Antioxidant Vitamins Reduce the Risk for Cancer: Part Two

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Part One (JOM 24.1) presented the evidence for vitamin C in reducing cancer risk.

Vitamin E Reduces the Risk for Breast Cancer

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for breast cancer. The results of several retrospective observational studies support the conclusion that increased consumption of vitamin E reduces the risk for breast cancer.[10,11,16-18,21,37-39,43,98] In a case-control study conducted in New York state, the multivariate-adjusted odds of developing breast cancer were reduced significantly among premenopausal women by any daily intakes of a-tocopherol equal to or greater than 2/3 of the RDA (OR, daily vitamin E intakes > 10 mg vs < 7 mg: 0.55; 95% C.I.: 0.34, 0.88; 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).[10] 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 E, although it became less important with increasing consumption of vegetables. In a case-control study of women conducted in western New York state, 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 a-tocopherol, despite the almost universal prevalence of vitamin E deficiency among these women (OR, premenopausal women with daily a-

tocopherol intake > 10.4 mg vs < 6.4 mg: 0.5; 95% C.I.: 0.2, 1.0; OR, postmenopausal women with daily a-tocopherol intake > 10.4 mg vs < 6.4 mg: 0.5; 95% C.I.: 0.3, 1.0; both adjusted for age, education, age at menarche, age at first pregnancy and BMI).11 These protective effects was not enjoyed by similar premenopausal women who had a positive family history of breast cancer, indicating that chronic vitamin E deficiency cannot overcome factors that predispose a woman of any age to breast cancer.[11]

In a case-control study conducted in China (the Shanghai Breast Cancer Study), the odds of women developing breast cancer were reduced significantly among women who consumed more than the RDA for vitamin E, compared to vitamin E deficient women (OR, vitamin E intake > 19.9 mg/day vs < 9.4 mg/day: 0.72; 95% C.I.: 0.54, 0.96).37 In an extension of this study, the multivariate-adjusted odds of developing breast cancer were reduced significantly among women with diets deficient in vitamin E and who consumed dietary supplements of vitamin E (OR, vitamin E deficient diet plus vitamin E supplement vs vitamin E deficient diet alone: 0.8; 95% C.I.: 0.6, 1.0; adjusted for age, education, age at menarche, parity, BMI, menopausal status, level of recreational exercise, history of fibroadenoma, history of breast cancer in first-degree relatives and phase of study).38 In addition, in a case-control study nested within the Danish Diet, Cancer and Health Study of postmenopausal women, the odds of developing breast cancer were reduced significantly by the daily consumption of at least 25 mg of vitamin E, compared to the odds associated with the daily consumption of 10 to 15 mg (Incidence Rate Ratio: 0.59; 95% C.I.:

0.37, 0.95; adjusted for vitamin C intake, vitamin A intake, number of childbirths, age at first childbirth, history of surgery for benign breast disease, education, years of hormone replacement therapy, alcohol consumption and BMI).[43]

From the data obtained in a case-control study conducted in Italy it was determined that 8.6% of the risk of developing breast cancer is attributable to daily vitamin E intake less than 8.5 mg.[98] The impact of poor vitamin E nutrition on risk for breast cancer was confirmed further by the results of another case-control study conducted in Italy, in which the energy-adjusted odds of developing breast cancer were reduced significantly by increased vitamin E consumption (OR, 5th quintile of daily vitamin E intake vs 1st quintile: 0.75; p < 0.05)[39] and in another, the odds of developing breast cancer were inversely correlated with daily intakes of vitamin E.[21] Furthermore, in a case-control study conducted in Uruguay, the multivariate-adjusted odds of developing breast cancer were reduced significantly by even moderately increased daily vitamin E intakes (OR, 2nd quartile of vitamin E intake vs 1st quartile: 0.53; 95% C.I.: 0.35, 0.83; adjusted for 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)[17] and in a more recent case-control study conducted in Uruguay, the likelihood of breast cancer in premenopausal women was inversely correlated with vitamin E intake.[18] 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 a-tocopherol concentrations, compared to the odds among women with the lowest (OR: 0.37; 95% C.I.: 0.21, 0.67).[16] (Circulating concentrations of vitamin E can be used as biomarkers of exposure to dietary vitamin E; for example, for every doubling of a-tocopherol intake, plasma a-tocopherol concentration increases 10%).[23,99]

In contrast to this large body of evidence demonstrating that increased consumption of vitamin E reduces the risk for breast cancer, the prospective observational data collected during the 8-year prospective observational Nurses' Health Study II of 90,655 premenopausal women aged 26 to 46 years indicated that the multivariate-adjusted risk of developing breast cancer was not affected by differences in the daily intakes of vitamin E 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).[27] 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 E 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).[28] The results of a prospective observational study of 34,387 postmenopausal women in the state of Iowa in the US (the Iowa Women's Health Study) also indicated that the multivariate-adjusted risk of developing breast cancer was not affected by differences in vitamin E 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).[29]

Three other prospective observational studies also failed to reveal a relationship between vitamin C consumption and the incidence of breast cancer.[9,30,31] For example, 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 E intakes and the occurrence of breast cancer.[30] After the first 4.3 years of the 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 E intakes.[31] Interestingly the results of 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, differences in vitamin E intakes were unable to overcome the established procarcinogenic influence of excess body weight on the risk of developing breast cancer.[9]

The results of retrospective observational studies conducted in the US[32,33,100-103] also failed to demonstrate the protective effect of increased vitamin C consumption against breast cancer. In a case-control study conducted in western New York state, the odds of developing breast cancer were not affected by differences in vitamin E intakes[33] and in a more recent 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 E (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).[32] In case-control studies nested within prospective studies conducted in Missouri,[100] Washington County, MD,[101,102] and within the prospective Nurses' Health Study in the

US,[103] the odds of developing breast cancer were not affected by differences in serum a-tocopherol concentrations.

