consumption of vegetables. In this study, the multivariate-adjusted odds of developing breast cancer were reduced significantly in both premenopausal and postmenopausal women without a family history of breast cancer and who consumed the most vitamin C (OR, premenopausal women with daily vitamin C intake > 232 mg vs < 132 mg: 0.7; 95% C.I.: 0.5, 0.9; OR, postmenopausal women with daily vitamin C intake > 232 mg vs < 132 mg: 0.6; 95% C.I.: 0.4, 0.9; both adjusted for age, education, age at menarche, age at first pregnancy and BMI).²¹ These protective effects were not enjoyed by similar premenopausal women who had a positive family history of breast cancer, suggesting that these adequate but relatively modest intakes of vitamin C were insufficient to override other predisposing factors.²¹

In a case-control study conducted in Germany, the odds of developing breast

cancer were halved by vitamin C intakes greater than the RDA (OR, vitamin C intake > 134.4 mg/day vs < 58.5: 0.49; 95% C.I.: 0.28, 0.88; adjusted for age, total daily energy intake, age at menarche, age at first birth, age at menopause, family history of breast cancer, current smoking status, personal history of benign breast disease, BMI, daily alcohol consumption and current or recent use of hormone replacement therapy).²² In a case-control study conducted in Seoul, Korea, the odds of developing breast cancer were reduced significantly by daily vitamin C intakes greater than 210 mg (compared to daily vitamin C intakes less than 100 mg, OR: 0.37; 95% C.I.: 0.19, 0.84; adjusted for age at menarche, total number of menstrual periods, parity, total number of full-term live births, total months of breastfeeding, family history of breast cancer and BMI).²³

In a case-control study conducted in Moscow, USSR, the odds of developing breast cancer in postmenopausal women were reduced significantly by vitamin C intake (OR, greatest vitamin C intake vs the lowest: 0.20; 95% C.I.: 0.06, 0.70).²⁴ In another case-control study conducted in Navarra, Spain, the odds of developing breast cancer were reduced significantly by the consumption of vitamin C (OR, greatest vitamin C intake vs the lowest: 0.40, 95% C.I.: 0.2, 0.9).²⁵ In another case-control study of women conducted in western India, the odds of developing breast cancer were significantly lower among women who consumed the most vitamin C, compared to the odds among women who consumed the least (OR: 0.42; 95% C.I.: 0.22, 0.80).²⁶ In another case-control study conducted in Uruguay, the odds of developing breast cancer were reduced significantly by moderately increased daily vitamin C intakes (OR, 3rd quartile of vitamin C intake vs 1st quartile: 0.61; 95% C.I.: 0.40, 0.93; adjusted for age, residence, urban or rural status, family history of

breast cancer in a first-degree relative, BMI, age at menarche, parity, menopausal status and total energy intake).²⁷

In another more recent case-control study conducted in Uruguay, the likelihood of breast cancer in premenopausal women was inversely correlated with vitamin C intake.²⁸ The data collected from a cross-sectional ecological survey in 65 Chinese rural counties indicated that breast cancer mortality was inversely correlated with serum ascorbate concentrations.²⁹ In other case-control studies conducted in Shanghai, China,³⁰ Tianjin, China,³¹ Italy,³¹ and Switzerland,³² the odds of developing breast cancer were significantly inversely correlated with daily vitamin C intake. In addition, in a case-control study of women conducted in western India, the odds of developing breast cancer were significantly lower among women with the highest plasma ascorbate concentrations, compared to the odds among women with the lowest (OR: 0.23; 95% C.I.: 0.10, 0.53).²⁶ (Circulating concentrations of vitamin C can be used as biomarkers of exposure to dietary vitamin C; even small changes in vitamin C intake are reflected in changes in plasma ascorbate concentration.³³)

The results of a meta-analysis of retrospective case-control studies indicated that there was a statistically significant inverse association between vitamin C intake and risk for breast cancer.³⁴ In addition, other investigators performing a meta-analysis of published data on the relationship between breast cancer and the intake of vitamin C also concluded that the risk of developing breast cancer was reduced significantly by vitamin C consumption (RR, "high" daily consumption of vitamin C vs "low": 0.80; 95% C.I.: 0.68, 0.95).³⁵