Similarly, in a case-control study nested within the Canadian National Breast Screening Study of 56,837 women, the multivariate-adjusted odds of developing breast cancer were not affected by differences in the daily intakes of vitamin E or a-tocopherol from either foods or dietary supplements (adjusted for 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).[34] In case-control studies conducted in China (the Shanghai Nutrition and Breast Disease Study,[35] the Shanghai Breast Cancer Study[36] and studies conducted in Shanghai and Tianjin[20]), differences in vitamin E intakes had no effects on the age-adjusted odds of developing nonproliferative benign breast disease, proliferative benign breast disease without atypia or proliferative benign breast disease with atypical hypertrophy. In several European case-control studies conducted in Sweden,[104] Italy,[40] Greece[41] and the UK[105] and in a similar study conducted in western India,[16] the odds of developing breast cancer were not affected by differences in daily intakes of vitamin E.

In case-control studies conducted in Germany[12] and Seoul, Korea,[13] the odds of developing breast cancer were not affected by differences in vitamin E intakes; however, over 80% of the subjects in these studies were chronically vitamin E deficient.

One double-blind, randomized, placebo-controlled clinical trial directly addressed the effects of dietary supplementation with vitamin E in the prevention of breast cancer. In the 10-year Women's Health Study, in which 39,876 apparently healthy women over 45 years old consumed either placebo or 600 IU of vitamin E every other day, this amount and pattern of vitamin E supplementation did not affect the age-adjusted risk for breast cancer (RR,

vitamin E vs placebo: 1.00; 95% C.I.: 0.90, 1.12).[106] However, the extent to which separating episodes of vitamin E consumption by 48 hours prevents the establishment of an elevated steady-state of circulating a-tocopherol concentration is not known; a-tocopherol concentrations were not measured during this study.

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for breast cancer. The evidence documented by 11 retrospective observational studies[10,11,16-18,21,37-39,43,98] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for breast cancer. In addition, the results of two studies[12,13] confirm that vitamin E deficiency does not protect against breast cancer.

Vitamin E Reduces the Risk for Colon Cancer

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for colon cancer. The results of a prospective observational study of 35,215 women aged 50 to 69 years in Iowa (the Iowa Women's Health Study), largely as a result of the protective effect of supplemental vitamin E intakes greater than 30 mg/day (age-adjusted RR, supplemental vitamin E intake > 30 mg/day vs none: 0.44; 95% C.I.: 0.28, 0.71), women consuming the most vitamin E experienced significantly less risk for colon cancer (age-adjusted RR, total vitamin E intake > 35 mg/day vs < 6 mg/day: 0.32; 95% C.I.: 0.19, 0.54).[107] These protective effects remained significant after further adjustment of the calculated risk ratios for age, daily total energy intake, height, parity, vitamin A supplementation and daily intakes of seafood and skinless chicken (multivariate-adjusted RR, supplemental vitamin E intake > 30 mg/day vs none: 0.50; 95% C.I.: 0.28, 0.87; multivariate-adjusted RR, total vitamin E intake > 35 mg/day vs < 6 mg/day: 0.42; 95% C.I.: 0.22, 0.78).[107]

In addition, the results of retrospective observational studies support the conclusion that increased consumption of vitamin E reduces the risk for colon cancer.[99,108-113] In the case-control North Carolina Colon Cancer Study, a group of African-American men and women with "high" vitamin E intakes (median: 140 mg/day) experienced significantly less risk for colon cancer than was experienced by another otherwise similar group of African-American men and women with "low" vitamin E intakes (median: 6 mg/day; OR: 0.3; 95% C.I.: 0.1, 0.6).[108] In contrast, the odds of developing colon cancer were not affected by differences in vitamin E intakes among white men and women, over half of whom were vitamin E deficient.[108] On average, individuals with colon cancer consumed significantly less vitamin E but vitamin intakes appeared to have no effect on the relative incidence of microsatellite instability (a biomarker for risk for colon cancer).[109]

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 E (OR, daily supplemental vitamin E intake > 15 mg vs none: 0.61; 95% C.I.: 0.42, 0.87)[110] and in a case-control study conducted in Montreal, Quebec, Canada, the multivariate-adjusted odds of developing colon carcinoma were reduced significantly by increased consumption of vitamin E (OR, 2nd quartile of vitamin E intake vs 1st quartile: 0.54; 95% C.I.: 0.37, 0.80; adjusted for sex, age, marital status, history of colon carcinoma in first-degree relatives and total daily energy intake).[111] In a case-control study conducted in Shanghai, China, the odds of men developing colon cancer were reduced significantly by greater daily intake of vitamin E (OR, vitamin E intake > 32 mg/day vs < 26 mg/day: 0.6; 95% C.I.: 0.4, 0.9), although the odds of women developing colon cancer

were not affected by differences in vitamin E intakes.[99]

In a case-control study conducted in New York City, NY, the odds of adenomatous polyp recurrence were reduced significantly among patients who supplemented their diets with vitamin E (OR, vitamin E supplementation vs none: 0.62; 95 % C.I.: 0.39, 0.98).[112] Similarly, in Denmark, the odds of adenomatous polyp recurrence were inversely correlated with daily intakes of vitamin E.[113]

In contrast to these reports, when the data from 87,998 women in the prospective Nurses' Health Study were combined with the data from 47,344 men in the prospective Health Professionals Follow-Up Study, the risk for developing colon cancer was found to be unaffected by differences in vitamin E consumption.[114] In addition, in a case-control study conducted in Salt Lake City, Utah, the odds of developing colon cancer did not reflect differences in daily intakes of a-tocopherol.[115] In a 17-year prospective study of 2,974 men in Basel, Switzerland,[86,87] and in a case-control study nested within a prospective study in Washington County, MD,[101] differences in serum vitamin E concentrations had no effect on the risks of developing colon cancer.