In contrast to this large body of evidence demonstrating that increased consumption of vitamin C reduces the risk for breast cancer, the prospective

observational data collected from women during the Nurses' Health Study and Nurses' Health Study II in the US failed to reveal a relationship between vitamin C consumption and the incidence of breast cancer.³⁶⁻³⁸ After the first 6 years of the prospective Nurses' Health Study II of 58,628 women in the US, differences in total vitamin C intakes from foods and supplements had no effects on the adjusted risks of developing nonproliferative benign breast disease, proliferative benign breast disease without atypia or benign breast disease with atypical hyperplasia (adjusted for age, time period, total daily energy intake, supplement use, family history of breast cancer, oral contraceptive use and BMI).³⁶ After 8 years, the results of the prospective observational Nurses' Health Study II of 90,655 premenopausal women aged 26 to 46 years, the multivariate-adjusted risk of developing breast cancer was not affected by differences in the daily intakes of vitamin C from foods or from foods plus supplements (adjusted for age, smoking status, height, parity, age at first full-term birth, BMI, age at menarche, family history of breast cancer, personal history of benign breast disease, oral contraceptive use, menopausal status, alcohol consumption, daily energy intake and daily intake of animal fat).³⁷ Similarly, in the 14-year prospective Nurses' Health Study of 83,234 women in the US, the multivariate-adjusted risk of developing breast cancer was not affected by differences in daily intakes of vitamin C from foods alone or from foods and dietary supplements (adjusted for age, length of follow-up, daily energy intake, parity, age at first birth, age at menarche, history of breast cancer in a mother or sister, history of benign breast disease, alcohol consumption, BMI at age 18 years, change in body weight since age 18 years, height, age at menopause and postmenopausal hormone therapy).³⁸

Three other prospective observational

studies also failed to reveal a relationship between vitamin C consumption and the incidence of breast cancer.³⁹⁻⁴¹ In a prospective observational study of 34,387 postmenopausal women in the state of Iowa in the US (the Iowa Women's Health Study), the multivariate-adjusted risk of developing breast cancer was not affected by differences in vitamin C intakes (adjusted for age, daily energy intake, age at menarche, age at menopause, age at first live birth, parity, BMI at entry into study, BMI at age 18 years, family history of breast cancer, personal history of benign breast disease, alcohol consumption and education).³⁹ In addition, data obtained from 4,697 women, initially cancer-free and aged 15 years or older, after 25 years of observation failed to reveal a significant relationship between differences in daily vitamin C intakes and the occurrence of breast cancer⁴⁰ and after the first 4.3 years of a prospective observational study of 62,573 women aged 55 to 69 years (the Netherlands Cohort Study), the risk of developing breast cancer was not affected by differences in vitamin C intakes.⁴¹

The results of several retrospective observational studies⁴²⁻⁵² also failed to demonstrate the protective effect of increased vitamin C consumption against breast cancer. In a case-control study of women conducted in North Carolina, the multivariate-adjusted odds of developing breast cancer were not affected by dietary supplementation with any amount of vitamin C (adjusted for age, age at menarche, age at first full-term pregnancy, menopausal status, lactation history, family history, BMI, waist-to-hip circumference ratio, education, alcohol consumption, smoking history and daily intakes of fruits and vegetables).⁴² Similarly, the odds of developing breast cancer were not affected by differences in vitamin C intakes in upstate New York.⁴³ Investigators performing a case-control

study nested within the Canadian National Breast Screening Study of 56,837 women, also reported that the multivariate-adjusted odds of developing breast cancer were not affected by differences in the daily intakes of vitamin C from either foods or dietary supplements (adjusted for age, daily energy intake, age at menarche, surgical menopause, age at first live birth, education, family history of breast cancer, and personal history of benign breast disease).⁴⁴

In a set of case-control studies conducted in China (the Shanghai Nutrition and Breast Disease Study⁴⁵ and the Shanghai Breast Cancer Study⁴⁶⁻⁴⁸), differences in vitamin C intakes had no effects on the odds of developing nonproliferative benign breast disease, proliferative benign breast disease without atypia or proliferative benign breast disease with atypical hypertrophy. In case-control studies conducted in Italy, the energy-adjusted odds of developing breast cancer were not affected by differences in vitamin C consumption.^{49,50} In case-control studies conducted in Greece, the odds of developing breast cancer were not affected by differences in vitamin C intakes.^{51,52}

In a case-control study nested within the Danish Diet, Cancer and Health Study of postmenopausal women, the odds of developing breast cancer were reported to increase significantly with increased intake of vitamin C, an anomalous finding that the investigators could not explain and considered artefactual.⁵³

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for breast cancer. The evidence documented by a prospective observational study,¹⁹ 13 retrospective observational studies²⁰⁻³² and 2 meta-analyses^{34,35} supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for breast cancer.

Vitamin C Reduces the Risk for Cervical Cancer

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for cervical cancer. The results of several retrospective observational studies support the conclusion that increased consumption of vitamin C reduces the risk for cervical cancer.⁵⁴⁻⁵⁶ Most importantly, in a case-control study conducted in the Seattle, WA, area, the odds of developing cervical cancer were halved ($p < 0.05$) by increased daily intakes of vitamin C.⁵⁴ In addition, the results of a case-control study conducted in four Latin American countries indicated that the odds of developing cervical cancer were inversely correlated with vitamin C intakes.⁵⁵ In a case-control study conducted in India, the odds of developing cervical cancer and the severity of cervical cancer were both inversely correlated with serum ascorbate concentrations.⁵⁶

In contrast, the results of a 2-year, double-blind, placebo-controlled, randomized, factorial study in which women with colposcopically and histologically confirmed minor squamous atypia or cervical intra-epithelial neoplasia (CIN; an established precursor lesion to cervical cancer) supplemented their diets with either placebo, 30 mg beta-carotene, 500 mg vitamin C or 30 mg beta-carotene plus 500 mg vitamin C suggested that the rate of lesion regression was not accelerated by supplementation with this amount of vitamin C.⁵⁷ The results of several retrospective observational studies are consistent with this conclusion.⁵⁸⁻⁶⁰ In a case-control study conducted in the state of Hawaii, the multivariate-adjusted odds of developing cervical dysplasia (a precursor to cervical cancer) were not affected by differences in plasma ascorbate concentrations (adjusted for age, ethnicity, smoking status, alcohol consumption and presence or absence of human papillomavirus).⁵⁸ In a case-control study conducted

in the state of Alabama in the US, the multivariate-adjusted odds of developing cervical dysplasia were not affected by differences in vitamin C intakes (adjusted for age, race, age at first intercourse, number of sexual partners, parity, smoking status, use of oral contraceptives and presence of human papillomavirus infection).⁵⁹ In a case-control study conducted in the Portland, OR area, the age-adjusted odds of developing precancerous cytological abnormalities of the cervix were not affected by differences in daily vitamin C intakes.⁶⁰

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for cervical cancer. The evidence documented by three retrospective observational studies⁵⁴⁻⁵⁶ supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for cervical cancer.

Vitamin C Reduces the Risk for Colon Cancer

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for colon cancer. In a prospective study that compared patients with adenomatous colonic polyps (an accepted risk factor for colon cancer) to subjects without polyps, one month of dietary supplementation with vitamin C (750 mg/day) produced a significantly greater decrease in cell proliferation within crypts of macroscopically normal-appearing colonic mucosa in subjects with polyps than was produced by placebo consumption, while there was no change in subjects without polyps – suggesting that vitamin C does not interfere with normal cell cycling but does slow abnormally accelerated proliferation in the colon epithelium.⁶¹ Consistent with this evidence of a protective effect of supplemental vitamin C, in a prospective observational study of 35,215 women aged 50 to 69 years in Iowa (the Iowa Women's

Health Study), the age-adjusted risk of developing colon cancer was reduced 33% in women who consumed more than 60 mg of supplemental vitamin C daily, compared to the risk in women who did not consume vitamin C supplements (RR: 0.67; 95% C.I.: 0.49, 0.92).⁶²