One double-blind, randomized, placebo-controlled clinical trial directly addressed the effects of dietary supplementation with vitamin E in the prevention of colon cancer. In the 10-year Women's Health Study, in which 39,876 apparently healthy women over 45 years old consumed either placebo or 600 IU of vitamin E every other day, this amount and pattern of vitamin E supplementation did not affect the age-adjusted risk for colon cancer (RR, vitamin E vs placebo: 1.00; 95% C.I.: 0.77, 1.31).[106] However, the extent to which separating episodes of vitamin E consumption by 48 hours prevents the establishment of an elevated steady-state of circulating a-tocopherol concentration is not known; a-tocopherol concentrations were not measured during this study.

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for colon cancer. The evidence documented by a prospective observational study[107] and 7 retrospective observational studies[99,108-113] supports this conclusion and there is no evidence hat increased consumption of vitamin E may increase the risk for colon cancer.

Vitamin E Reduces the Risk for Colorectal Cancer

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for colorectal cancer. The results of several retrospective observational studies support the conclusion that increased consumption of vitamin E reduces the risk for colorectal cancer.[53,55,63] In a case-control study conducted in North Carolina, the multivariate-adjusted odds of developing colorectal adenoma were reduced significantly in men by intakes of vitamin E greater than the RDA (OR, vitamin E intake > 15.3 mg vs < 0.3 mg: 0.22; 95% C.I.: 0.07, 0.77; 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).[63] In a case-control study conducted in Italy, the multivariate-adjusted odds of developing colorectal cancer were reduced significantly by increased vitamin E intakes (OR, vitamin E intake > 12.3 mg/day vs < 12.3 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).[53] In another case-control study conducted in northern Italy, the odds of developing colorectal cancer were reduced significantly by vitamin E consumption (OR, 5th quintile of daily vitamin E intake vs 1st quintile: 0.60; p < 0.05).[55]

In contrast, the results of several other retrospective observational studies failed to reveal a relationship between increased

consumption of vitamin E and reduced risk for colorectal cancer.[52,63,116] In a case-control study conducted in North Carolina, the multivariate-adjusted odds of developing colorectal adenoma were not affected by differences in vitamin E intakes in 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).[63] In a case-control cross-sectional observational study of men and women in California, differences in vitamin E intakes, with or without supplements, had no effect on the odds of developing colorectal adenomatous polyps.[116] In a case-control study conducted in France, the multivariate-adjusted odds of developing colorectal adenoma were not affected by differences in the consumption of vitamin E.[52]

In a case-control study conducted in Los Angeles, CA, the multivariate-adjusted odds of developing colorectal adenoma were not affected by differences in vitamin E intakes from foods or from supplements among a study population that was almost entirely vitamin E deficient, even with vitamin E supplementation (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).[62] In this study, varying the degree of vitamin E deficiency did not reduce the risk for colorectal adenoma. Similarly, in a case-control study conducted in the Canton of Vaud, Switzerland, the multivariate-adjusted odds of developing colorectal cancer were not affected by differences in daily intakes of vitamin E in another population that was largely vitamin E deficient (adjusted for age, sex, education, smoking status, alcohol consumption, BMI, level of physical activity and daily intakes of energy and dietary fiber).[54]

In a case-control study conducted in Los Angeles, CA, the multivariate-adjusted

odds of developing colorectal adenoma were not affected by differences in plasma a-tocopherol concentration (adjusted for location, sex, age, date examined, ethnicity, serum total cholesterol concentration, serum triglyceride concentration, BMI, exercise, smoking, alcohol consumption, daily caloric intake, daily intakes of saturated fat, fruits, vegetables, folate and calcium, use of nonsteroidal anti-inflammatory drugs and plasma Ferritin concentration).[117] Similarly, in three case-control studies conducted in Japan, no relationship was observed between colorectal adenoma or cancer and circulating vitamin E concentrations.[118-120]

The results of a double-blind, randomized placebo-controlled clinical trial in which men and women supplemented their diets with either placebo, β-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 E 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).[58] This finding was confirmed in another 2-year double-blind, randomized, placebo-controlled human clinical trial, patients who were thought to be free of colorectal polyps after polyp removal and who added either placebo or a supplement containing 400 mg of vitamin C and 400 mg of vitamin E to their diets exhibited no difference in the multivariate-adjusted risk of developing new polyps (adjusted for age and the usual frequency of consumption of meats and fish).[59] 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.[61]

The results of secondary endpoint analyses 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 -carotene or placebo for 5 to 8 years indicated that supplementation with 50 mg of vitamin E was associated with a significant increase in the incidence of colorectal polyps,[121] although the incidence of colorectal cancer was not affected.[60,122] This report is hardly credible; the incidence of new colorectal adenoma reported in the subjects who did not receive supplemental vitamin E was over 10 times the projected incidence of such cancers among the general US male population in 2008[123] and an additional 2- to 10-fold increase would be expected to dominate the findings of every clinical trial that employed at least 50 mg of vitamin E. This has not happened.[3,106,124-127]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for colorectal cancer. The evidence documented by three retrospective observational studies[53,55,63] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for colorectal cancer.

Vitamin E Reduces the Risk for Adenocarcinoma of the Esophagus

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for adenocarcinoma of the esophagus. The results of several retrospective observational studies[70,128,129] support the conclusion that the consumption of increased amounts of vitamin E reduces the risk for adenocarcinoma of the esophagus. In a 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 13 mg of vitamin E daily (RR, adenocarcinoma, daily vitamin E intake > 13 mg vs < 13 mg: 0.13; 95% C.I.: 0.09, 0.54; adjusted for unspecified "known risk factors").[70] In a case-control study in Uruguay, the multivariate-adjusted odds of developing esophageal cancer were reduced significantly by daily vitamin E intakes greater than the lowest quartile of intake (OR: 0.41; 95% C.I.: 0.22, 0.76; adjusted for age, gender, residence, urban or rural status, education, BMI, smoking status, alcohol consumption, total energy intake and daily intakes of β-carotene, -carotene , lutein, lycopene, β-cryptoxanthin, vitamin E, glutathione, quercetin, kaempferol, total flavonoids, β-sitosterol, campesterol and stigmasterol).[128] In a case-control study conducted in China (the General Population Trial in Linxian, China), although the mean serum concentration of a-tocopherol did not differ between men and women with esophageal cancer and cancer-free men and women, for every 25% increase in serum a-tocopherol concentration above the mean, the risk for esophageal cancer decreased significantly by 10%.[129]

On the other hand, a secondary endpoint 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 -carotene or placebo for 5 to 8 years, determined that 5 to 8 years of daily supplementation with 50 mg of vitamin E was unable to overcome the procarcinogenic effects of lifelong cigarette smoking on the incidence of esophageal cancer.[130] However, the results of this epidemiologic analysis is relevant only to populations that match the parent experiment's subjects – middle-aged male life-long cigarette smokers.

The results of three retrospective observational studies[71,73,131] failed to reveal a protective effect of increased vitamin E intakes against adenocarcinoma of the esophagus. 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 E intakes.[71] In a case-control study of the impact of vitamin E 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 E intakes in a vitamin E deficient population (adjusted for age, sex, BMI and smoking status).[73] In a case-control study conducted in the state of Hawaii, mean serum a-tocopherol concentrations of subjects with and without esophageal cancer were not different.[131]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for adenocarcinoma of the esophagus. The evidence documented by three retrospective observational studies[70,128,129] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for adenocarcinoma of the esophagus.

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

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for squamous cell carcinoma of the esophagus. The results of several retrospective observational studies[69,70,128,129,132] support the conclusion that the consumption of increased amounts of vitamin E reduces the risk for squamous cell carcinoma of the esophagus. In a case-control study conducted in the US, compared to men and women with daily vitamin E intakes less than the 25th percentile, men and women with daily vitamin E intakes greater than the 75th percentile exhibited significantly reduced odds of developing esophageal squamous cell carcinoma (OR: 0.37; 95% C.I.: 0.27, 0.60; adjusted for sex, state of residence, age, race, income bracket, education, BMI, cigarette smoking, alcoholic beverage consumption and total daily energy intake).[69] Similarly, in a case-control study conducted in France, the multivariate-adjusted odds of developing squamous cell carcinoma of the esophagus were reduced significantly by less-deficient intakes of vitamin E (OR, daily vitamin E intake > 7 mg vs < 7: 0.49; 95% C.I.: 0.28, 0.87; adjusted for interviewer, age smoking status and daily consumption of beer aniseed aperitives, hot Cakvados, whisky, total alcohol and total energy).[132] This protection was strongest among the heaviest consumers of alcoholic beverages. 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 13 mg of vitamin E daily (RR, daily vitamin E intake > 13 mg vs < 13 mg: 0.17; 95% C.I.: 0.09, 0.48; adjusted for unspecified "known risk factors").[70]

In a case-control study in Uruguay, the multivariate-adjusted odds of developing esophageal cancer were reduced significantly by daily vitamin E intakes greater than the lowest quartile of intake (OR: 0.41; 95% C.I.: 0.22, 0.76; adjusted for age, gender, residence, urban or rural status, education, BMI, smoking status, alcohol consumption, total energy intake and daily intakes of β-carotene , lutein, lycopene, β-cryptoxanthin, vitamin E, glutathione, quercetin, kaempferol, total flavonoids, β-sitosterol, campesterol and stigmasterol).[128] In a case-control study conducted in China (the General Population Trial in Linxian, China), although the mean serum concentration of a-tocopherol did not differ between men and women with esophageal cancer and cancer-free men and women, for every 25% increase in serum a-tocopherol concentration above

the mean, the risk for esophageal cancer decreased significantly by 10%.[129]

In contrast, a secondary end-point 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 β-carotene or placebo for 5 to 8 years, determined that 5 to 8 years of daily supplementation with 50 mg of vitamin E was unable to overcome the procarcinogenic effects of lifelong cigarette smoking on the incidence of esophageal cancer.[130] However, the results of this epidemiologic analysis is relevant only to populations that match the parent experiment's subjects – middle-aged male life-long cigarette smokers.

Data obtained during four retrospective observational studies[73,82,131,133] failed to reveal a protective effect of increased vitamin E intakes against squamous cell carcinoma of the esophagus. In two case-control studies conducted in Uruguay, the multivariate-adjusted odds of developing squamous cell carcinoma of the esophagus were not affected by differences in vitamin E intakes (adjusted for age, sex, residence, urban or rural status, birthplace, education, BMI, smoking status, years since quit smoking, number of cigarettes smoked per day, alcohol consumption, mate tea consumption and total daily energy intake;[133] adjusted for age, residence, urban or rural status, education, family history of prostate cancer, BMI and total daily energy intake).[82] In a case-control study of the impact of vitamin E 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 E intakes in a vitamin E deficient population (adjusted for age, sex, BMI and smoking status).[73] In a case-control study conducted in the state of Hawaii,

mean serum a-tocopherol concentrations of subjects with and without esophageal cancer were not different.[131]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for squamous cell carcinoma of the esophagus. The evidence documented by five retrospective observational studies[69,70,128,129,132] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for squamous cell carcinoma of the esophagus. In addition, the evidence documented by a retrospective observational study[73] demonstrates that squamous cell carcinoma of the esophagus is not prevented by vitamin E deficiency.