The results of several retrospective observational studies also support the conclusion that increased consumption of vitamin C reduces the risk for colon cancer.⁶³⁻⁶⁵ In the case-control North Carolina Colon Cancer Study, a group of men and women with "high" vitamin C intakes (median: 644 mg/day) experienced half the risk for colon cancer than was experienced by another otherwise similar group of men and women with "low" vitamin C intakes (median: 59 mg/day; OR: 0.5; 95% C.I.: 0.3, 0.8).⁶³ The responses of whites and African-Americans to vitamin C intake were not different.⁶³ On average, individuals with colon cancer consumed significantly less vitamin C, although vitamin intakes appeared to have no effect on the relative incidence of microsatellite instability (a biomarker for risk for colon cancer).⁶⁴ Similarly, in a case-control study conducted in the Seattle, Washington area, the age- and sex-adjusted odds of developing colon cancer were reduced significantly in men and women who supplemented their diets with vitamin C (OR, daily supplemental vitamin C intake > 500 mg vs none: 0.61; 95% C.I.: 0.40, 0.91).⁶⁵

In a case-control study conducted in Shanghai, China, the odds of men developing colon cancer also were reduced significantly by greater daily intake of vitamin C (OR, vitamin C intake > 30 mg/day vs < 30 mg/day: 0.7; 95% C.I.: 0.5, 0.9), although the odds of women developing colon cancer were not affected by differences in vitamin C intakes.⁶⁶ However, in a 17-year prospective study of 2,974 men in Basel, Switzerland, in which dietary and lifestyle patterns were assumed to remain static,

differences in prestudy serum vitamin C concentrations had no effect on the risk of developing colon cancer, a result that may reflect changing dietary and lifestyle patterns during the last quarter of the 20th century more than inherent relationships between vitamin C and the colon epithelium.^{2,3}

In a case-control study conducted in Denmark, the odds of adenomatous polyp recurrence were inversely correlated with daily intakes of vitamin C.⁶⁷ In contrast, in other case-control studies, the odds of adenomatous polyp occurrence⁶⁸ or recurrence⁶⁹ were not affected by differences in daily vitamin C intakes.

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for colon cancer. The evidence documented by a prospective clinical trial of vitamin C supplementation,⁶¹ a prospective observational study⁶² and 5 retrospective observational studies⁶³⁻⁶⁷ supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for colon cancer.

Vitamin C Reduces the Risk for Colorectal Cancer

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for colorectal cancer. The results of the 14-year prospective observational American Cancer Society Cancer Prevention Study II of 711,891 men and women who were initially cancer-free indicated that the age- and sex-adjusted risk of developing colorectal cancer was reduced significantly by 10 or more years of dietary supplementation with any amount of vitamin C (OR: 0.77; 95% C.I.: 0.6, 0.90).⁷⁰ In addition, the results of several retrospective observational studies support the conclusion that increased consumption of vitamin C reduces the risk for colorectal cancer.⁷¹⁻⁷⁶

In a case-control study conducted in

France, the multivariate-adjusted odds of developing colorectal adenoma were reduced significantly by the consumption of greater amounts of vitamin C (OR, men, daily vitamin C consumption > 114 mg vs < 61 mg; 0.6; 95% C.I.: 0.4, 0.9; OR, women, daily vitamin C consumption > 114 mg vs < 61 mg; 0.6; 95% C.I.: 0.4, 0.9; both adjusted for age, sex, BMI, tobacco use, daily energy intake and alcohol consumption).⁷¹ In a case-control study conducted in Italy, the multivariate-adjusted odds of developing colorectal cancer were reduced significantly by increased vitamin C intakes (OR, vitamin C intake > 188 mg/day vs < 189 mg/day: 0.72; 95% C.I.: 0.6, 0.9; adjusted for age, study center, sex, education, level of physical activity and daily intakes of energy and dietary fiber).⁷² In a case-control study conducted in the Canton of Vaud, Switzerland, the multivariate-adjusted odds of developing colorectal cancer were reduced significantly by “intermediate” intakes of vitamin C (median: 112 mg/day) compared to “low” intakes (median: 65 mg/day; OR: 0.51; 95% C.I.: 0.3, 0.8; adjusted for age, sex, education, smoking status, alcohol consumption, BMI, level of physical activity and daily intakes of energy and dietary fiber).⁷³ Consistent with these findings, the results of a case-control study conducted in northern Italy indicated that the odds of developing colorectal cancer were reduced significantly by vitamin C consumption (OR, 5th quintile of daily vitamin C intake vs 1st quintile: 0.40; $p < 0.05$)⁷⁴ and in a case-control study conducted in western New York state, the odds of developing colorectal cancer were inversely correlated with vitamin C intakes.⁷⁵ In addition, men in Turkey with colorectal tumors had significantly lower mean plasma vitamin C concentration than healthy men.⁷⁶