Vitamin E may Reduce the Risk for Laryngeal Cancer

The scientific evidence suggests that increased consumption of vitamin E may reduce the risk for laryngeal cancer. The results of a retrospective observational study[134] support the conclusion that the consumption of increased amounts of vitamin E reduces the risk for laryngeal cancer. In a case-control study conducted in Uruguay, the multivariate-adjusted odds of developing laryngeal cancer were inversely correlated with vitamin E intake (adjusted for age, sex, residence, urban or rural status, education, BMI, smoking status, years since quit smoking, number of cigarettes smoked per day by current smokers, age at start of smoking and total daily energy intake).[134] Increased vitamin E intake was most effective in the prevention of cancer of the superglottis and less effective in the prevention of cancer of the glottis. Risk reduction was weakened by continuation of cigarette smoking.

In contrast, a post hoc secondary end-point 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 -carotene or placebo for 5 to 8 years, determined that 5 to 8 years of daily supplementation with 50 mg of vitamin E was unable to overcome the procarcinogenic effects of lifelong cigarette smoking on the incidence of laryngeal cancer.[130] However, the results of this epidemiologic analysis is relevant only to populations that match the parent experiment's subjects – middle-aged male life-long cigarette smokers.

On the other hand, the results of two retrospective observational studies[131,135] failed to reveal a protective effect of increased vitamin E intakes against laryngeal cancer. In a case-control study conducted in Japan, the multivariate-adjusted odds of developing laryngeal cancer were not affected by differences in vitamin E intakes (adjusted for age, sex, smoking status, alcohol consumption, use of multivitamin supplements, total daily energy intake, dental hygiene and year of first hospital visit)[135] and in a case-control study conducted in the state of Hawaii, mean serum a-tocopherol concentrations of subjects with and without laryngeal cancer were not different.[131]

The scientific evidence suggests that increased consumption of vitamin E may reduce the risk for laryngeal cancer. The evidence documented by a retrospective observational study[134] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for laryngeal cancer.

Vitamin E Reduces the Risk for Melanoma

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for melanoma. The results of a case-control study conducted in Washington County, MD, indicated that the odds of developing malignant melanoma were inversely correlated with age, education, and energy intake-adjusted vitamin E intakes.[136] Although the odds of men in the US developing malignant melanoma were not affected by differences in the intakes of vitamin E from foods and supplements, the odds of women developing malignant melanoma were halved when daily total vitamin E intakes from foods and supplements exceeded the RDA (OR: 0.41; 95% C.I.: 0.21, 0.81).[137] Consistent with these reports, the results of observing the 39,268 male and female participants in the Finnish Social Insurance Institution's Mobile Clinic Health Survey, aged 15-99 and initially free from cancer, prospectively for 8 years indicated that serum a-tocopherol concentrations were inversely correlated with the risk of developing melanoma.[138]

In contrast, the results of combining the data obtained from 73,525 female participants in the prospective observational Nurses' Health Study and from 88,553 prospective observational Nurses' Health Study II indicated that the multivariate-adjusted risk of developing melanoma was not affected by differences in vitamin E intakes from foods or dietary supplements (adjusted for age, skin reaction after 2 hours of sun exposure during childhood, number of sunburns over lifetime, number of sunburns during adolescence, number of moles on left arm, number of moles on lower legs, hair color, family history of melanoma, state of residence, menopausal status, use of oral contraceptives, use of postmenopausal hormone therapies, parity, height and BMI).[139] In a case-control study conducted in Boston, MA, the multivariate-adjusted odds of developing malignant melanoma were not affected by differences in plasma a-tocopherol concentrations or vitamin E intakes (adjusted for age, sex, plasma lipid concentrations, hair color and the ability to suntan).[140] In a series of case-control studies nested within a prospective study in Washington County, MD, prediagnostic serum vitamin E concentrations were not associated with the odds of developing melanoma.[101,141]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for melanoma. The evidence documented by a prospective observational study[138] and 2 retrospective observational studies[136,137] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for melanoma.

Vitamin E Reduces the Risk for Cancer of the Oral Cavity

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for cancer of the oral cavity. The results of four retrospective observational studies[135,142-144] support the conclusion that increased consumption of vitamin E reduces the risk for cancer of the oral cavity. In a case-control study conducted in New York City, the odds of developing cancer of the oral cavity were inversely correlated with dietary supplementation with vitamin E.[142] In another case-control study conducted in the US, the odds of developing cancer of the oral cavity were inversely correlated with vitamin E supplementation (OR, supplementation vs none: 0.5; 95% C.I.: 0.4, 0.6).[143] In a case-control study conducted in Japan, the multivariate-adjusted odds of developing cancer of the oral cavity were reduced significantly in men and women by greater intakes of vitamin E (OR, daily vitamin E intake > 7.7 mg vs < 4.0 mg: 0.54; 95% C.I.: 0.33, 0.88; adjusted for age, sex, smoking status, alcohol consumption, use of multivitamin supplements, total daily energy intake, dental hygiene and year of first hospital visit).[135] In a case-control study conducted in Italy and Switzerland, the multivariate-adjusted odds of developing either pharyngeal cancer or cancer of the oral cavity were reduced significantly by increased intake of vitamin E (OR: 0.74; p < 0.05; adjusted for age, sex, center, education, occupation, body mass index, smoking and drinking habits and non-alcohol energy intake).[144]