In contrast, the results of a double-blind, randomized placebo-controlled clinical trial in which men and women

supplemented their diets with either placebo, beta-carotene (25 mg/day), vitamin C (1000 mg/day) plus vitamin E (400 mg/day) or all three antioxidants for 4 years indicated that combined dietary supplementation with this amount of vitamin C did not affect the incidence of colorectal adenoma (RR: 1.08; 95% C.I.: 0.91, 1.29; adjusted for age, sex, number of prior adenomas, actual length of time between clinical evaluations and study center).⁷⁷ Consistent with this finding, in a 2-year double-blind randomized placebo-controlled human clinical trial in which patients who were thought to be free of colorectal polyps after polyp removal added either placebo or a supplement containing 400 mg of vitamin C and 400 mg of vitamin E to their diets, the multivariate-adjusted risk of developing new polyps was not affected by the combined supplement (adjusted for age and the usual frequency of consumption of meats and fish).⁷⁸

Also consistent with these findings, the results of a secondary endpoint analysis of the data obtained during the prospective, double-blind, randomized and placebo-controlled Alpha-Tocopherol, Beta-Carotene Cancer Prevention study of 29,133 middle-aged male cigarette smokers in Finland who supplemented their diets with 50 mg of vitamin E, 20 mg of beta-carotene or placebo for 5 to 8 years indicated that the risk of developing colorectal cancer was not affected by the intake of vitamin C, although more than 50% of these subjects consumed less than the RDA for vitamin C.⁷⁹ However, the placebo-controlled trials were of inadequate duration to measure accurately the incidence of new polyps or tumors; even in patients who have undergone polypectomy, the minimum time before re-examination recommended by the 2006 Consensus Update on Guidelines for Colonoscopy after Polypectomy of the US Multi-Society Task Force on Colorectal

Cancer and the American Cancer Society is 5 years.⁸⁰

The results of two retrospective observational studies failed to support the conclusion that increased consumption of vitamin C reduces the risk for colorectal cancer.^{81,82} In a case-control study conducted in Los Angeles, CA, the multivariate-adjusted odds of developing colorectal adenoma or colorectal adenomatous polyps were not affected by differences in vitamin C intakes from foods or from supplements (adjusted for daily intakes of calories, saturated fat, folate and fiber, alcohol consumption, current smoking status, BMI, race, level of daily physical activity and use of nonsteroidal anti-inflammatory drugs).⁸¹ In another case-control study conducted in North Carolina, the multivariate-adjusted odds of developing colorectal adenoma were not affected by differences in vitamin C intakes in men or women (adjusted for age, BMI, daily energy intake, smoking status, use of dietary supplements, family history of colon cancer and daily intakes of fat, dietary fiber and alcohol).⁸²

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for colorectal cancer. The evidence documented by a prospective observational study⁷⁰ and six retrospective observational studies⁷¹⁻⁷⁶ supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for colorectal cancer.