However, the results of four retrospective observational studies[131,145-147] failed to document a relationship between vitamin E and cancer of the oral cavity. For example, in a case-control study conducted in Melbourne, Australia, the odds of developing squamous cell cancer of the oral cavity were not affected by differences in dietary vitamin E intakes.[145] In a case-control study conducted in Japan, the odds of developing oral leukoplakia, a precursor of cancer of the oral cavity, were not affected by differences in serum a-tocopherol concentrations.[146] In a case-control study conducted in the state of Hawaii, mean serum a-tocopherol concentrations of subjects with and without any upper aerodigestive tract cancer were not different.[131] In a case-control study conducted in Washington County, MD, the odds of developing cancer of the oral cavity were not affected by prediagnostic serum a-tocopherol concentration.[147]

In addition, in 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 -carotene or placebo for 5 to 8 years, supplementation with 50 mg of vitamin E daily did not appear to affect the prevalence of either oral leukoplakia or dysplastic lesions of the buccal epithelium or the incidence of upper aerodigestive tract cancers (cancers of the oral cavity, pharynx, esophagus or larynx).[130,148]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for cancer of the oral cavity. The evidence documented by four retrospective observational studies[135,142-144] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for cancer of the oral cavity.

Vitamin E Reduces the Risk for Ovarian Cancer

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for ovarian cancer. The results of retrospective observational studies support the conclusion that increased consumption of vitamin E reduces the risk for ovarian cancer.[74,79,149] In a case-control study of women conducted in North Carolina, total daily intakes of vitamin E in excess of 75 mg reduced significantly the odds of developing epithelial ovarian cancer (OR: 0.44; 95% C.I.: 0.21, 0.94) and dietary supplementation with any amount of vitamin E also reduced significantly the odds of developing epithelial ovarian cancer (OR: 0.33; 95% C.I.: 0.18, 0.60).[74] Consistent with this report, in a case-control study conducted in Canada, any amount of supplementation with vitamin E for more than 10 years halved the adjusted odds of developing ovarian cancer (OR: 0.49; 95% C.I.: 0.30, 0.81; adjusted for age, residence, education, alcohol consumption, cigarette smoking, BMI, daily energy intake, recreational physical activity, parity, years of menstruation and menopausal status).[79] In a case-control study conducted in Italy, the risk of developing epithelial ovarian cancer was reduced significantly among women who regularly consumed more than the median amount of vitamin E daily, compared to the risk of women who regularly consumed less than the median amount of vitamin E daily (RR: 0.6; 95% C.I.: 0.4. 0.7; adjusted for age, study center, year of entry into study, BMI, parity, use of oral contraceptives, occupational physical activity and daily energy intake).[149]

In contrast, the results two prospective[75,77] and three retrospective observational studies[78,80,150] failed to discern a relationship between vitamin C and ovarian cancer. Among 97,275 initially cancer-free women participating in the 8-year prospective California Teachers Study of women,[77] and among 80,326 initially cancer-free women participating in the 16-year prospective Nurses' Health Study,[75] the risks of developing ovarian cancer were not affected by differences in vitamin E intakes. In a case-control study conducted in Hawaii and Los Angeles, CA, differences in vitamin E intakes did not affect the odds of premenopausal or postmenopausal women developing ovarian cancer.[78] In a case-control study nested within a prospective study conducted in Washington County, MD, the odds of developing ovarian cancer were not affected by differences in cholesterol-adjusted serum a-tocopherol concentrations.[150] In a case-control study conducted in New Hampshire and eastern Massachusetts, differences in daily intakes of vitamin E had no effect on the odds of premenopausal or postmenopausal women developing ovarian cancer.[80]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for ovarian cancer. The evidence documented by three retrospective observational studies[74,79,149] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for ovarian cancer.

Vitamin E Reduces the Risk for Pancreatic Cancer

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for pancreatic cancer. The results of retrospective observational studies conducted in Shanghai, China, support the conclusion that increased consumption of vitamin C reduces the risk for pancreatic cancer.[151,152] In one study, the multivariate-adjusted odds of developing pancreatic cancer were reduced significantly in men (but not women) consuming "high" amounts of vitamin E (OR, daily vitamin E consumption > 41 mg vs < 26 mg: 0.57; 95% C.I.: 0.35, 0.93; adjusted for age, income, smoking, green tea drinking and daily caloric intake).[151] In the other,

the multivariate-adjusted odds of developing pancreatic cancer were reduced significantly in both men and women consuming "high" amounts of vitamin E (OR, men, 4th quartile of daily vitamin E consumption vs 1st quartile: 0.5; 95% C.I.: 0.3, 0.7; women, 4th quartile of daily vitamin E consumption vs 1st quartile: 0.5; 95% C.I.: 0.3, 0.8; both adjusted for age, income, smoking, green tea drinking and daily caloric intake).[152]

However, in a case-control study nested within a prospective study in Washington County, MD, prediagnostic serum vitamin E concentrations were not associated with the odds of developing pancreatic cancer.[101] In addition, the results of a secondary endpoint analysis of the data obtained in 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 β-carotene or placebo for 5 to 8 years indicated that supplementation with 50 mg of vitamin E daily had no effect on the incidence of pancreatic carcinoma.[153] In addition, an epidemiologic analysis of that data indicated that the risk of developing pancreatic cancer was not affected by differences in the intake of vitamin E.[154] Similarly, the results of observing a cohort of 13,979 initially cancer-free residents of a retirement community for 9 years indicated that the risk of developing pancreatic cancer was not affected by differences in the daily consumption of vitamin E.[155]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for pancreatic cancer. The evidence documented by two retrospective observational studies[151,152] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for pancreatic cancer.