Vitamin C Reduces the Risk for Endometrial Cancer

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for endometrial cancer. The results of three retrospective observational studies⁸³⁻⁸⁵ support the conclusion that the consumption of increased amounts of vitamin C reduces the risk for endometrial cancer. In a case-control study nested within the Western New York Diet Study,

the multivariate-adjusted odds of developing endometrial cancer were reduced significantly in women who consumed amounts of vitamin C greater than the median (OR, daily vitamin C intake > 172 mg vs < 129 mg; 0.6; 95% C.I.: 0.4, 0.9; adjusted for age, education, BMI, diabetes, hypertension, pack-years of cigarette smoking, age at menarche, parity, use of oral contraceptives, menopausal status, postmenopausal use of estrogen and daily energy intake).⁸³ Similarly, the results of a case-control study conducted in Shanghai, China, indicated that the multivariate-adjusted odds of developing endometrial cancer were reduced significantly among women with greater daily vitamin C intakes (OR, daily vitamin C intake > 42 mg/1000 kcal vs < 30 mg/1000 kcal: 0.6; 95% C.I.: 0.4, 0.9; adjusted for age, education, menopausal status, diagnosis of diabetes, alcohol consumption, BMI, level of physical activity and dietary intakes of animal products, fruits and vegetables and energy).⁸⁴ In another case-control study, conducted in the Swiss Canton of Vaud and in Northern Italy, the energy-adjusted odds of developing endometrial carcinoma were reduced significantly by increased intake of vitamin C (OR, 5th quintile of daily vitamin c intake vs 1st quintile: 0.6; $p < 0.05$).⁸⁵

In contrast, the data obtained from the 10-year prospective Canadian National Breast Screening Study of 56,837 women indicated that the risk for endometrial cancer was not associated with differences in daily intakes of vitamin C.⁸⁶ Similarly, in a case-control study conducted in the state of Hawaii, the multivariate-adjusted odds of developing endometrial cancer were not affected by differences in the intake of vitamin C from foods (adjusted for parity, use of oral contraceptives, use of unopposed estrogen, history of diabetes and BMI).⁸⁷

The scientific evidence indicates that increased consumption of vitamin C re-

duces the risk for endometrial cancer. The evidence documented by three retrospective observational studies⁸³⁻⁸⁵ supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for endometrial cancer.

Vitamin C Reduces the Risk for Adenocarcinoma of the Esophagus

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for adenocarcinoma of the esophagus. The results of two retrospective observational studies^{88,89} support the conclusion that the consumption of increased amounts of vitamin C reduces the risk for adenocarcinoma of the esophagus. In a case-control study conducted in the US, compared to men and women with daily vitamin C intakes less than the 25th percentile, men and women with daily vitamin C intakes greater than the 75th percentile exhibited significantly reduced odds of developing esophageal adenocarcinoma (OR: 0.45; 95% C.I.: 0.33, 0.61; adjusted for sex, state of residence, age, race, income bracket, education, BMI, cigarette smoking, alcoholic beverage consumption and total daily energy intake).⁸⁸ In a similar case-control study conducted in Germany, the multivariate-adjusted odds of developing adenocarcinoma of the esophagus were reduced significantly in men who consumed more than 100 mg of vitamin C daily (RR, daily vitamin C intake > 100 mg vs < 100 mg: 0.33; 95% C.I.: 0.11, 0.92; adjusted for unspecified "known risk factors").⁸⁹

On the other hand, in a case-control study conducted in New York state, the odds of developing adenocarcinoma of the esophagus were not affected by differences in vitamin C intakes.⁹⁰ In another case-control study conducted in northeast China, the multivariate-adjusted odds of developing any esophageal cancer were not affected by differences in daily vitamin C intakes (adjusted for alcohol consump-

tion, smoking status, income and occupation).⁹¹ In a case-control study of the impact of vitamin C deficiency on adenocarcinoma of the esophagus conducted in Sweden, the multivariate-adjusted odds of developing squamous cell carcinoma of the esophagus were not affected by differences in vitamin C intakes in a vitamin C deficient population (adjusted for age, sex, BMI and smoking status).⁹²

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for adenocarcinoma of the esophagus. The evidence documented by two retrospective observational studies^{88,89} supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for adenocarcinoma of the esophagus.

Vitamin C Reduces the Risk for Squamous Cell Carcinoma of the Esophagus

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for squamous cell carcinoma of the esophagus. The results of several retrospective observational studies^{88,89,93-96} support the conclusion that the consumption of increased amounts of vitamin C reduces the risk for squamous cell carcinoma of the esophagus.