Vitamin E Reduces the Risk for Pharyngeal Cancer

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for pharyngeal cancer. The results of a case-control study conducted in Italy and Switzerland indicated that the multivariate-adjusted odds of developing either cancer of the oral cavity or pharyngeal cancer were reduced significantly by increased intake of vitamin E (OR: 0.74; p < 0.05; adjusted for age, sex, center, education, occupation, body mass index, smoking and drinking habits and non-alcohol energy intake).[144]

However, in 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 β-carotene or placebo for 5 to 8 years, supplementation with 50 mg of vitamin E daily had no effect on the incidence of upper aerodigestive tract cancers (cancers of the oral cavity, pharynx, esophagus or larynx).[130] Consistent with this report, in a case-control study conducted in Japan, the multivariate-adjusted odds of developing pharyngeal cancer were not affected by differences in vitamin E intakes (adjusted for age, sex, smoking status, alcohol consumption, use of multivitamin supplements, total daily energy intake, dental hygiene and year of first hospital visit).[135] Similarly, in a case-control study conducted in Melbourne, Australia, the odds of developing either squamous cell cancer of the oral cavity or pharyngeal cancer were not affected by differences in dietary vitamin E intakes.[145] In addition, the results of a case-control study conducted in the state of Hawaii indicated that the mean serum a-tocopherol concentrations of subjects with and without upper aerodigestive tract cancer were not different.[131]

The scientific evidence indicates that

increased consumption of vitamin E reduces the risk for pharyngeal cancer. The evidence documented by a retrospective observational study[144] supports this conclusion and there is no evidence that increased consumption of vitamin E may increase the risk for pharyngeal cancer.

Vitamin E Reduces the Risk for Prostate Cancer

The scientific evidence suggests that the consumption of increased amounts of vitamin E reduces the risk for prostate cancer. In 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 β-carotene or placebo, it was determined that 5 to 8 years of daily dietary supplementation with 50 mg of vitamin E produced a significant decrease in the incidence of new prostate cancer (RR: 0.52; 95% C.I.: 0.29, 0.95; adjusted for age, presence of benign prostatic hyperplasia, living in an urban area, presence or absence of concurrent dietary supplementation with β-carotene and serum total cholesterol concentration).[122,156-158] Consistent with this result, two groups of analysts performing systematic reviews of human clinical trials concluded that daily supplementation with 50 mg of vitamin E significantly reduces the risk for developing prostate cancer.[159,160]

In addition, an analysis of the effects of prestudy serum a-tocopherol concentrations on the development of prostate cancer 19 years later in participants in 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 -carotene or placebo for 5 to 8 years found that even though differences in serum a-tocopherol concentrations had no effect on the odds of developing prostate cancer during the study,[161] 19 years later the risks for any prostate cancer and for advanced prostate cancer were inversely correlated with prestudy serum a-tocopherol concentrations (risk estimates were adjusted for age at blood sample collection, trial intervention arm, serum total cholesterol concentration, body weight, urban residence and education).[162] These findings are even more remarkable given the continued cigarette smoking by the subjects during and after the study and the data from a 20-year prospective observational study of 17,633 white males aged 35 years and older (the Lutheran Brotherhood Cohort Study) that confirm that the use of tobacco products increases the risk of developing prostate cancer.[163]

The results of prospective observational studies also support the conclusion that increased consumption of vitamin E reduces the risk for prostate cancer.[86-88,164,165] For example, although the results of an 8-year prospective observational study (the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) suggest that among all men, differences in vitamin E or a-tocopherol intakes from foods or dietary supplements do not affect the multivariate-adjusted risk of developing prostate cancer (adjusted for age, daily energy intake, race, study center, family history of prostate cancer, BMI, smoking status, physical activity, daily consumption of fats and red meats, history of diabetes and aspirin use) among current smokers and nonsmokers who had quit smoking within 10 years, daily dietary supplementation with more than 400 IU of vitamin E reduces significantly the risk of developing advanced prostate cancer (OR, daily dietary supplementation with more than 400 IU of vitamin E vs none: 0.29; 95% C.I.: 0.12, 0.68; adjusted for age, daily energy intake, race, study center, family history of prostate cancer, BMI, smoking

status, physical activity, daily consumption of fats and red meats, history of diabetes and aspirin use).[88] Similarly, among current smokers and nonsmokers who had quit smoking within 10 years and who had consumed any amount of supplemental vitamin E for at least 10 years, daily dietary supplementation with vitamin E reduces significantly the risk of developing advanced prostate cancer (OR, supplementation with any amount of vitamin E for at least 10 years vs none: 0.30; 95% C.I.: 0.09, 0.96; adjusted for age, daily energy intake, race, study center, family history of prostate cancer, BMI, smoking status, physical activity, daily consumption of fats and red meats, history of diabetes and aspirin use). Consistent with this report, in a 17-year prospective study of 2,974 men in Basel, Switzerland, serum vitamin E concentrations < 30.02 uM increased significantly the risk of developing prostate cancer among cigarette smokers (RR: 19.89; 95% C.I.: 3.60, 109.80).[86,87] On the other hand, the results of the double-blind, randomized placebo-controlled Prevention Research Veteran Affairs E-vitamin Nutrition Trial indicated that daily supplementation with 400 IU of vitamin E produced a significant increase in mean serum a-tocopherol concentration without affecting mean serum prostate specific antigen concentration[164] and the results of a 10-year prospective observational study of 35,242 men conducted in Washington State indicated that the risk for advanced (regionally invasive or distant metastatic) prostate cancer was reduced significantly by daily supplementation with at least 400 IU of vitamin E (HR: 0.43; 95% C.I.: 0.19, 1.0; adjusted for age, family history of prostate cancer, history of benign prostatic hyperplasia, income, use of multivitamins and serum prostate specific antigen concentration).[165]

The results of retrospective observational studies also support the conclusion that increased consumption of vitamin E reduces the risk for prostate cancer.[95,166-168]