Among men participating in a case-control study conducted in the US, white men who consumed the most vitamin C from vegetables or who consumed dietary supplements containing vitamin C cut their risk of developing squamous cell carcinoma of the esophagus in half ($p < .05$; adjusted for age, residence, smoking and alcohol consumption).⁹³ Similarly, in the same study, black men who consumed the most vitamin C from fruit also cut their risk of developing squamous cell carcinoma of the esophagus in half ($p < .05$; adjusted for age, residence, smoking and alcohol consumption).⁹³ In another case-control study conducted in the US, compared to men and women with daily vitamin

C intakes less than the 25th percentile, men and women with daily vitamin C intakes greater than the 75th percentile exhibited significantly reduced odds of developing squamous cell carcinoma of the esophagus (OR: 0.53; 95% C.I.: 0.36, 0.79; adjusted for sex, state of residence, age, race, income bracket, education, BMI, cigarette smoking, alcoholic beverage consumption and total daily energy intake).⁸⁸

In a case-control study conducted in Uruguay, the multivariate-adjusted odds of developing squamous cell carcinoma of the esophagus also were reduced significantly by increased intakes of vitamin C (OR, 2nd quartile of vitamin C intake vs 1st quartile: 0.59; 95% C.I.: 0.37, 0.92; adjusted for age, sex, residence, urban or rural status, birthplace, education, BMI, smoking status, years since quit smoking, number of cigarettes smoked per day by current smokers, alcohol consumption, mate tea consumption and total daily energy intake).⁹⁴ In a case-control study conducted in France, the multivariate-adjusted odds of developing squamous cell cancer of the esophagus were reduced significantly by intakes of vitamin C greater than the RDA (OR, daily vitamin C intake > 90 mg vs < 60: 0.44; 95% C.I.: 0.24, 0.81; adjusted for interviewer age, smoking status and daily consumption of beer aniseed aperitives, hot Cakvados, whisky, total alcohol and total energy).⁹⁵ In a case-control study conducted in Germany, the multivariate-adjusted odds of developing squamous cell carcinoma of the esophagus were reduced significantly in men who consumed more than 100 mg of vitamin C daily (RR, squamous cell carcinoma, daily vitamin C intake > 100 mg vs < 100 mg: 0.31; 95% C.I.: 0.11, 0.88; adjusted for unspecified "known risk factors").⁸⁹ In another case-control study conducted in Uruguay, the multivariate-adjusted odds of developing any esophageal cancer were reduced significantly by daily vitamin C intakes greater than the lowest

quartile of intake (OR: 0.36; 95% C.I.: 0.19, 0.67; adjusted for age, gender, residence, urban or rural status, education, BMI, smoking status, alcohol consumption, total energy intake and daily intakes of alpha-carotene, beta-carotene, lutein, lycopene, beta-cryptoxanthin, vitamin E, glutathione, quercetin, kaempferol, total flavonoids, beta-sitosterol, campesterol and stigmasterol).⁹⁶

On the other hand, in one case-control study conducted in northeast China, the multivariate-adjusted odds of developing any esophageal cancer were not affected by differences in daily vitamin C intakes (adjusted for alcohol consumption, smoking status, income and occupation).⁹¹ In another case-control study of the impact of vitamin C deficiency on squamous cell carcinoma of the esophagus conducted in Sweden, the multivariate-adjusted odds of developing squamous cell carcinoma of the esophagus were not affected by differences in vitamin C intakes in a vitamin C deficient population (adjusted for age, sex, BMI and smoking status).⁹²

The scientific evidence indicates that increased consumption of vitamin C reduces the risk for squamous cell carcinoma of the esophagus. The evidence documented by six retrospective observational studies^{88,89,93-96} supports this conclusion and there is no evidence that increased consumption of vitamin C may increase the risk for squamous cell carcinoma of the esophagus. In addition, the evidence documented by a retrospective observational study⁹² demonstrates that squamous cell carcinoma of the esophagus is not prevented by vitamin C deficiency.

Part 2 of 4 will follow in the next issue of the Journal of Orthomolecular Medicine.

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