In a case-control study conducted in Serbia, the odds of developing prostate cancer were reduced significantly by greater daily intakes of a-tocopherol (OR: 0.15, 95% C.I.: 0.05, 0.53)95 and in a case-control study conducted in Athens, Greece, the odds of developing prostate cancer were inversely correlated with vitamin E intakes.[166]

In a case-control study nested within a prospective study conducted in Washington County, MD, the multivariate-adjusted odds of developing prostate cancer were reduced significantly when serum a-tocopherol concentration was greater than 1.31 mg/dl, serum gamma-tocopherol concentration was greater than 0.28 mg/dl and serum selenium concentrations was either less than 0.79 ppm (OR: 0.34; 95% C.I.: 0.12, 0.99; adjusted for age, education and hours since last meal when blood was obtained) or greater than 0.79 ppm (OR: 0.27; 95% C.I.: 0.10, 0.72; adjusted for age, education and hours since last meal when blood was obtained).167 Consistent with this report, in a case-control study conducted in India, mean erythrocyte ascorbic acid content and mean plasma vitamin E concentration were significantly lower among patients with prostate cancer.[168]

In contrast to this body of supportive evidence, the results of prospective[85,89,169,170] and retrospective[91,94,96,97,101,171-174] observational studies did not provide support for the conclusion that increased consumption of vitamin C reduces the risk for prostate cancer. After 10 years of observation, those among the 47,780 men participating in the prospective US Health Professionals Follow-Up Study who consumed dietary supplements containing vitamin E exhibited no change in their multivariate-adjusted risk of developing prostate cancer (adjusted for period of study, age, family history of prostate cancer, vasectomy status, smoking status, current BMI, BMI at age 21 years, physical activity level at entry into study, daily energy intake and daily intakes of calcium, lycopene,

fructose and total fat).[169] Similarly, among the 72,704 men of the American Cancer Society Cancer Prevention Study II Nutrition Cohort, the risk of developing prostate cancer was not affected by the intakes of vitamin E from either foods or supplements,[170] among the 475,726 men participating in the 18-year prospective observational American Cancer Society Cancer Prevention Study II, daily dietary supplementation with vitamin E did not affect the multivariate-adjusted rate of death from prostate cancer (adjusted for age, race, education, smoking status, family history or prostate cancer, exercise, BMI, alcohol consumption, vegetable consumption and dietary supplementation with multivitamins, vitamin A and vitamin C)[85] and the results of a 6.3-year prospective observational study of 58,279 men aged 55 to 69 years (the Netherlands Cohort Study) indicated that the age- and sex-adjusted risk of developing prostate cancer was not affected by differences in vitamin E intakes in that study population.[89]

In case-control studies conducted in Sweden[94] and Montreal, Quebec, Canada,[96] the odds of developing either any form of prostate cancer or advanced prostate cancer were not affected by differences in daily intakes of vitamin E (adjusted for age and daily energy intake). In a case-control study conducted in the state of Washington in the US, the multivariate-adjusted odds of developing prostate cancer were not affected by the use of any dietary supplements of vitamin E (adjusted for dietary intakes of fat and total energy, race, age, family history of prostate cancer, BMI, serum prostate specific antigen concentration and education).[91]

In a case-control study nested within the prospective Beta-Carotene and Retinol Efficacy Trial (CARET) of dietary supplementation of 18,314 high-risk subjects (heavy smokers and workers exposed to asbestos) with placebo, beta-carotene or retinyl palmitate, the multivariate-adjusted odds of developing prostate cancer were not affected by differences in prestudy serum a-tocopherol concentrations (adjusted for study center, asbestos exposure, age, sex, smoking status during study, year of entry into study and cigarette smoking history prior to the study).[171] Similarly, in a case-control study nested within the 8-country European Prospective Investigation into Cancer and Nutrition (EPIC), the multivariate-adjusted odds of developing prostate cancer were not affected by differences in prestudy plasma a-tocopherol concentrations (adjusted for BMI, smoking status, alcohol consumption, level of physical activity, marital status and education).[172] In individual case-control studies nested within a prospective study in Washington County, MD, prediagnostic serum vitamin E concentrations were not associated with the odds of developing prostate cancer[101,173] and when the data from 2 case-control studies conducted in Washington County, MD were combined, the odds of developing prostate cancer were found to be unaffected by differences in serum concentrations of a-tocopherol.[97] In a case-control study conducted in Hawaii, the multivariate-adjusted odds of developing prostate cancer were not affected by differences in serum a-tocopherol concentrations.[174]

The scientific evidence indicates that increased consumption of vitamin E reduces the risk for prostate cancer. The evidence documented by a secondary endpoint analysis of the data obtained during a prospective trial,[122,156-158] the results of two systematic reviews,[159,160] 6 prospective observational studies[86-88,163,165,166] and 4 retrospective observational studies[95,166-168] supports this conclusion and there is no evidence that increased consumption of vitamin E increases the risk for prostate cancer.

Conclusions

The foregoing credible scientific evidence establishes that adequate intakes of vitamin C and vitamin E safely reduce the

risk for cancer in general. Individually, vitamin C reduces the risk for bladder cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, endometrial cancer, adenocarcinoma of the esophagus, squamous cell carcinoma of the esophagus, gastric carcinoma, lung cancer, cancer of the oral cavity, ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, renal cell cancer, and cancer of the salivary glands. Vitamin C also may reduce the risk of laryngeal cancer. Individually, vitamin E reduces the risk for bladder cancer, brain cancer, breast cancer, cervical cancer, colon cancer, colorectal cancer, adenocarcinoma of the esophagus, squamous cell carcinoma of the esophagus, gastric carcinoma, lung cancer, melanoma, cancer of the oral cavity, ovarian cancer, pancreatic cancer, pharyngeal cancer, prostate cancer, and renal cell cancer. Vitamin E also may reduce the risk of laryngeal cancer and rectal cancer.

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